US 20170105985A1

(19) **United States**

(12) **Patent Application Publication**

Hakonarson et al.

(10) **Pub. No.: US 2017/0105985 A1**

(43) **Pub. Date: Apr. 20, 2017**

(54) **NONSELECTIVE METABOTROPIC GLUTAMATE RECEPTOR ACTIVATORS FOR TREATMENT OF ATTENTION DEFICIT DISORDER AND 22Q SYNDROME**

(71) Applicant: **THE CHILDREN'S HOSPITAL OF PHILADELPHIA**, Philadelphia, PA (US)

(72) Inventors: **Hakon Hakonarson**, Malvern, PA (US); **Charlly Kao**, Philadelphia, PA (US)

(73) Assignee: **THE CHILDREN'S HOSPITAL OF PHILADELPHIA**, Philadelphia, PA (US)

(21) Appl. No.: **15/258,828**

(22) Filed: **Sep. 7, 2016**

Related U.S. Application Data

(60) Provisional application No. 62/215,628, filed on Sep. 8, 2015, provisional application No. 62/215,633, filed on Sep. 8, 2015, provisional application No. 62/215,636, filed on Sep. 8, 2015, provisional application No. 62/215,673, filed on Sep. 8, 2015.

Publication Classification

(51) **Int. Cl.**
A61K 31/454 (2006.01)

(52) **U.S. Cl.**
CPC ***A61K 31/454*** (2013.01)

(57) **ABSTRACT**

This application relates to methods of treating attention deficit hyperactivity disorder (ADHD), 22q deletion and/or duplication syndrome, and co-morbidities with a nonselective activator of metabotropic glutamate receptors, such as fasoracetam, for example, in subjects having a genetic alteration in at least one metabotropic glutamate receptor (mGluR) network gene.

Tier 1 Gene	GeneRange (hg19)	GeneRange +500kb(hg19)	GeneRange (hg18)	StartSNP (GeneRange +500kb)	EndSNP (GeneRange +500kb)
ACAT1	chr11:107992257-108018891	chr11:107492257-108518891	chr11:107497467-107523485	rs7925970	kgp3957860
ACCN1	chr17:31340105-32483825	chr17:30840105-32983825	chr17:28364218-29507938	rs2519865	kgp10854156
ACTR2	chr2:65454828-65498390	chr2:64954828-65998390	chr2:65308405-65351891	rs1477043	kgp4266233
ADCY1	chr7:45614124-45762714	chr7:45114124-46262714	chr7:45580649-45729239	rs2289367	kgp13398740
ADRBK1	chr11:67033904-67054029	chr11:66533904-67554029	chr11:66790480-66810605	kgp7862175	kgp2126040
ALDOA	chr16:30064410-30081741	chr16:29564410-30581741	chr16:29971972-29989236	kgp733881	kgp6386467,rs33997546
APP	chr21:27252860-27543446	chr21:26752860-28043446	chr21:26174731-26465003	rs7281883	kgp2004872
ARL15	chr5:53180613-53606403	chr5:52680613-54106403	chr5:53216370-53642160	kgp10474479	rs10058571
ATXN7L3	chr17:42269172-42275529	chr17:41769172-42775529	chr17:39624698-39631055	rs11650560	rs6503398
BDKRB2	chr14:96671134-96710666	chr14:96171134-97210666	chr14:95740887-95780419	kgp19731302	kgp1905230
CA8	chr8:61101422-61193954	chr8:60601422-61693954	chr8:61263976-61356508	kgp9568230	kgp1623935
CACNA1B	chr9:140772240-141019076	chr9:140272240-141519076	chr9:139892061-140136452	kgp18327422	kgp12374930
CACYBP	chr1:174968570-174981163	chr1:174468570-175481163	chr1:173235193-173247786	rs1013769	kgp15391194
CALM1	chr14:90863326-90874619	chr14:90363326-91374619	chr14:89933125-89944363	kgp828819	kgp22766175
CHRM3	chr1:239549864-240049896	chr1:239049864-240549896	chr1:237616487-238116519	kgp1999037	rs1537850
CIC	chr19:42788816-42799949	chr19:42288816-43299949	chr19:47480656-47491789	kgp21495548	kgp22794755
CNP	chr17:40118758-40129754	chr17:39618758-40629754	chr17:37372284-37383280	kgp4988562	kgp1573374

Fig. 1-1

Tier 1 Gene	GeneRange (hg19)	GeneRange +500kb(hg19)	GeneRange (hg18)	StartSNP (GeneRange +500kb)	EndSNP (GeneRange +500kb)
CNTN4	chr3:2140549-3099645	chr3:1640549-3599645	chr3:2117246-3074645	kgp7465125	kgp11488181,rs9811783
CRHR1	chr17:954314-1170453	chr17:454314-1670453	chr17:4121744 8-41268973	kgp12243700	kgp2967880
CTNNA2	chr2:79412356-80875988	chr2:78912356-81375988	chr2:79265864-80729416	kgp2692843	kgp6161954
DISC1	chr1:231664398-232177019	chr1:231164398-232677019	chr1:229829183-230243641	kgp15830047	kgp10247084
DPP6	chr7:153584418-154685995	chr7:153084418-155185995	chr7:153215351-154316928	rs1822707	rs7781545
DYNLL1	chr12:120907659-120936298	chr12:120407659-121436298	chr12:119392042-119420681	rs2393569	rs1169303
FPR1	chr19:52249022-52255150	chr19:51749022-52755150	chr19:56940837-56946962	rs11084062	kgp21351572
GAPDH	chr12:6643656-6647536	chr12:6143656-7147536	chr12:6513917-6517797	kgp12277967	kgp3951989
GNA15	chr19:3136190-3163766	chr19:2636190-3663766	chr19:3087190-3114766	kgp9441497	rs8109485
GNAI2	chr3:50263723-50296786	chr3:49763723-50796786	chr3:50238727-50271790	rs1049256	kgp1163947
GNAO1	chr16:56225250-56391356	chr16:55725250-56891356	chr16:54782751-54948857	rs36013	kgp16402238
GNAQ	chr9:80335190-80646219	chr9:79835190-81146219	chr9:79525010-79836012	rs3802497	kgp478959
GRIK1	chr21:30909253-31312282	chr21:30409253-31812282	chr21:29831124-30234153	kgp6759057	kgp13183414
GRIK3	chr1:37261127-37499844	chr1:36761127-37999844	chr1:37033714-37272431	kgp15160339	kgp6185747
GRM1	chr6:146348781-146758731	chr6:145848781-147258731	chr6:146390474-146800424	kgp17333275	rs17076442
GRM3	chr7:86273229-86494192	chr7:85773229-86994192	chr7:86111165-86332128	rs7809507	rs6950721
GRM5	chr11:88237743-88796816	chr11:87737743-89296816	chr11:87881005-88436464	kgp11022062	rs7123374
GRM7	chr3:6902801-7783218	chr3:6402801-8283218	chr3:6877926-7758217	rs17288121	kgp10770379
GRM8	chr7:126078651-126893147	chr7:125578651-127393147	chr7:125865887-126680383	rs11767202	kgp13721602
GSN	chr9:123963760-124095120	chr9:123463760-124595120	chr9:123003581-123134941	rs10984984	kgp10246924
HOMER1	chr5:78669785-78809700	chr5:78169785-79309700	chr5:78705541-78845456	kgp22480767	rs2438612

Fig. 1-2

Tier 1 Gene	GeneRange (hg19)	GeneRange +500kb(hg19)	GeneRange (hg18)	StartSNP (GeneRange +500kb)	EndSNP (GeneRange +500kb)
HTR2A	chr13:47407512-47471169	chr13:46907512-47971169	chr13:46305513-46368995	rs4942513	rs2185411
LARP7	chr4:113558119-113578742	chr4:113058119-114078742	chr4:113777568-113798191	kgp20778198	rs10516593
MAPK1	chr22:22113946-22221970	chr22:21613946-22721970	chr22:20443946-20551970	rs2019503	rs5758017
MTHFD1	chr14:64854758-64926725	chr14:64354758-65426725	chr14:63924845-63996474	kgp8236539	kgp19721535
MX1	chr21:42792519-42831141	chr21:42292519-43331141	chr21:41714311-41753008	rs7280789	kgp9356591
NARG1	chr4:140222675-140311935	chr4:139722675-140811935	chr4:140442125-140531385	kgp951257	kgp22761518
NEGR1	chr1:71868624--72748405	chr1:71368624-73248405	chr1:71641212-72520993	kgp15840593	kgp15187386
NLN	chr5:65018022--65125111	chr5:64518022-65625111	chr5:65053840-65155145	kgp8540617	kgp6780911
NMI	chr2:152126981-152146430	chr2:151626981-152646430	chr2:151835227-151854676	rs9789673	rs4303715
PCBP3	chr21:47063682-47355618	chr21:46563682-47855618	chr21:45888110-46180046	rs13047590	rs17371795
PDE1C	chr7:31792631--32338383	chr7:31292631-32838383	chr7:31759156-32305466	rs960434	rs10264489
PPP2R1A	chr19:52693054-52729678	chr19:52193054-53229678	chr19:57385045-57421483	kgp3827878	kgp21490256
PRPSAP1	chr17:74306867-74350279	chr17:73806867-74850279	chr17:71818609-71861526	kgp13936725	kgp5222426
PSMD11	chr17:30771501-30808042	chr17:30271501-31308042	chr17:27795614-27832155	kgp12010810	rs8065019
PSMD13	chr11:236807-252984	chr11:1-752984	chr11:226807-242984	kgp9815230	kgp7252222
PXN	chr12:120648241-120703574	chr12:120148241-121203574	chr12:119132632-119187946	kgp9790305	kgp10851563
QRICH2	chr17:74270129-74303761	chr17:73770129-74803761	chr17:71781724-71815356	kgp9494493	kgp13978344
RANBP1	chr22:20105023-20114706	chr22:19605023-20614706	chr22:18485023-18494704	kgp15081773	kgp240898
RAP2A	chr13:98086474-98120252	chr13:97586474-98620252	chr13:96884476-96918245	kgp1964422	kgp12456635
RCC1	chr1:28832454--28865708	chr1:28332454-29365708	chr1:28717331-28738194	kgp4972332	kgp10549261
RGS12	chr4:3315873-3441640	chr4:2815873-3941640	chr4:3285671-3411438	kgp6603457	kgp12100218

Fig. 1-3

Tier 1 Gene	GeneRange (hg19)	GeneRange +500kb(hg19)	GeneRange (hg18)	StartSNP (GeneRange +500kb)	EndSNP (GeneRange +500kb)
RIF1	chr2:152266396-152333860	chr2:151766396-152833860	chr2:151974645-152040665	rs13010870	kgp14366130
RUVBL2	chr19:49497155-49519182	chr19:48997155-50019182	chr19:54188967-54210994	kgp2866116	rs6509434
RYR1	chr19:38924339-39078204	chr19:38424339-39578204	chr19:43616179-43770044	kgp21463042	kgp10827233
RYR2	chr1:237205701-237997288	chr1:236705701-238497288	chr1:235272324-236063911	kgp15265824	kgp855991
SDC3	chr1:31342312--31381480	chr1:30842312-31881480	chr1:31114899-31154067	kgp3545961	rs1039630
SELE	chr1:169691780-169703220	chr1:169191780-170203220	chr1:167958404-167969844	kgp11738441	kgp5736867
SERPINB9	chr6:2887503-2903545	chr6:2387503-3403545	chr6:2832502-2848506	rs4959652	kgp9198993
SETD4	chr21:37415981-37451687	chr21:36915981-37951687	chr21:36337851-36373557	rs8131794	kgp10193814
SGTB	chr5:64961754--65017941	chr5:64461754-65517941	chr5:64997510-65053697	rs2367239	rs253229
SHANK1	chr19:51165083-51220195	chr19:50665083-51720195	chr19:55856895-55912007	kgp8880890	kgp5265049
SLC7A10	chr19:33699569-33716756	chr19:33199569-34216756	chr19:38391410-38408548	kgp3880561	kgp21532613
SORD	chr15:45315301-45367287	chr15:44815301-45867287	chr15:43102632-43154331	rs3752691	rs17627219
STRAP	chr12:16035287-16056410	chr12:15535287-16556410	chr12:15926554-15947677	kgp9763258	kgp18858589
TK1	chr17:76170159-76183285	chr17:75670159-76683285	chr17:73681754-73694880	kgp13960604	kgp4569268
TNIK	chr3:170780291-171178197	chr3:170280291-171678197	chr3:172264363-172660546	kgp17660929	kgp3100328
USP24	chr1:55532031--55681039	chr1:55032031-56181039	chr1:55304619-55453350	kgp3052862	kgp5594096
VHL	chr3:10183318--10195354	chr3:9683318-10695354	chr3:10158318-10168746	kgp6652387	rs9942062

Fig. 1-4

Tier 2 Gene	GeneRange(hg19)	GeneRange+500kb(hg19)	GeneRange(hg18)	StartSNP (GeneRange+500kb)	EndSNP (GeneRange+500kb)
ACAT2	chr6:160182988-160200087	chr6:159682988-160700087	chr12:51783540-51804590	kgp17016252	rs3119312
ACCN2	chr12:50451486-50477394	chr12:49951486-50977394	chr12:48737753-48763661	kgp6083801	kgp2326833
ACP1	chr2:264868-278282	chr2:1-778282	chr2:254871-268282	kgp14878812	kgp6217001
ACTB	chr7:5566778-5570232	chr7:5066778-6070232	chr7:5533304-5536758	kgp10503129	rs17136342
ADA	chr20:43248162-43280376	chr20:42748162-43780376	chr20:42681576-42713790	kgp505723	rs2207199
ADD1	chr4:2845583-2931802	chr4:2345583-3431802	chr4:2815381-2901587	kgp5601859	kgp5383382
ADD2	chr2:70834749-70995375	chr2:70334749-71495375	chr2:70688257-70848837	kgp14188216	kgp4077094
ADORA1	chr1:203096835-203136533	chr1:202596835-203636533	chr1:201363458-201403156	rs16850143	rs12568960
ADRA1B	chr5:159343739-159400017	chr5:158843739-159900017	chr5:159276317-159332595	rs17056747	kgp2774549
ADRA2A	chr10:112836789-112840662	chr10:112336789-113340662	chr10:112826910-112830560	kgp3219023	rs10787379
ADRA2C	chr4:3768295-3770253	chr4:3268295-4270253	chr4:3737872-3740016	kgp21189210	kgp21320659
ADRB2	chr5:148206155-148208197	chr5:147706155-148708197	chr5:148186348-148188381	kgp6738042	rs352336
ANXA2	chr15:60639349-60690185	chr15:60139349-61190185	chr15:58426641-58477477	kgp19904124	kgp1248561
APTX	chr9:32972603-33001639	chr9:32472603-33501639	chr9:32962607-33015110	kgp8123814	kgp22778750
AQP1	chr7:30893009-30965131	chr7:30393009-31465131	chr7:30917992-30931656	kgp13347683	rs11983505
ARHGAP24	chr4:86396283-86923823	chr4:85896283-87423823	chr4:86615307-87142847	kgp12192788	kgp20991115
ARRB1	chr11:74971165-75062875	chr11:74471165-75562875	chr11:74654129-74740521	kgp13077708	kgp12867051
ARRB2	chr17:4613788-4624795	chr17:4113788-5124795	chr17:4560537-4571544	kgp10630047	rs2304905

Fig. 2-1

Tier 2 Gene	GeneRange(hg19)	GeneRange+500kb(hg19)	GeneRange(hg18)	StartSNP (GeneRange+500kb)	EndSNP (GeneRange+500kb)
BDKRB1	chr14:96722546-96731100	chr14:96222546-97231100	chr14:95792311-95800853	rs10146784	kgp10194056
BTBD2	chr19:1985446-2015702	chr19:1485446-2515702	chr19:1936446-1966702	kgp9698924	rs12985186
BTG2	chr1:203274663-203278729	chr1:202774663-203778729	chr1:201541286-201545352	kgp11073362	kgp22834576
C17orf44	chr17:8123966-8127361	chr17:7623966-8627361	chr17:8064691-8068086	kgp14083005	kgp8066962
C1orf116	chr1:207191865-207206101	chr1:206691865-207706101	chr1:205258488-205272724	kgp15208593	rs12094477
C7orf25	chr7:42948871-42971805	chr7:42448871-43471805	chr7:42915396-42938330	kgp13766903	kgp8523923
CALB2	chr16:71392615-71424342	chr16:70892615-71924342	chr16:69950126-69981843	rs1774414	kgp16319275
CALM2	chr2:47387220-47403740	chr2:46887220-47903740	chr2:47146583-47257154	kgp12094177	kgp4237241
CALM3	chr14:90863326-90874619	chr14:90363326-91374619	chr19:51796351-51805879	kgp828819	kgp22766175
CAMK1	chr3:9799028-9811668	chr3:9299028-10311668	chr3:9774030-9786661	kgp4340327	kgp1318661
CAMK2B	chr7:44256748-44365230	chr7:43756748-44865230	chr7:44223273-44331749	rs10245456	kgp10338229
CAMK4	chr5:110559946-110820748	chr5:110059946-111320748	chr5:110587980-110848647	kgp11981357	kgp22673631
CCNB1	chr5:68462836-68474070	chr5:67962836-68974070	chr5:68498668-68509826	kgp5100830	rs28529133
CDC42	chr1:22379119-22419436	chr1:21879119-22919436	chr1:22251706-22292023	kgp15282552	rs209696
CENTG1	chr12:58118076-58135944	chr12:57618076-58635944	chr12:56404343-56422211	kgp22774357	rs12825103
CHGB	chr20:5891973-5906005	chr20:5391973-6406005	chr20:5840167-5854003	kgp19217529	kgp5406173
CHP	chr15:41523436-41574083	chr15:41023436-42074083	chr15:39310728-39361375	kgp9389002	kgp10815429
CHRM2	chr7:136553398-136701771	chr7:136053398-137201771	chr7:136203938-136352311	rs2882248	kgp11051162
CMPK	chr2:6988440-7005950	chr2:6488440-7505950	chr2:6905891-6923401	rs16865056	kgp6717309
CNR1	chr6:88849584-88875767	chr6:88349584-89375767	chr6:88910155-88932281	kgp11366911	kgp5424340

Fig. 2-2

Tier 2 Gene	GeneRange(hg19)	GeneRange+500kb(hg19)	GeneRange(hg18)	StartSNP (GeneRange+500kb)	EndSNP (GeneRange+500kb)
COPB2	chr3:139076432-139108522	chr3:138576432-139608522	chr3:140559122-140591212	kgp17652827	rs2554152
CYCS	chr7:25158269-25164980	chr7:24658269-25664980	chr7:25124799-25131480	kgp22782658	kgp9259047
DCN	chr12:91539034-91576806	chr12:91039034-92076806	chr12:90063165-90100937	rs11105720	rs1602946
DHCR7	chr11:71145456-71159477	chr11:70645456-71659477	chr11:70823104-70837125	rs2016495	kgp4157665
DLST	chr14:75348593-75370450	chr14:74848593-75870450	chr14:74418371-74440198	kgp6099186	rs11621369
DRD2	chr11:113280316-113346001	chr11:112780316-113846001	chr11:112785526-112851211	kgp12732525	rs1062613
DRD3	chr3:113847556-113918254	chr3:113347556-114418254	chr3:115330246-115400944	kgp18078164	kgp7361746
DSTN	chr20:17550598-17588652	chr20:17050598-18088652	chr20:17498598-17536652	kgp19350858	rs1581925
ECHS1	chr10:135175986-135186908	chr10:134675986-135686908	chr10:135025979-135036898	kgp21664075	kgp22837031
EGFR	chr7:55086724-55275031	chr7:54586724-55775031	chr7:55054218-55242525	kgp12053718	kgp3314724
EIF3S3	chr8:117657055-117768062	chr8:117157055-118268062	chr8:117726236-117837243	kgp10576753	rs1793723
ERBB2	chr17:37844392-37884915	chr17:37344392-38384915	chr17:35097918-35138441	kgp11528115	kgp670921
F2R	chr5:76011867-76031595	chr5:75511867-76531595	chr5:76047623-76067351	kgp22518836	kgp1549629
F2RL2	chr5:75911306-75919240	chr5:75411306-76419240	chr5:75947062-75954996	kgp10188048	kgp8041699
F2RL3	chr19:16999825-17002830	chr19:16499825-17502830	chr19:16860825-16863830	kgp9756004	kgp12567834
F3	chr1:94994731-95007413	chr1:94494731-95507413	chr1:94767460-94779903	kgp22732356	kgp5203715
FKBP3	chr14:45584801-45604009	chr14:45084801-46104009	chr14:44654858-44674272	kgp8973198	kgp19724486
FSCN1	chr7:5632435-5646287	chr7:5132435-6146287	chr7:5598979-5612812	kgp11535801	kgp22733484
FURIN	chr15:91411884-91426687	chr15:90911884-91926687	chr15:89212888-89227691	kgp19755110	kgp7570879
FYN	chr6:111981534-112194655	chr6:111481534-112694655	chr6:112089177-112301320	kgp9553033	kgp10843976

Fig. 2-3

Tier 2 Gene	GeneRange(hg19)	GeneRange+500kb(hg19)	GeneRange(hg18)	StartSNP (GeneRange+500kb)	EndSNP (GeneRange+500kb)
GLP1R	chr6:39016556-39055520	chr6:38516556-39555520	chr6:39124534-39163498	kgp11427391	kgp8067157
GLP2R	chr17:9729380-9793022	chr17:9229380-10293022	chr17:9670105-9733747	kgp13857921	kgp14095302
GNAI1	chr7:79764139-79848725	chr7:79264139-80348725	chr7:79602075-79686661	kgp3340161	kgp96572
GNAI3	chr1:110091185-110138452	chr1:109591185-110638452	chr1:109892708-109939975	rs28503409	kgp2138201
GNB2L1	chr5:180663927-180670906	chr5:180163927-181170906	chr5:180596533-180603512	kgp9825803	kgp22785368
GOT1	chr10:101156626-101190530	chr10:100656626-101690530	chr10:101146617-101180336	kgp21656902	kgp21815940
GP1BA	chr17:4835591-4838325	chr17:4335591-5338325	chr17:4776371-4779067	kgp13949132	kgp11186643
GPR26	chr10:125425870-125456913	chr10:124925870-125956913	chr10:125415860-125444113	kgp7582662	kgp21578542
GRB2	chr17:73314156-73401790	chr17:72814156-73901790	chr17:70825751-70913385	kgp13841089	kgp14035219
GRB7	chr17:37894161-37903538	chr17:37394161-38403538	chr17:35147712-35157064	kgp14102913	kgp13833584
GRIA1	chr5:152870083-153193429	chr5:152370083-153693429	chr5:152850276-153173622	rs1438937	rs10057369
GRM2	chr3:51741080-51752625	chr3:51241080-52252625	chr3:51716127-51727665	rs4367100	rs13060808
GRM4	chr6:33989627-34113869	chr6:33489627-34613869	chr6:34097605-34231377	kgp17076142	rs6909637
GRM6	chr5:178405329-178422124	chr5:177905329-178922124	chr5:178337935-178354730	rs603852	rs11249632
HBXIP	chr1:110943876-110950546	chr1:110443876-111450546	chr1:110745399-110752069	kgp8686658	rs1936942
HD	chr6:125596496-125623282	chr6:125096496-126123282	chr6:125638195-125664981	rs11154263	rs11967627
HNRPA3	chr2:178077422-178088685	chr2:177577422-178588685	chr2:177785668-177796931	kgp14203861	rs1344924
HOMER3	chr19:19017768-19045219	chr19:18517768-19545219	chr19:18901011-18912983	rs13344313	rs4808199
HRPT2	chr1:193091088-193223942	chr1:192591088-193723942	chr1:191357711-191490565	kgp2473538	kgp12065536
HSP90AB1	chr6:44214848-44221614	chr6:43714848-44721614	chr6:44322826-44329592	kgp5836209	kgp8706663

Fig. 2-4

Tier 2 Gene	GeneRange(hg19)	GeneRange+500kb(hg19)	GeneRange(hg18)	StartSNP (GeneRange+500kb)	EndSNP (GeneRange+500kb)
IL8RB	chr2:218989997-219001975	chr2:218489997-219501975	chr2:218698242-218710220	kgp22730583	rs1055816
IMPDH2	chr3:49061761-49066875	chr3:48561761-49566875	chr3:49036765-49041879	kgp22731595	kgp5626213
IQGAP2	chr5:75699148-76003957	chr5:75199148-76503957	chr5:75734904-76039713	kgp22490664	rs11739698
ITGB1	chr10:33189245-33247293	chr10:32689245-33747293	chr10:33229251-33287299	kgp12034252	rs11009395
ITGB7	chr12:53585106-53601000	chr12:53085106-54101000	chr12:51871373-51887267	kgp19011413	kgp3313746
ITPR1	chr3:4535031-4889524	chr3:4035031-5389524	chr3:4510033-4864286	kgp17889944	kgp1749057
KIAA0090	chr1:19544583-19578046	chr1:19044583-20078046	chr1:19417170-19450633	rs624761	rs1009631
KIAA1683	chr19:18367905-18385319	chr19:17867905-18885319	chr19:18228907-18246235	kgp6435620	rs10412356
LAMA4	chr6:112429133-112575828	chr6:111929133-113075828	chr6:112535826-112682521	kgp16962466	kgp17024247
LRP2BP	chr4:186285031-186300172	chr4:185785031-186800172	chr4:186522026-186537166	kgp7238414	rs9994907
LRRC59	chr17:48458593-48474914	chr17:47958593-48974914	chr17:45813597-45829831	kgp1609816	kgp13856216
LTA	chr6:2825414-2827639	chr6:2825414-2827639	chr6:2787675-2789683	kgp11675228	rs6912537
LYAR	chr4:4269428-4291896	chr4:3769428-4791896	chr4:4320337-4342744	kgp22780996	kgp7317116
LYN	chr8:56792385-56925006	chr8:56292385-57425006	chr8:56954939-57086494	kgp8836202	rs2670027
MAP4	chr3:47892179-48130769	chr3:47392179-48630769	chr3:47867188-48105715	kgp17741397	rs35623035
MAPT	chr17:43971747-44105699	chr17:43471747-44605699	chr17:41327543-41461546	kgp22730329	kgp13941400
MARK4	chr19:45754515-45808541	chr19:45254515-46308541	chr19:50446681-50500381	kgp10230030	kgp21456098
MC4R	chr18:58038563-58040001	chr18:57538563-58540001	chr18:56189543-56190981	kgp7049183	kgp1258536
MGC11082	chr18:3602998-3604385	chr18:3102998-4104385	chr18:3592998-3594385	kgp15965827	kgp12318627
MRPL14	chr6:44081372-44095191	chr6:43581372-44595191	chr6:44189349-44203169	kgp17033193	rs527322

Fig. 2-5

Tier 2 Gene	GeneRange(hg19)	GeneRange+500kb(hg19)	GeneRange(hg18)	StartSNP (GeneRange+500kb)	EndSNP (GeneRange+500kb)
MRPS16	chr10:75006445-75012451	chr10:74506445-75512451	chr10:74678606-74682457	kgp21628722	rs12243089
MTNR1A	chr4:187454808-187476537	chr4:186954808-187976537	chr4:187691802-187713531	rs12648771	rs4476657
MTNR1B	chr11:92702788-92715948	chr11:92202788-93215948	chr11:92342436-92355596	kgp10063029	rs2658801
MYC	chr8:128748314-128753680	chr8:128248314-129253680	chr8:128817497-128822855	kgp3177285	kgp1944877
MYO6	chr6:76458908-76629254	chr6:75958908-77129254	chr6:76515628-76685974	kgp17262775	kgp17183304
NANS	chr9:100818958-100845365	chr9:100318958-101345365	chr9:99847709-99885178	rs10817759	rs2778908
NCK1	chr3:136581049-136667968	chr3:136081049-137167968	chr3:138063762-138150658	kgp117446	kgp10600232
NFKBIA	chr14:35870715-35873960	chr14:35370715-36373960	chr14:34940466-34943711	kgp19552677	kgp19707730
NPY2R	chr4:156129780-156138228	chr4:155629780-156638228	chr4:156349230-156357678	kgp3956236	kgp20850236
NUDC	chr1:27248223-27272887	chr1:26748223-27772887	chr1:27120810-27145474	rs11247955	kgp15594139
OPRD1	chr1:29138653-29190208	chr1:28638653-29690208	chr1:29011240-29062795	kgp9104521	kgp15855740
PAFAH1B3	chr19:42801184-42806952	chr19:42301184-43306952	chr19:47493024-47498563	kgp21540635	kgp22735078
PCBP1	chr2:70314584-70316334	chr2:69814584-70816334	chr2:70168204-70169836	kgp14596264	kgp6568959
PCDHA4	chr5:140186671-140391929	chr5:139686671-140891929	chr5:140166855-140372115	kgp6468526	kgp10727572
PCID1	chr11:32605313-32624037	chr11:32105313-33124037	chr11:32561889-32580613	kgp13035948	rs10836023
PCMT1	chr6:150070830-150132557	chr6:149570830-150632557	chr6:150112657-150174249	kgp17277449	kgp10169289
PDCD5	chr19:33072093-33078358	chr19:32572093-33578358	chr19:37763943-37770169	kgp21531284	rs7259333
PDE1B	chr12:54943176-54973023	chr12:54443176-55473023	chr12:53229670-53259290	kgp18962385	rs11171250
PDE6G	chr17:79617488-79623607	chr17:79117488-80123607	chr17:77227893-77234038	kgp317116	kgp13898509
PGM1	chr1:64058946-64125916	chr1:63558946-64625916	chr1:63831534-63898505	kgp175729	kgp15416792

Fig. 2-6

Tier 2 Gene	GeneRange(hg19)	GeneRange+500kb(hg19)	GeneRange(hg18)	StartSNP (GeneRange+500kb)	EndSNP (GeneRange+500kb)
PHKB	chr16:47495209-47735434	chr16:46995209-48235434	chr16:46052710-46292935	kgp8481371	rs16945930
PHKG2	chr16:30759619-30772497	chr16:30259619-31272497	chr16:30667237-30676183	kgp16316196	kgp22773724
PICK1	chr22:38453261-38471708	chr22:37953261-38971708	chr22:36783207-36801654	kgp5170623	kgp1759680
PIK3CA	chr3:178866310-178952497	chr3:178366310-179452497	chr3:180349004-180435191	rs7615444	rs1025864
PIK3R1	chr5:67511583-67597649	chr5:67011583-68097649	chr5:67547359-67633405	kgp7844449	rs7737296
PLA2G7	chr6:46672052-46703430	chr6:46172052-47203430	chr6:46780011-46811110	kgp4678268	kgp9155835
PLCB1	chr20:8113295-8865547	chr20:7613295-9365547	chr20:8061295-8813547	kgp19226483	rs2076234
PLCB3	chr11:64018994-64036924	chr11:63518994-64536924	chr11:63775697-63793195	kgp9427286	rs484886
PLCG2	chr16:81812898-81991899	chr16:81312898-82491899	chr16:80370430-80549400	kgp4622733	kgp3230988
PPIH	chr1:43124047-43142429	chr1:42624047-43642429	chr1:42896634-42915016	kgp1870818	rs11210802
PRDX1	chr1:45976706-45988562	chr1:45476706-46488562	chr1:45749293-45760196	rs3806405	kgp15560310
PRKCA	chr17:64298925-64806862	chr17:63798925-65306862	chr17:61729387-62237324	kgp13847618	kgp13994829
PRLHR	chr10:120352915-120355160	chr10:119852915-120855160	chr10:120342905-120345150	rs853584	kgp21690663
PRMT1	chr19:50180408-50191707	chr19:49680408-50691707	chr19:54872307-54883516	kgp1460116	kgp5315133
PSAT1	chr9:80912058-80945009	chr9:80412058-81445009	chr9:80101878-80134829	kgp2581728	kgp9769053
PSEN1	chr14:73603142-73690399	chr14:73103142-74190399	chr14:72672931-72756862	kgp8405661	kgp19611371
PSMA1	chr11:14526421-14665180	chr11:14026421-15165180	chr11:14482997-14621739	kgp12643195	kgp13010596
PSMC1	chr14:90722893-90738966	chr14:90222893-91238966	chr14:89792646-89808719	rs10140098	kgp19595798
PSMD1	chr2:231921577-232037540	chr2:231421577-232537540	chr2:231629852-231745717	rs1678155	kgp11602861
PSMD6	chr3:63996230-64009658	chr3:63496230-64509658	chr3:63971270-63984698	kgp9706776	kgp17718198

Fig. 2-7

Tier 2 Gene	GeneRange(hg19)	GeneRange+500kb(hg19)	GeneRange(hg18)	StartSNP (GeneRange+500kb)	EndSNP (GeneRange+500kb)
PSME1	chr14:24605377-24608176	chr14:24105377-25108176	chr14:23675217-23678016	kgp11494860	kgp2234181
PTHR2	chr2:209353736-209704818	chr2:208853736-210204818	chr2:209061981-209413063	kgp14652386	rs1020407
PYGL	chr14:51371934-51411248	chr14:50871934-51911248	chr14:50441686-50480984	kgp10991856	rs7146882
PYGM	chr11:64513860-64528187	chr11:64013860-65028187	chr11:64270436-64284763	kgp12876954	rs675671
RAB2	chr8:61429469-61536203	chr8:60929469-62036203	chr8:61592023-61698757	kgp7067636	rs3864667
RALA	chr7:39663151-39747723	chr7:39163151-40247723	chr7:39629686-39714242	kgp22733616	rs11768838
RCC2	chr1:17733250-17766250	chr1:17233250-18266250	chr1:17605865-17638807	kgp15535308	kgp7647703
RGS2	chr1:192778168-192781407	chr1:192278168-193281407	chr1:191044793-191048026	rs10921130	kgp11065785
RHOA	chr3:49396578-49449526	chr3:48896578-49949526	chr3:49371582-49424530	kgp11466037	rs868891
RPA2	chr1:28218048-28241236	chr1:27718048-28741236	chr1:28090635-28113823	rs12033326	kgp15705538
RPLP2	chr11:809935-812876	chr11:309935-1312876	chr11:799935-802876	kgp11473410	kgp7750669
RPN2	chr20:35807455-35870025	chr20:35307455-36370025	chr20:35240887-35303439	kgp9846122	kgp19260650
RPS14	chr5:149823791-149829319	chr5:149323791-150329319	chr5:149803984-149809512	kgp22444746	kgp22218062
RRM1	chr11:4137307-4223759	chr11:3637307-4723759	chr11:4072499-4116682	rs6578398	kgp4491491
S100A6	chr1:153507075-153508717	chr1:153007075-154008717	chr1:151773699-151775341	kgp15193014	rs10908627
SACS	chr13:23902964-24007841	chr13:23402964-24507841	chr13:22800964-22905841	kgp16818396	rs2765089
SARS	chr1:109756514-109780804	chr1:109256514-110280804	chr1:109558062-109582308	kgp5910329	rs1803687
SCTR	chr2:120197418-120282028	chr2:119697418-120782028	chr2:119913888-119998498	kgp12364473	kgp22762988
SET	chr9:131445933-131458675	chr9:130945933-131958675	chr9:130485754-130498496	kgp11282765	kgp18608937
SF3B14	chr2:24290453-24299314	chr2:23790453-24799314	chr2:24143957-24152818	kgp14521970	rs12474894

Fig. 2-8

Tier 2 Gene	GeneRange(hg19)	GeneRange+500kb(hg19)	GeneRange(hg18)	StartSNP (GeneRange+500kb)	EndSNP (GeneRange+500kb)
SHBG	chr17:7517381-7536700	chr17:7017381-8036700	chr17:7458106-7477395	kgp7760759	rs6503086
SIAH1	chr16:48390274-48482309	chr16:47890274-48982309	chr16:46947777-47039810	kgp4639784	kgp7644930
SLC2A1	chr1:43391045-43424847	chr1:42891045-43924847	chr1:43163632-43197434	kgp2036523	rs2782652
SLC6A3	chr5:1392904-1445543	chr5:892904-1945543	chr5:1445909-1498538	kgp22585075	kgp9690399
SNCA	chr4:90645249-90759447	chr4:90145249-91259447	chr4:90865727-90978470	kgp11552673	kgp8195783
SNRPB2	chr20:16710608-16722417	chr20:16210608-17222417	chr20:16658628-16670037	kgp19326624	kgp19208923
SOCS6	chr18:67956136-67997434	chr18:67456136-68497434	chr18:66107116-66148414	kgp10928836	rs4243325
SOCS7	chr17:36508006-36561846	chr17:36008006-37061846	chr17:33761530-33809545	rs12936144	rs4794796
SRC	chr20:35973087-36033821	chr20:35473087-36533821	chr20:35406501-35467235	kgp19359278	kgp9150551
STAU1	chr20:47729875-47805288	chr20:47229875-48305288	chr20:47163282-47238695	rs11905650	kgp19233876
STX12	chr1:28099693-28150963	chr1:27599693-28650963	chr1:27972280-28023550	kgp22731625	kgp15287949
SYK	chr9:93564011-93660842	chr9:93064011-94160842	chr9:92603890-92698304	kgp12394293	rs894962
TBCA	chr5:76986994-77072185	chr5:76486994-77572185	chr5:77022750-77107941	rs2928164	rs10059285
TBXA2R	chr19:3594503-3606831	chr19:3094503-4106831	chr19:3545503-3557658	kgp21472781	kgp1760692
TCP1	chr6:160199529-160210735	chr6:159699529-160710735	chr6:160119519-160130725	kgp16923201	kgp10518192
TEAD3	chr6:35441373-35464861	chr6:34941373-35964861	chr6:35549351-35572839	rs847861	kgp3339
TFAM	chr10:60145175-60155897	chr10:59645175-60655897	chr10:59815181-59825903	kgp9406331	kgp6514369
TGM2	chr20:36756863-36793700	chr20:36256863-37293700	chr20:36190277-36227114	rs6067098	kgp9992037
TJP1	chr15:29992356-30114706	chr15:29492356-30614706	chr15:27779648-27901998	kgp19895791	rs2604694
TLR10	chr4:38773859-38784611	chr4:38273859-39284611	chr4:38450646-38460984	kgp9612652	rs6531705

Fig. 2-9

Tier 2 Gene	GeneRange(hg19)	GeneRange+500kb(hg19)	GeneRange(hg18)	StartSNP (GeneRange+500kb)	EndSNP (GeneRange+500kb)
TMEM4	chr12:56704213-56710128	chr12:56204213-57210128	chr12:54990480-54996395	kgp6718939	kgp6565807
TPI1	chr12:6976583-6980110	chr12:6476583-7480110	chr12:6846966-6850253	kgp3883976	kgp18849054
TRAF2	chr9:139776384-139821067	chr9:139276384-140321067	chr9:138896205-138940888	rs3812570	kgp9465784
TRMT112	chr11:64084164-64085033	chr11:63584164-64585033	chr11:63840740-63841609	kgp1242205	rs2957154
TUBA1	chr12:49521565-49525304	chr12:49021565-50025304	chr12:47807832-47811571	kgp4948752	kgp18737983
TUBA1A	chr12:49578582-49582861	chr12:49078582-50082861	chr12:47864849-47869128	kgp5373125	kgp1407179
TUBA1B	chr12:49521566-49525304	chr12:49021566-50025304	chr12:47807832-47866883	kgp4948752	kgp18737983
TUBA2	chr12:49578793-49580616	chr12:49078793-50080616	chr12:47865060-47866883	kgp18983720	kgp75177
TUBB	chr6:1981087-1986127	chr6:1981087-1986127	chr6:1935034-1940074	kgp17000846	kgp16908954
TUBG1	chr17:40761357-40767256	chr17:40261357-41267256	chr17:38015219-38020777	rs12600570	kgp3534380
TXN	chr9:113006091-113018920	chr9:112506091-113518920	chr9:112046130-112058599	kgp18601393	kgp652846
TXNDC4	chr9:102741463-102861330	chr9:102241463-103361330	chr9:101781284-101901151	kgp22740558	rs10989168
TXNL2	chr10:131934639-131977932	chr10:131434639-132477932	chr10:131824629-131867922	kgp21587397	rs2921907
TYMS	chr18:657603-673499	chr18:157603-1173499	chr18:647603-663499	kgp1671520	kgp5560925
UBQLN4	chr1:156005091-156023516	chr1:155505091-156523516	chr1:154271715-154290140	rs12746592	kgp204451
UCHL1	chr4:41258897-41270446	chr4:40758897-41770446	chr4:40953685-40965203	rs10029833	kgp21157719
VIPR1	chr3:42530790-42579065	chr3:42030790-43079065	chr3:42519120-42554064	rs794894	kgp10771397
YWHAQ	chr2:9724105-9771106	chr2:9224105-10271106	chr2:9641556-9688557	kgp7327726	rs1138729
ZAP70	chr2:98330030-98356323	chr2:97830030-98856323	chr2:97696462-97722755	kgp10723114	kgp14308801

Fig. 2-10

Tier 3 Gene	GeneRange(hg19)	GeneRange+500kb(hg19)	GeneRange(hg18)	StartSNP (GeneRange+500kb)	EndSNP (GeneRange+500 kb)
ABI3	chr17:47287588-47300587	chr17:46787588-47800587	chr17:44642587-44655586	rs7211412	kgp13987803
ACTA1	chr1:229566992-229569843	chr1:229066992-230069843	chr1:227633615-227636466	kgp706951	kgp9594907
ACTN2	chr1:236849769-236927558	chr1:236349769-237427558	chr1:234916392-234994181	kgp12139182	kgp9945691
ADCY5	chr3:123001142-123167392	chr3:122501142-123667392	chr3:124486088-124650082	kgp5729470	kgp18234294
ADCY8	chr8:131792546-132052835	chr8:131292546-132552835	chr8:131861728-132122017	rs11778881	kgp4563992
ADCYAP1R1	chr7:31092075-31151093	chr7:30592075-31651093	chr7:31058666-31112836	kgp6410265	kgp5976045
ADD3	chr10:111756107-111895323	chr10:111256107-112395323	chr10:111746097-111885313	kgp2922347	kgp21705322
AFAP1	chr4:7760439-7941653	chr4:7260439-8441653	chr4:7811339-7992553	kgp10066670	kgp2565038
AGTR1	chr3:148415657-148460790	chr3:147915657-148960790	chr3:149898347-149943480	kgp17969929	rs9827666
AHCYL1	chr1:110527386-110566364	chr1:110027386-111066364	chr1:110328830-110367887	kgp15280262	kgp8467474
AKAP12	chr6:151561133-151679694	chr6:151061133-152179694	chr6:151603201-151719602	kgp17415975	kgp17180004
AKAP13	chr15:85923870-86292586	chr15:85423870-86792586	chr15:83724874-84093590	rs11073778	kgp10945265
AKAP5	chr14:64932216-64941221	chr14:64432216-65441221	chr14:64001969-64010974	rs945029	rs4499147
AKAP9	chr7:91570188-91739987	chr7:91070188-92239987	chr7:91408127-91577925	kgp7513665	kgp8102448
AKR1C3	chr10:5005453-5149878	chr10:4505453-5649878	chr10:4995453-5139878	rs1679414	kgp8379007
AKT1	chr14:105235686-105262080	chr14:104735686-105762080	chr14:104306731-104333125	kgp10896929	kgp7260890
ANK2	chr4:113739238-114304896	chr4:113239238-114804896	chr4:113958687-114524345	kgp8454825	kgp10144793
ANKRD24	chr19:4183350-4224811	chr19:3683350-4724811	chr19:4134350-4175811	kgp3226366	rs7255543

Fig. 3-1

Tier 3 Gene	GeneRange(hg19)	GeneRange+500kb(hg19)	GeneRange(hg18)	StartSNP (GeneRange+500kb)	EndSNP (GeneRange+500kb)
ANXA6	chr5:150480266-150537443	chr5:149980266-151037443	chr5:150460460-150517560	kgp22603058	rs11747938
ANXA7	chr10:75135188-75173841	chr10:74635188-75673841	chr10:74805194-74843847	kgp21588521	kgp5026768,rs2227568
APLP2	chr11:129939715-130014706	chr11:129439715-130514706	chr11:129445010-129519910	kgp22802171	rs7116475
AR	chrX:66763873-66950461	chrX:66263873-67450461	chrX:66680598-66860844	rs478505	kgp22776402
ARF1	chr1:228270360-228286913	chr1:227770360-228786913	chr1:226336983-226353536	kgp7035482	kgp5092378
ARF3	chr12:49329991-49351252	chr12:48829991-49851252	chr12:47616258-47637519	kgp9963537	kgp19162961
ARHGAP1	chr11:46698631-46722120	chr11:46198631-47222120	chr11:46655207-46678696	rs11038804	kgp12872953
ARHGEF1	chr19:42399421-42434296	chr19:41899421-42934296	chr19:47079106-47103444	kgp21546138	kgp9753873
ARL3	chr10:104433483-104474190	chr10:103933483-104974190	chr10:104423477-104464180	rs4919614	kgp2065500
ARL8B	chr3:5163929-5222601	chr3:4663929-5722601	chr3:5138929-5197601	kgp5083934	kgp17728482
ASCL2	chr11:2289727-2292182	chr11:1789727-2792182	chr11:2246303-2248758	kgp12845252	kgp7129584
ATF3	chr1:212738675-212794119	chr1:212238675-213294119	chr1:210805319-210860739	rs10863936	kgp12569686
ATN1	chr12:7033625-7053815	chr12:6533625-7553815	chr12:6903886-6924076	kgp18714644	kgp19128481
ATP1B1	chr1:169075946-169101960	chr1:168575946-169601960	chr1:167342570-167368584	rs10800363	kgp305361
ATP2B1	chr12:89981825-90049844	chr12:89481825-90549844	chr12:88505956-88573975	kgp4237218	kgp19117315
ATP2B2	chr3:10365706-10749716	chr3:9865706-11249716	chr3:10342743-10724716	kgp7774534	rs7625756
ATXN1	chr6:16299342-16761721	chr6:15799342-17261721	chr6:16407321-16869700	kgp2173519	rs6921352
ATXN3	chr14:92524895-92572965	chr14:92024895-93072965	chr14:91594648-91642718	kgp11986238	rs2146498
ATXN7	chr3:63850232-63989136	chr3:63350232-64489136	chr3:63825272-63964176	rs9311874	kgp797614
AVPR1A	chr12:63540215-63546590	chr12:63040215-64046590	chr12:61826482-61832857	rs952865	kgp3671976
B4GALT1	chr9:33110638-33167356	chr9:32610638-33667356	chr9:33100638-33157356	kgp18539535	kgp18370584

Fig. 3-2

Tier 3 Gene	GeneRange(hg19)	GeneRange+500kb(hg19)	GeneRange(hg18)	StartSNP (GeneRange+500kb)	EndSNP (GeneRange+500 kb)
BANK1	chr4:102341117-102995969	chr4:101841117-103495969	chr4:102560140-103214992	rs6851921	kgp20796561
BCAP31	chrX:152965946-152990201	chrX:152465946-153490201	chrX:152619145-152643081	rs6627302	kgp22764947
BCAR1	chr16:75262927-75301951	chr16:74762927-75801951	chr16:73820428-73859452	kgp7158675	kgp16367309
BCL2	chr18:60790578-60986657	chr18:60290578-61486657	chr18:58941558-59137637	rs435439	rs1720898
BMI1	chr10:22610138-22620414	chr10:22110138-23120414	chr10:22645304-22660192	kgp3019331	rs12775513
BMPR2	chr2:203241049-203432474	chr2:202741049-203932474	chr2:202949294-203140719	rs2072504	kgp3183288
BOC	chr3:112930411-113006305	chr3:112430411-113506305	chr3:114413101-114488995	kgp12164746	kgp3299668
BPGM	chr7:134331530-134364567	chr7:133831530-134864567	chr7:133982094-134015107	kgp13720725	kgp8542611
BRCA1	chr17:41196311-41322420	chr17:40696311-41822420	chr17:38449839-38530994	kgp1014784	kgp13921789
BRCA2	chr13:32889616-32973809	chr13:32389616-33473809	chr13:31787616-31871809	rs2146284	rs9596502
BRD7	chr16:50352928-50402845	chr16:49852928-50902845	chr16:48910441-48960330	kgp3843480	kgp6018549
BRF2	chr8:37701397-37707431	chr8:37201397-38207431	chr8:37820560-37826569	rs7818467	kgp22772561
BRMS1	chr11:66104803-66112582	chr11:65604803-66612582	chr11:65861379-65869158	kgp22746103	kgp12809093
BTK	chrX:100604434-100645770	chrX:100104434-101145770	chrX:100491097-100532426	kgp22759057	kgp22747202
C1orf128	chr1:24104887-24114722	chr1:23604887-24614722	chr1:23977474-23987309	kgp283495	kgp2701674
C1orf42	chr1:152486978-152488481	chr1:151986978-152988481	chr1:150753602-150755105	kgp15694971	rs4363385
C1QBP	chr17:5336098-5342471	chr17:4836098-5842471	chr17:5276822-5283195	kgp14047547	rs17825455
C20orf20	chr20:61427804-61431945	chr20:60927804-61931945	chr20:60898282-60902390	kgp9228388	kgp19363625
C20orf24	chr20:35234136-35240960	chr20:34734136-35740960	chr20:34636369-34674374	rs6060820	rs1744760
C4orf14	chr4:57829515-57843826	chr4:57329515-58343826	chr4:57524272-57538583	kgp22756132	kgp1831456
C4orf17	chr4:100432160-100463460	chr4:99932160-100963460	chr4:100651222-100682483	kgp20878925	kgp21204347

Fig. 3-3

Tier 3 Gene	GeneRange(hg19)	GeneRange+500kb(hg19)	GeneRange(hg18)	StartSNP (GeneRange+500kb)	EndSNP (GeneRange+500 kb)
C5orf25	chr5:175665369-175772990	chr5:175165369-176272990	chr5:175598008-175705596	kgp7679859	rs480782
C9orf25	chr9:34398181-34458568	chr9:33898181-34958568	chr9:34388181-34448568	kgp22772722	rs7031962
CABIN1	chr22:24407764-24574596	chr22:23907764-25074596	chr22:22737764-22904596	kgp5637302	kgp5793536
CABP1	chr12:121078421-121105127	chr12:120578421-121605127	chr12:119562804-119589510	kgp18737891	rs503720
CACNA1C	chr12:2162415-2807115	chr12:1662415-3307115	chr12:2032676-2677376	kgp9477564	kgp1276729
CALCR	chr7:93053798-93204042	chr7:92553798-93704042	chr7:92891734-93041978	kgp3815436	kgp10249142
CALD1	chr7:134464163-134655480	chr7:133964163-135155480	chr7:134114710-134306012	rs16874469	kgp22829820
CAMK2A	chr5:149599053-149669403	chr5:149099053-150169403	chr5:149579247-149649529	kgp9269229	kgp22536863
CAMK2G	chr10:75572258-75634349	chr10:75072258-76134349	chr10:75242264-75304349	kgp5617603	kgp4007437
CAMKK1	chr17:3763616-3796337	chr17:3263616-4296337	chr17:3710365-3743086	kgp4927794	kgp13998561
CAMKK2	chr12:121675494-121736111	chr12:121175494-122236111	chr12:120159877-120220494	kgp3636283,rs1800556	kgp3169612
CAPN2	chr1:223889294-223963720	chr1:223389294-224463720	chr1:221966741-222030343	rs2430408	kgp15138476
CASP3	chr4:185548849-185570629	chr4:185048849-186070629	chr4:185785843-185807623	kgp8529169	rs2046535
CASP6	chr4:110609784-110624629	chr4:110109784-111124629	chr4:110829233-110844078	kgp20840443	kgp20817413
CASP7	chr10:115438934-115490664	chr10:114938934-115990664	chr10:115428924-115480654	kgp12503193	rs12266538
CASP8	chr2:202098165-202152434	chr2:201598165-202652434	chr2:201806410-201860679	kgp6115041	rs12468196
CASR	chr3:121902529-122005344	chr3:121402529-122505344	chr3:123385219-123488034	kgp18115887	rs13095775
CAV1	chr7:115929905-116201239	chr7:115429905-116701239	chr7:115717141-115988466	kgp13705413	kgp1550529,rs13222576
CBL	chr11:119076989-119178859	chr11:118576989-119678859	chr11:118582199-118684069	kgp4184476	rs10892470
CBX1	chr17:46147413-46178883	chr17:45647413-46678883	chr17:43502412-43533882	kgp4510682	kgp14007862
CCDC106	chr19:56158953-56164526	chr19:55658953-56664526	chr19:60850765-60856338	kgp2072564	rs901476

Fig. 3-4

Tier 3 Gene	GeneRange(hg19)	GeneRange+500kb(hg19)	GeneRange(hg18)	StartSNP (GeneRange+500kb)	EndSNP (GeneRange+500 kb)
CCND1	chr11:69455872-69469242	chr11:68955872-69969242	chr11:69165053-69178423	kgp12357966	rs1893085
CCNE1	chr19:30302900-30315215	chr19:29802900-30815215	chr19:34994740-35007059	kgp21358604	kgp21349680
CCR4	chr3:32993065-32996403	chr3:32493065-33496403	chr3:32968069-32971407	rs4955290	kgp3855989
CCR5	chr3:46411632-46417697	chr3:45911632-46917697	chr3:46386636-46392701	kgp17737690	rs936173
CD163	chr12:7623411-7656414	chr12:7123411-8156414	chr12:7514676-7547681	rs9668071	kgp3219786
CD5	chr11:60869929-60895323	chr11:60369929-61395323	chr11:60626505-60651899	rs7927817	kgp13056421
CD9	chr12:6309481-6347437	chr12:5809481-6847437	chr12:6179133-6217688	rs9669580	kgp1124940
CDC2	chr10:62538235-62553924	chr10:62038235-63053924	chr10:62208241-62223930	kgp21922934	rs3125326
CDKN2C	chr1:51433607-51440309	chr1:50933607-51940309	chr1:51206195-51212897	rs17106219	kgp15324656
CENTA1	chr7:937537-994306	chr7:437537-1494306	chr7:904063-960832	kgp4856315,rs3924019	kgp11391801
CETN3	chr5:89689528-89705603	chr5:89189528-90205603	chr5:89725284-89741359	rs277054	kgp22368793
CFTR	chr7:117120016-117308718	chr7:116620016-117808718	chr7:116907252-117095954	kgp13265715	kgp13590397
CHAT	chr10:50822349-50901939	chr10:50322349-51401939	chr10:50487146-50543156	kgp8189482	kgp8898453
CHD3	chr17:7788122-7816075	chr17:7288122-8316075	chr17:7728847-7756800	rs7208523	kgp11776706
CHUK	chr10:101948123-101989344	chr10:101448123-102489344	chr10:101938113-101979334	kgp6141810	kgp9150190
CISH	chr3:50643884-50649262	chr3:50143884-51149262	chr3:50618929-50624207	kgp5610191	rs6783700
CKAP1	chr19:36605888-36616849	chr19:36105888-37116849	chr19:41297728-41308689	rs7249516	rs3108171
CKMT2	chr5:80529138-80562217	chr5:80029138-81062217	chr5:80564894-80597973	kgp9822295	kgp7416171
CLTB	chr5:175819455-175843540	chr5:175319455-176343540	chr5:175752061-175776146	rs4867811	kgp1551194
CLU	chr8:27454433-27472328	chr8:26954433-27972328	chr8:27510367-27528244	kgp886026	rs4732823
CMIP	chr16:81478774-81745367	chr16:80978774-82245367	chr16:80036394-80302866	rs11150329	kgp16425289

Fig. 3-5

Tier 3 Gene	GeneRange(hg19)	GeneRange+500kb(hg19)	GeneRange(hg18)	StartSNP (GeneRange+500kb)	EndSNP (GeneRange+500 kb)
CNGA2	chrX:150903217-150914036	chrX:150403217-151414036	chrX:150653873-150664692	rs1202896	kgp22766776
CNKSR2	chrX:21392535-21672813	chrX:20892535-22172813	chrX:21302900-21580700	kgp22768242	kgp22744096
CNN1	chr19:11649578-11661138	chr19:11149578-12161138	chr19:11510578-11522138	kgp11148982	rs8100428
CNR2	chr1:24200459-24239817	chr1:23700459-24739817	chr1:24073046-24112404	rs9887921	kgp7256331
COIL	chr17:55015560-55038411	chr17:54515560-55538411	chr17:52370559-52393410	rs7219528	kgp13879956
CORO1B	chr11:67205517-67211292	chr11:66705517-67711292	chr11:66962093-66967839	kgp8733070	kgp12910446
COX17	chr3:119388371-119396243	chr3:118888371-119896243	chr3:120871061-120878933	rs2903301	rs7634938
CPE	chr4:166300096-166419482	chr4:165800096-166919482	chr4:166519546-166638932	rs4541465	kgp20841166
CRADD	chr12:94071150-94288616	chr12:93571150-94788616	chr12:92595281-92768662	kgp18995270	rs10859694
CREM	chr10:35415768-35501886	chr10:34915768-36001886	chr10:35455806-35541892	kgp21684668	rs654221
CRIPT	chr2:46844324-46852881	chr2:46344324-47352881	chr2:46697811-46705687	kgp11216746	kgp5110136
CSNK2A1	chr20:463337-524482	chr20:1-1024482	chr20:411337-472482	kgp19358001	kgp2852236
CSNK2A2	chr16:58191811-58231782	chr16:57691811-58731782	chr16:56749312-56789283	kgp3607479	kgp9299300
CSNK2B	chr6:2919235-2923423	chr6:2919235-2923423	chr6:31741635-31748206	kgp7558035	kgp17052091
CTNNB1	chr3:41236400-41280845	chr3:40736400-41780845	chr3:41211404-41255849	kgp17791054	kgp17873276
DAPK3	chr19:3958451-3971038	chr19:3458451-4471038	chr19:3909451-3922038	kgp9392695	kgp6448823
DBN1	chr5:176883613-176900694	chr5:176383613-177400694	chr5:176816219-176833300	rs3733876	kgp6700800
DDIT4	chr10:74033676-74035797	chr10:73533676-74535797	chr10:73703682-73705803	kgp21593001	kgp10561095
DDX5	chr17:62494373-62502484	chr17:61994373-63002484	chr17:59926199-59932869	kgp14113893	rs4239089
DEFB1	chr8:6728096-6735529	chr8:6228096-7235529	chr8:6715508-6722939	kgp20078124	rs12680482
DGKD	chr2:234263152-234380743	chr2:233763152-234880743	chr2:233927891-234045482	rs12477794	rs28902188

Fig. 3-6

Tier 3 Gene	GeneRange(hg19)	GeneRange+500kb(hg19)	GeneRange(hg18)	StartSNP (GeneRange+500kb)	EndSNP (GeneRange+500kb)
DGKZ	chr11:46354454-46402104	chr11:45854454-46902104	chr11:46311314-46358680	rs2090602	kgp22737291
DIRAS2	chr9:93372113-93405108	chr9:92872113-93905108	chr9:92411933-92444928	rs7860989	kgp10944799
DLG1	chr3:196769430-197026143	chr3:196269430-197526143	chr3:198253827-198510540	kgp18074003	rs841672
DLG3	chrX:69664704-69725339	chrX:69164704-70225339	chrX:69581448-69642062	kgp22756738	kgp22752290
DLG4	chr17:7093209-7123369	chr17:6593209-7623369	chr17:7033933-7063781	kgp10999626	rs3744258
DNM1	chr9:130965662-131017527	chr9:130465662-131517527	chr9:130005483-130057348	kgp1183767	rs4836625
DNM3	chr1:171810620-172381857	chr1:171310620-172881857	chr1:170077260-170648480	kgp15671556	rs2213746
DNMT2	chr10:17184981-17243681	chr10:16684981-17743681	chr10:17224987-17283687	kgp1566842	kgp21855354
DPYSL2	chr8:26371708-26515693	chr8:25871708-27015693	chr8:26427707-26571610	rs11998023	rs12544814
DRD1	chr5:174867674-174871163	chr5:174367674-175371163	chr5:174800280-174803769	kgp4432341	kgp8293487
DRD1IP	chr5:174867675-174871163	chr5:174367675-175371163	chr5:174800281-174803769	kgp4432341	kgp8293487
DST	chr6:56479153-56716714	chr6:55979153-57216714	chr6:56430743-56816422	kgp1980963	rs12209200
DVL1	chr1:1270657-1284492	chr1:770657-1784492	chr1:1260520-1274355	kgp4076808	kgp15201879
DVL2	chr17:7128660-7137863	chr17:6628660-7637863	chr17:7069384-7078587	kgp1788685	kgp2456831,rs3744255
DVL3	chr3:183873283-183891314	chr3:183373283-184391314	chr3:185355977-185374008	kgp10156744	kgp4088221
EDF1	chr9:139756570-139760738	chr9:139256570-140260738	chr9:138876391-138880559	rs3829109	kgp4292076
EDG3	chr9:91606324-91620069	chr9:91106324-92120069	chr9:90796144-90809889	kgp18366537	kgp113389
EDG5	chr19:10332109-10341948	chr19:9832109-10841948	chr19:10193109-10202948	kgp21505357	kgp12277401
EDG8	chr19:10623418-10628668	chr19:10123418-11128668	chr19:10484418-10489668	rs4804478	kgp9055694
EEF1D	chr8:144661866-144679845	chr8:144161866-145179845	chr8:144733040-144750726	kgp20077380	kgp4311396
EEF2	chr19:3976053-3985461	chr19:3476053-4485461	chr19:3927053-3936461	kgp21334437	rs10406730

Fig. 3-7

Tier 3 Gene	GeneRange(hg19)	GeneRange+500kb(hg19)	GeneRange(hg18)	StartSNP (GeneRange+500kb)	EndSNP (GeneRange+500kb)
EFNB1	chrX:68048839-68066029	chrX:67548839-68566029	chrX:67965564-67982754	rs7879567	kgp22774708
EFNB2	chr13:107142078-107187388	chr13:106642078-107687388	chr13:105940096-105985338	rs9587049	kgp1472981
EIF1B	chr3:40351172-40353915	chr3:39851172-40853915	chr3:40326176-40328919	kgp17543799	kgp724180
ENO2	chr12:7023613-7032859	chr12:6523613-7532859	chr12:6893874-6903120	kgp6644683	kgp18788179
EPB41	chr1:29213602-29446558	chr1:28713602-29946558	chr1:29086214-29319545	kgp15837735	kgp8194212
EPB41L1	chr20:34679425-34820721	chr20:34179425-35320721	chr20:34142839-34284135	rs1886695	kgp10646202
EPB41L2	chr6:131160487-131384462	chr6:130660487-131884462	chr6:131202180-131426058	kgp3398782	kgp16921144
EPHB2	chr1:23037330-23241823	chr1:22537330-23741823	chr1:22909917-23114410	rs2473249	kgp22776625
ESR1	chr6:152011630-152424408	chr6:151511630-152924408	chr6:152053323-152466101	rs9478984	rs818451
ESR2	chr14:64693750-64805268	chr14:64193750-65305268	chr14:63763503-63875021	kgp3039416	kgp8515773
ESRRG	chr1:216676587-217311097	chr1:216176587-217811097	chr1:214743210-215377720	kgp2104463	kgp3054869
ETHE1	chr19:44010870-44031396	chr19:43510870-44531396	chr19:48702710-48723236	rs11668932	kgp561363
EWSR1	chr22:29663997-29696515	chr22:29163997-30196515	chr22:27994016-28026515	rs6005868	rs4823054
F11R	chr1:160965000-161008774	chr1:160465000-161508774	chr1:159231624-159275404	rs678456	kgp10744728
FADD	chr11:70049268-70053508	chr11:69549268-70553508	chr11:69726916-69731134	kgp12619639	kgp12640488
FAS	chr10:90729552-90775542	chr10:90229552-91275542	chr10:90740267-90765522	kgp6970830	kgp1640747
FBLIM1	chr1:16083153-16113084	chr1:15583153-16613084	chr1:15955740-15985671	rs16851480	kgp15648830
FER	chr5:108083522-108523373	chr5:107583522-109023373	chr5:108111421-108551272	rs11958626	rs845734
FEZ1	chr11:125315640-125366206	chr11:124815640-125866206	chr11:124820857-124871333	rs10160591	kgp12966369
FEZ2	chr2:36779403-36825332	chr2:36279403-37325332	chr2:36632904-36678836	kgp10246319	kgp9712350
FFAR1	chr19:35842444-35843367	chr19:35342444-36343367	chr19:40534294-40535197	rs8106116	kgp21511691

Fig. 3-8

Tier 3 Gene	GeneRange(hg19)	GeneRange+500kb(hg19)	GeneRange(hg18)	StartSNP (GeneRange+500kb)	EndSNP (GeneRange+500kb)
FFAR2	chr19:35939202-35941865	chr19:35439202-36441865	chr19:40631042-40633705	rs2112502	rs7247246
FKBP1A	chr20:1349620-1373816	chr20:849620-1873816	chr20:1297621-1321745	kgp4567229	kgp10348674
FLJ31945	chr13:50699952-50702599	chr13:50199952-51202599	chr13:49597953-49600600	kgp9786864	kgp16621897
FLJ41278	chr12:65277553-65371302	chr12:64777553-65871302	chr12:63563820-63657569	rs6581555	kgp1662303
FLNA	chrX:153576899-153603006	chrX:153076899-154103006	chrX:153230093-153256200	rs7049293	rs28412378
FLNB	chr3:57994126-58157982	chr3:57494126-58657982	chr3:57969166-58133017	rs7629743	rs11130670
FREQ	chr9:132934856-132999583	chr9:132434856-133499583	chr9:131974677-132039404	kgp12208188	kgp18380808
FRS2	chr12:69864128-69973562	chr12:69364128-70473562	chr12:68150395-68259829	kgp19095191	kgp12534834
FSHR	chr2:49189295-49381666	chr2:48689295-49881666	chr2:49043155-49235134	kgp297164	kgp11229604
FXN	chr9:71650478-71715094	chr9:71150478-72215094	chr9:70840163-70878772	rs265076	kgp213209
FXR1	chr3:180630233-180700539	chr3:180130233-181200539	chr3:182113145-182177647	kgp22773686	kgp3235523
G6PD	chrX:153759605-153775787	chrX:153259605-154275787	chrX:153412799-153428981	rs2239471	kgp22745531
GABRR1	chr6:89887222-89927496	chr6:89387222-90427496	chr6:89944690-89983779	kgp3728710	kgp17056993
GABRR2	chr6:89967238-90024967	chr6:89467238-90524967	chr6:90023957-90081686	kgp16994883	kgp9012178
GALR2	chr17:74070891-74073573	chr17:73570891-74573573	chr17:71582486-71585168	rs1042861	rs16967307
GAP43	chr3:115342150-115440334	chr3:114842150-115940334	chr3:116825141-116922842	rs10511341	kgp18168870
GC	chr4:72607410-72671237	chr4:72107410-73171237	chr4:72826274-72888622	rs10013437	kgp12025264
GFAP	chr17:42982993-42992920	chr17:42482993-43492920	chr17:40338518-40348394	rs8066197	rs12947718
GFI1	chr1:92940317-92952433	chr1:92440317-93452433	chr1:92712905-92725021	kgp80379	kgp15436210
GFI1B	chr9:135853893-135867084	chr9:135353893-136367084	chr9:134843714-134856903	kgp1227599	kgp22817803
GFPT1	chr2:69546900-69614386	chr2:69046900-70114386	chr2:69405910-69467829	kgp7360674	kgp14824626

Fig. 3-9

Tier 3 Gene	GeneRange(hg19)	GeneRange+500kb(hg19)	GeneRange(hg18)	StartSNP (GeneRange+500kb)	EndSNP (GeneRange+500 kb)
GH1	chr17:61994562-61996198	chr17:61494562-62496198	chr17:59348294-59349930	kgp6455446	kgp10132757
GIT1	chr17:27900486-27916610	chr17:27400486-28416610	chr17:24924612-24940736	kgp14082001	rs8065059
GIT2	chr12:110367606-110434194	chr12:109867606-110934194	chr12:108851991-108918483	kgp8064273	kgp556710
GJA1	chr6:121756744-121770873	chr6:121256744-122270873	chr6:121798443-121812572	kgp5203283	kgp1494786
GJB1	chrX:70435061-70445065	chrX:69935061-70945065	chrX:70351786-70361777	kgp22820938	rs35542412
GMFB	chr14:54941208-54955744	chr14:54441208-55455744	chr14:54010958-54025494	kgp5212952	kgp7377769
GNA12	chr7:2767740-2883959	chr7:2267740-3383959	chr7:2734266-2850485	kgp9177535	kgp13694655
GNAS	chr20:57414794-57486250	chr20:56914794-57986250	chr20:56848189-56919645	rs471661	rs729997
GNAZ	chr22:23412668-23467221	chr22:22912668-23967221	chr22:21742668-21797221	kgp15075658	rs9680742
GPM6A	chr4:176554087-176923648	chr4:176054087-177423648	chr4:176791081-177160642	rs6849435	kgp8852764
GPSM2	chr1:109419602-109476957	chr1:108919602-109976957	chr1:109221125-109274567	kgp15175401	kgp15178378
GRB14	chr2:165349322-165478360	chr2:164849322-165978360	chr2:165057568-165186606	kgp8982508	kgp14153450
GRIA2	chr4:158141294-158287226	chr4:157641294-158787226	chr4:158361185-158506676	kgp22818527	rs6836401
GRIA3	chrX:122318095-122624766	chrX:121818095-123124766	chrX:122145776-122452447	rs7057244	rs12559968
GRIA4	chr11:105480799-105852819	chr11:104980799-106352819	chr11:104986009-105358029	kgp12888967	kgp2959570
GRIN1	chr9:140033608-140063214	chr9:139533608-140563214	chr9:139153429-139183029	kgp18425565	kgp18521447
GRIN2A	chr16:9847264-10276611	chr16:9347264-10776611	chr16:9762922-10184112	kgp16441783	rs9932893
GRIN2B	chr12:13714409-14133022	chr12:13214409-14633022	chr12:13605676-14024289	rs3741818	kgp7391296
GRK1	chr13:114321596-114438637	chr13:113821596-114938637	chr13:113369597-113373973	kgp16671784	rs11147317
GRK4	chr4:2965342-3042474	chr4:2465342-3542474	chr4:2935140-3012272	rs846252	rs6821202
GSK3A	chr19:42734337-42746736	chr19:42234337-43246736	chr19:47426177-47438576	kgp21481263	kgp10870487

Fig. 3-10

Tier 3 Gene	GeneRange(hg19)	GeneRange+500kb(hg19)	GeneRange(hg18)	StartSNP (GeneRange+500kb)	EndSNP (GeneRange+500 kb)
GSK3B	chr3:119540801-119813264	chr3:119040801-120313264	chr3:121028235-121295203	kgp17616951	kgp4570827
GSTM4	chr1:110198697-110208123	chr1:109698697-110708123	chr1:110000225-110009648	rs595635	kgp15760598
HABP4	chr9:99212413-99253618	chr9:98712413-99753618	chr9:98252234-98293439	kgp18578220	kgp18630342
HAND1	chr5:153854531-153857824	chr5:153354531-154357824	chr5:153834724-153838017	kgp7530958	rs2431184
HAND2	chr4:174447651-174451378	chr4:173947651-174951378	chr4:174684226-174687953	kgp20847640	kgp20778226
HARS	chr5:140053489-140070971	chr5:139553489-140570971	chr5:140033673-140051155	rs6874491	rs12654953
HDAC6	chrX:48660286-48683380	chrX:48160286-49183380	chrX:48545430-48568324	kgp22835768	rs2015487
HES1	chr3:193853930-193856401	chr3:193353930-194356401	chr3:195336627-195339090	kgp11414670	rs7649259
HLA-A	chr6:1150035-1295564	chr6:1150035-1295564	chr6:30018304-30085130	rs9392258	rs9391920
HLA-C	chr6:2585738-2671188	chr6:2585738-2671188	chr6:2486041-2572197	rs9392400	kgp1905253
HLA-DQA2	chr6:4166320-4171833	chr6:4166320-4171833	chr6:3895192-3901275	kgp17451336	kgp17218419
HMGB1	chr13:31032878-31191510	chr13:30532878-31691510	chr13:29930878-30089510	rs1557088	kgp8054835
HMGN1	chr21:40714240-40721047	chr21:40214240-41221047	chr21:39636110-39643140	kgp4524272	kgp8317624
HMGN2	chr1:26798901-26803133	chr1:26298901-27303133	chr1:26671488-26675720	rs1429936	kgp8260087
HMMR	chr5:162887516-162918953	chr5:162387516-163418953	chr5:162820240-162851525	kgp9548441	rs1363073
HMOX2	chr16:4524718-4560348	chr16:4024718-5060348	chr16:4464719-4500349	kgp16414002	kgp7117794
HMP19	chr5:173472723-173536182	chr5:172972723-174036182	chr5:173405329-173468788	kgp22404239	rs12186684
HOMER2	chr15:83517728-83621476	chr15:83017728-84121476	chr15:81314789-81412477	rs1267659	kgp4123064
HRH4	chr18:22040592-22059921	chr18:21540592-22559921	chr18:20294590-20313919	rs7235445	kgp7887799
HSP90AA1	chr14:102547074-102606086	chr14:102047074-103106086	chr14:101616827-101675839	kgp3260354	kgp19714004
HSPA1A	chr6:31783290-31785719	chr6:31283290-32285719	chr6:31891315-31893698	kgp4709627	rs9296020

Fig. 3-11

Tier 3 Gene	GeneRange(hg19)	GeneRange+500kb(hg19)	GeneRange(hg18)	StartSNP (GeneRange+500kb)	EndSNP (GeneRange+500 kb)
HSPA1B	chr6:3089162-3091686	chr6:3089162-3091686	chr6:3043109-3045633	kgp6503147	kgp5869121
HSPA4	chr5:132387661-132440709	chr5:131887661-132940709	chr5:132415560-132468608	kgp22352512	kgp7658141
HSPB1	chr7:75931874-75933614	chr7:75431874-76433614	chr7:75769858-75771546	kgp4195218	kgp10852432
HSPB3	chr5:53751430-53752214	chr5:53251430-54252214	chr5:53787201-53787964	rs16881895	rs3815916
HSPB8	chr12:119616594-119632551	chr12:119116594-120132551	chr12:118100977-118116934	kgp18981306	kgp18823622
HSPBP1	chr19:55773590-55791751	chr19:55273590-56291751	chr19:60465518-60483540	kgp3134010	kgp21533588
HSPE1	chr2:198364720-198368187	chr2:197864720-198868187	chr2:198073364-198076416	kgp9884304	kgp12004769
HSPH1	chr13:31710762-31736502	chr13:31210762-32236502	chr13:30608762-30634502	kgp16548529	kgp16811501
HTATIP	chr11:20385289-20405329	chr11:19885289-20905329	chr11:20341865-20361905	rs2707094	kgp309631
HTR2B	chr2:231972949-231989824	chr2:231472949-232489824	chr2:231681198-231698068	rs6761068	rs4973459
HTR2C	chrX:113818550-114144624	chrX:113318550-114644624	chrX:113724806-114050880	rs7055827	kgp22830072
HTR6	chr1:19991779-20006055	chr1:19491779-20506055	chr1:19864366-19878642	kgp15912015	kgp10523409
IGSF4	chr11:115044345-115375241	chr11:114544345-115875241	chr11:114549555-114880451	rs1607260	rs7928212
IKBKB	chr8:42128819-42190171	chr8:41628819-42690171	chr8:42247985-42309122	kgp9748756	kgp3164559
IKBKE	chr1:206643585-206670223	chr1:206143585-207170223	chr1:204710418-204736845	kgp15543770	kgp6359437
IKBKG	chrX:153770458-153793261	chrX:153270458-154293261	chrX:153423652-153446455	rs633	kgp22831959
IL4R	chr16:27325250-27376099	chr16:26825250-27876099	chr16:27232751-27283600	kgp11144142	kgp16489203
IL5RA	chr3:3108007-3152058	chr3:2608007-3652058	chr3:3086420-3127031	kgp10211459	kgp22835987
IL8RA	chr2:219027567-219031716	chr2:218527567-219531716	chr2:218735812-218739961	kgp14521358	rs16859170
INSR	chr19:7112265-7294011	chr19:6612265-7794011	chr19:7063265-7245011	kgp5914741	kgp21453659
IQCB1	chr3:121488609-121553926	chr3:120988609-122053926	chr3:122971299-123036616	rs11921531	rs6438722

Fig. 3-12

Tier 3 Gene	GeneRange(hg19)	GeneRange+500kb(hg19)	GeneRange(hg18)	StartSNP (GeneRange+500kb)	EndSNP (GeneRange+500 kb)
IQGAP1	chr15:90931472-91045475	chr15:90431472-91545475	chr15:88732476-88846479	kgp1876985	kgp20028694
IRAK1	chrX:153275956-153285342	chrX:152775956-153785342	chrX:152929150-152938536	kgp22756383	rs6643680
IRS1	chr2:227596032-227663506	chr2:227096032-228163506	chr2:227304276-227371750	kgp12414080	kgp9391097
IRS4	chrX:107975726-107979607	chrX:107475726-108479607	chrX:107862367-107866295	kgp22794644	rs5985712
ITGB2	chr21:46305867-46348753	chr21:45805867-46848753	chr21:45130296-45173181	kgp13225366	rs11702782
ITGB3BP	chr1:63906440-63988944	chr1:63406440-64488944	chr1:63679049-63761423	rs1572109	kgp5171315
ITGB4	chr17:73717515-73753899	chr17:73217515-74253899	chr17:71229110-71265494	kgp2663142	kgp4575494
ITGB5	chr3:124481794-124606144	chr3:123981794-125106144	chr3:125964484-126088834	kgp5281659	kgp17765518
ITPKA	chr15:41786055-41795757	chr15:41286055-42295757	chr15:39573413-39583039	kgp22747722	kgp10507061
ITPKB	chr1:226819390-226926876	chr1:226319390-227426876	chr1:224886013-224991987	rs1219671	rs7519099
ITPR3	chr6:33589155-33664348	chr6:33089155-34164348	chr6:33697138-33772326	rs3117030	kgp4515850
IXL	chr19:39881963-39891203	chr19:39381963-40391203	chr19:44573803-44583043	kgp986483	kgp6117029
JAK1	chr1:65298905-65432619	chr1:64798905-65932619	chr1:65071493-65205207	kgp8976721	kgp9745392
KCNE1	chr21:35818987-35884573	chr21:35318987-36384573	chr21:34740857-34806443	kgp13187567	kgp5041106
KCNE4	chr2:223916861-223920355	chr2:223416861-224420355	chr2:223625105-223628599	kgp14948218	kgp14631899
KCNH2	chr7:150642043-150675402	chr7:150142043-151175402	chr7:150272981-150305947	kgp13542655	kgp7948285
KCNJ2	chr17:68164813-68176183	chr17:67664813-68676183	chr17:65676408-65687778	rs6501341	kgp2814913
KCNN2	chr5:113698015-113832197	chr5:113198015-114332197	chr5:113725914-113860096	kgp9619904	rs10056549
KCNN4	chr19:44270684-44285409	chr19:43770684-44785409	chr19:48962524-48977249	rs6509074	kgp21388839
KCNQ2	chr20:62037541-62103993	chr20:61537541-62603993	chr20:61507985-61574437	rs16983364	kgp19265466
KCNQ3	chr8:133133104-133493004	chr8:132633104-133993004	chr8:133210437-133562186	kgp20244043	rs4074676

Fig. 3-13

Tier 3 Gene	GeneRange(hg19)	GeneRange+500kb(hg19)	GeneRange(hg18)	StartSNP (GeneRange+500kb)	EndSNP (GeneRange+500 kb)
KCNQ5	chr6:73331570-73908573	chr6:72831570-74408573	chr6:73388555-73962301	kgp7790415	rs9446983
KDR	chr4:55944425-55991762	chr4:55444425-56491762	chr4:55639405-55686519	kgp11624145	rs10022874
KIAA1377	chr11:101785745-101871793	chr11:101285745-102371793	chr11:101290955-101377003	kgp12804311	rs9667864
KIAA1549	chr7:138516126-138666064	chr7:138016126-139166064	chr7:138166666-138255110	rs11769851	kgp10209774
KIF3A	chr5:132028322-132073265	chr5:131528322-132573265	chr5:132056221-132101164	rs3805685	rs4958109
KIT	chr4:55524094-55606881	chr4:55024094-56106881	chr4:55218851-55301638	kgp4467115	kgp9403472
KLHL20	chr1:173684079-173755840	chr1:173184079-174255840	chr1:171950702-172022463	rs13374515	kgp5594942
KLHL3	chr5:136953188-137071779	chr5:136453188-137571779	chr5:136981087-137099678	rs2966736	rs10040989
KLK10	chr19:51515999-51523431	chr19:51015999-52023431	chr19:56207811-56215243	kgp9495392	kgp21503250
KRAS	chr12:25358179-25403854	chr12:24858179-25903854	chr12:25249446-25295121	kgp19038229	kgp1316534
KRT10	chr17:38974368-38978863	chr17:38474368-39478863	chr17:36227894-36232373	kgp7164026	kgp6621387
KRT18	chr12:53342654-53346685	chr12:52842654-53846685	chr12:51628921-51632952	rs406857	rs11834179
LCK	chr1:32716839-32751766	chr1:32216839-33251766	chr1:32489426-32524353	rs12037400	kgp6229337
LGALS2	chr22:37966252-37976024	chr22:37466252-38476024	chr22:36296198-36305970	kgp14999686	rs8135665
LMNA	chr1:156052368-156108548	chr1:155552368-156608548	chr1:154318992-154375172	kgp11675488	rs12408758
LMNB1	chr5:126112314-126172712	chr5:125612314-126672712	chr5:126140731-126200608	kgp5014465	kgp22418220
LOC100133669	chr8:144063447-144099807	chr8:143563447-144599807	chr8:144134822-144171182	rs10875483	kgp10850793
LOC154092	chr6:134758853-134825158	chr6:134258853-135325158	chr6:134800546-134866851	kgp11630779	kgp22793805
LOC339290	chr18:5238098-5246505	chr18:4738098-5746505	chr18:5222874-5228525	kgp5290787	kgp989326
LOC340357	chr8:12623570-12668910	chr8:12123570-13168910	chr8:12667941-12713281	kgp22754906	kgp20305069
LOC400604	chr17:48944039-48945732	chr17:48444039-49445732	chr17:46299038-46300731	kgp11815481	kgp10163248

Fig. 3-14

Tier 3 Gene	GeneRange(hg19)	GeneRange+500kb(hg19)	GeneRange(hg18)	StartSNP (GeneRange+500kb)	EndSNP (GeneRange+500 kb)
LOC613126	chr7:91763906-91771854	chr7:91263906-92271854	chr7:91601842-91609790	kgp13774218	rs3731343
LTB4R	chr14:24780704-24787242	chr14:24280704-25287242	chr14:23850544-23855992	kgp19673807	rs8007336
LTF	chr3:46477495-46526724	chr3:45977495-47026724	chr3:46452499-46501728	kgp17788490	kgp1176589
LXN	chr3:158384202-158390482	chr3:157884202-158890482	chr3:159866899-159873176	rs6764092	kgp7955381
LYST	chr1:235824344-236030220	chr1:235324344-236530220	chr1:233890968-234096843	rs2295815	kgp9270301
MAD2L1BP	chr6:43597278-43608688	chr6:43097278-44108688	chr6:43705256-43716666	rs1537638	kgp1522302
MAGED1	chrX:51546154-51645450	chrX:51046154-52145450	chrX:51562894-51662190	kgp22779908	kgp22784919
MAP1A	chr15:43809805-43823818	chr15:43309805-44323818	chr15:41597097-41611110	kgp12180163	kgp10318377
MAP1LC3A	chr20:33134691-33148149	chr20:32634691-33648149	chr20:32598352-32611810	kgp19388199	kgp5639543
MAP2K1	chr15:66679210-66783882	chr15:66179210-67283882	chr15:64466264-64570936	kgp19795142	kgp382480
MAP2K4	chr17:11924134-12047051	chr17:11424134-12547051	chr17:11864859-11987776	rs16944942	rs9915536
MAP2K5	chr15:67835020-68099455	chr15:67335020-68599455	chr15:65622074-65886506	kgp19854650	kgp20006731
MAP3K10	chr19:40697650-40721482	chr19:40197650-41221482	chr19:45389490-45413314	kgp6290284	rs2561531
MAP3K3	chr17:61699774-61773670	chr17:61199774-62273670	chr17:59053505-59127402	kgp14048701	kgp5230870
MAP3K7	chr6:91225352-91296907	chr6:90725352-91796907	chr6:91282073-91353628	rs9451316	rs9451576
MAP3K7IP1	chr22:39745953-39827887	chr22:39245953-40327887	chr22:38075899-38157833	kgp10431646	rs137981
MAP3K7IP2	chr6:149639062-149732747	chr6:149139062-150232747	chr6:149680755-149774440	kgp9485571	kgp9110056
MAP3K8	chr10:30722949-30750762	chr10:30222949-31250762	chr10:30762871-30790767	kgp22034763	kgp11496819
MAP6	chr11:75297962-75379479	chr11:74797962-75879479	chr11:74975610-75057127	rs11236323	kgp695651
MAPK14	chr6:35995453-36079013	chr6:35495453-36579013	chr6:36103550-36186513	rs4711420	kgp10854130
MAPK3	chr16:30125425-30134630	chr16:29625425-30634630	chr16:30032926-30042131	kgp11463254	kgp2105557

Fig. 3-15

Tier 3 Gene	GeneRange(hg19)	GeneRange+500kb(hg19)	GeneRange(hg18)	StartSNP (GeneRange+500kb)	EndSNP (GeneRange+500 kb)
MARCKS	chr6:114178526-114184652	chr6:113678526-114684652	chr6:114285219-114291345	kgp17187839	kgp1113238
MBP	chr18:74690788-74844774	chr18:74190788-75344774	chr18:72819776-72973762	kgp5208536	rs12960102
MCC	chr5:112357795-112824527	chr5:111857795-113324527	chr5:112385694-112852426	kgp22530369	kgp22589538
MGMT	chr10:131265453-131565783	chr10:130765453-132065783	chr10:131155455-131455358	kgp11264334	kgp1514587
MIP	chr12:56843285-56848435	chr12:56343285-57348435	chr12:55130150-55134696	kgp19052399,rs11834873	kgp18750923
MLF2	chr12:6857935-6876641	chr12:6357935-7376641	chr12:6728196-6746902	kgp18998724	rs1001653
MLLT3	chr9:20344967-20622514	chr9:19844967-21122514	chr9:20334967-20612514	kgp18504776	rs1016129
MNAT1	chr14:61201458-61435398	chr14:60701458-61935398	chr14:60271222-60505151	kgp5293246	rs7142051
MPHOSPH6	chr16:82181766-82203829	chr16:81681766-82703829	chr16:80739267-80761330	kgp406017	rs3852734
MRPS12	chr19:39421347-39423659	chr19:38921347-39923659	chr19:44113187-44115499	kgp21348524	kgp21366907
MRPS6	chr21:35445822-35515334	chr21:34945822-36015334	chr21:34367692-34437204	kgp11037760	rs2834555
MRVI1	chr11:10594637-10715535	chr11:10094637-11215535	chr11:10551213-10672111	rs7946995	kgp11739225
MSN	chrX:64887510-64961793	chrX:64387510-65461793	chrX:64804235-64878518	rs7887705	kgp22760405
MYF5	chr12:81110707-81113447	chr12:80610707-81613447	chr12:79634838-79637578	rs12313692	kgp5599463
MYF6	chr12:81101407-81103256	chr12:80601407-81603256	chr12:79625576-79627382	rs7954738	rs7972054
MYLK	chr3:123331142-123603149	chr3:122831142-124103149	chr3:124813832-125085839	kgp9270532	rs510324
MYO10	chr5:16662015-16936385	chr5:16162015-17436385	chr5:16715015-16989385	kgp22359577	kgp12241403
MYO7A	chr11:76839309-76926286	chr11:76339309-77426286	chr11:76516957-76603934	rs2186677	kgp304899
MYO9B	chr19:17186590-17324104	chr19:16686590-17824104	chr19:17047595-17185104	kgp21430919	kgp4164870
MYOC	chr1:171604556-171621823	chr1:171104556-172121823	chr1:169871179-169888396	rs1736563	kgp1482992
MYOD1	chr11:17741109-17743678	chr11:17241109-18243678	chr11:17697685-17700254	kgp10809253	rs12285714

Fig. 3-16

Tier 3 Gene	GeneRange(hg19)	GeneRange+500kb(hg19)	GeneRange(hg18)	StartSNP (GeneRange+500kb)	EndSNP (GeneRange+500 kb)
MYOG	chr1:203052256-203055377	chr1:202552256-203555377	chr1:201318879-201322000	rs4950858	rs2798625
MYOT	chr5:137022409-137223540	chr5:136522409-137723540	chr5:137231472-137251440	kgp22294838	kgp5559791
MYT1L	chr2:1792884-2335045	chr2:1292884-2835045	chr2:1771891-2314052	kgp356515	kgp7720594
NACA	chr12:57106210-57119326	chr12:56606210-57619326	chr12:55392477-55405593	rs4759218	kgp11483848
NCALD	chr8:102698769-103137135	chr8:102198769-103637135	chr8:102767945-103206311	kgp11277997	rs16869664
NCF1C	chr7:74572383-74587816	chr7:74072383-75087816	chr7:74210380-74225695	kgp7635479	kgp954065
NCL	chr2:232319458-232329205	chr2:231819458-232829205	chr2:232027702-232037449	rs13415867	kgp12447433
NCOR2	chr12:124808956-125052010	chr12:124308956-125552010	chr12:123397062-123617963	rs11057368	kgp12274490
NEUROD1	chr2:182540832-182545392	chr2:182040832-183045392	chr2:182249438-182253626	kgp7038037	rs12612546
NF2	chr22:29999544-30094589	chr22:29499544-30594589	chr22:28329544-28424589	kgp15024372	kgp10478391
NFASC	chr1:204797781-204991950	chr1:204297781-205491950	chr1:203064445-203258572	rs12044614	kgp11817505
NFATC1	chr18:77155771-77289323	chr18:76655771-77789323	chr18:75256759-75390311	rs12150804	kgp11226294
NFATC2	chr20:50007764-50179168	chr20:49507764-50679168	chr20:49441171-49612777	rs761240	kgp19325060
NFKB2	chr10:104154228-104162281	chr10:103654228-104662281	chr10:104144218-104152271	kgp11777223	rs7897654
NFKBIB	chr19:39390339-39399534	chr19:38890339-39899534	chr19:44082454-44091374	kgp21403480	kgp4374047
NFKBIE	chr6:44225902-44233525	chr6:43725902-44733525	chr6:44333880-44341503	rs866236	kgp11221406
NGB	chr14:77731833-77737655	chr14:77231833-78237655	chr14:76801586-76807408	kgp4649405	rs11622713
NHP2L1	chr22:42069936-42084913	chr22:41569936-42584913	chr22:40399882-40414859	kgp22806642	kgp282841
NOS1	chr12:117645946-117799607	chr12:117145946-118299607	chr12:116135361-116283965	rs11068156	kgp763518
NP	chr14:20937541-20945248	chr14:20437541-21445248	chr14:20007381-20015088	kgp8768601	kgp19427360
NPHP1	chr2:110880913-110962639	chr2:110380913-111462639	chr2:110238202-110319928	rs10496434	kgp3845148

Fig. 3-17

Tier 3 Gene	GeneRange(hg19)	GeneRange+500kb(hg19)	GeneRange(hg18)	StartSNP (GeneRange+500kb)	EndSNP (GeneRange+500 kb)
NRBP1	chr2:27650656-27665124	chr2:27150656-28165124	chr2:27504160-27518628	kgp14600002	kgp14258181
NRGN	chr11:124609828-124617102	chr11:124109828-125117102	chr11:124115038-124122312	kgp483624	kgp5783287
NUCB1	chr19:49403306-49426540	chr19:48903306-49926540	chr19:54095380-54118339	kgp282275	kgp9015400
OBSCN	chr1:228395860-228566575	chr1:227895860-229066575	chr1:226462483-226633198	kgp22809391	kgp706951
OGG1	chr3:9791627-9808353	chr3:9291627-10308353	chr3:9765704-9783342	rs17744749	rs1642974
OPRK1	chr8:54138275-54164194	chr8:53638275-54664194	chr8:54300828-54326747	kgp11808605	kgp7186378
OPRM1	chr6:154360442-154568001	chr6:153860442-155068001	chr6:154402135-154609693	kgp22790919	kgp7491549
P2RY1	chr3:152552735-152555843	chr3:152052735-153055843	chr3:154035425-154038533	rs4472028	kgp1812100
PA2G4	chr12:56498102-56507694	chr12:55998102-57007694	chr12:54784369-54793961	kgp18842835	rs12308290
PABPC4	chr1:40026484-40042521	chr1:39526484-40542521	chr1:39799074-39815003	rs6692557	rs6681804
PAEP	chr9:138453603-138458622	chr9:137953603-138958622	chr9:137593424-137598443	kgp4360258	rs11103302
PAFAH1B1	chr17:2496922-2588909	chr17:1996922-3088909	chr17:2443672-2535659	kgp13951566	kgp4861640
PAM	chr5:102201526-102366808	chr5:101701526-102866808	chr5:102229425-102393316	rs10075318	kgp4660412
PARD6A	chr16:67694850-67696681	chr16:67194850-68196681	chr16:66252351-66254182	kgp16268099,rs1106304	kgp16328412
PARD6B	chr20:49348080-49370278	chr20:48848080-49870278	chr20:48781487-48803685	kgp19335956	kgp19356310
PARD6G	chr18:77915116-78005397	chr18:77415116-78505397	chr18:76016105-76106388	kgp15973881	rs12960632
PAWR	chr12:79985744-80084790	chr12:79485744-80584790	chr12:78509875-78608921	rs2950386	kgp19124809
PCNT	chr21:47744035-47865682	chr21:47244035-48365682	chr21:46568463-46690110	kgp13165624	rs10483083
PCP4	chr21:41239346-41301322	chr21:40739346-41801322	chr21:40161216-40223192	kgp5198475	rs2837624
PDC	chr1:186412697-186430239	chr1:185912697-186930239	chr1:184679337-184696862	kgp15446019	kgp15206197
PDCD8	chrX:129263338-129299861	chrX:128763338-129799861	chrX:129091019-129127542	rs3131260	kgp22747824

Fig. 3-18

Tier 3 Gene	GeneRange(hg19)	GeneRange+500kb(hg19)	GeneRange(hg18)	StartSNP (GeneRange+500kb)	EndSNP (GeneRange+500 kb)
PDCL	chr9:125580375-125590935	chr9:125080375-126090935	chr9:124620443-124630661	kgp11050939	rs7341862
PDE1A	chr2:183007182-183387507	chr2:182507182-183887507	chr2:182715427-183095498	kgp205462	kgp14271078
PDE4DIP	chr1:144676436-145076186	chr1:144176436-145576186	chr1:143388229-143787436	rs7548928	kgp15506281
PDE6D	chr2:232597146-232645974	chr2:232097146-233145974	chr2:232305390-232354218	kgp448503	rs11686328
PDIA2	chr16:330605-337209	chr16:1-837209	chr16:270606-277210	kgp4861413	rs3817833
PDLIM7	chr5:176910394-176924602	chr5:176410394-177424602	chr5:176843000-176857208	kgp10474318	kgp9286031
PDPK1	chr16:2587969-2653189	chr16:2087969-3153189	chr16:2527970-2593190	rs11876	rs2741932
PEA15	chr1:160175124-160185162	chr1:159675124-160685162	chr1:158441750-158451786	kgp15388960	kgp4800109
PELO	chr5:52083773-52098452	chr5:51583773-52598452	chr5:52119530-52134209	kgp7417119	kgp22419632
PFDN1	chr5:139624634-139682689	chr5:139124634-140182689	chr5:139604818-139662873	kgp2976589	rs3733707
PFDN4	chr20:52824501-52836492	chr20:52324501-53336492	chr20:52257908-52269899	kgp2671049	kgp19401284
PFDN5	chr12:53689234-53693234	chr12:53189234-54193234	chr12:51975501-51979501	kgp9320945	kgp18934893
PFKFB2	chr1:207207760-207254368	chr1:206707760-207754368	chr1:205293242-205320991	rs6666087	kgp15524399
PFN1	chr17:4848946-4851825	chr17:4348946-5351825	chr17:4789691-4792570	kgp459103	rs11869909
PGK1	chrX:77359665-77382324	chrX:76859665-77882324	chrX:77246321-77268980	kgp22784498	kgp22747606
PHKA1	chrX:71798663-71934029	chrX:71298663-72434029	chrX:71715388-71850754	kgp22784635	kgp22830838,rs5982097
PHKA2	chrX:18910415-19002480	chrX:18410415-19502480	chrX:18820336-18912401	kgp22820040	kgp22735291
PHKG1	chr7:56148674-56160689	chr7:55648674-56660689	chr7:56116168-56128183	rs4947514	kgp13251786
PIAS4	chr19:4007748-4038067	chr19:3507748-4538067	chr19:3958748-3989067	kgp21496330	rs966384
PIK3C3	chr18:39535198-39661446	chr18:39035198-40161446	chr18:37789196-37915444	kgp16093917	kgp16001617
PIK3CG	chr7:106505722-106547592	chr7:106005722-107047592	chr7:106292958-106334828	kgp13830163	kgp58259

Fig. 3-19

Tier 3 Gene	GeneRange(hg19)	GeneRange+500kb(hg19)	GeneRange(hg18)	StartSNP (GeneRange+500kb)	EndSNP (GeneRange+500 kb)
PLCB2	chr15:40580097-40600174	chr15:40080097-41100174	chr15:38367389-38387466	rs594863	kgp19835274
PLCD1	chr3:38048986-38071154	chr3:37548986-38571154	chr3:38023990-38046137	rs155528	kgp8999289
PLD1	chr3:171318194-171528504	chr3:170818194-172028504	chr3:172801338-173011198	kgp17613784	kgp17918658
PLD2	chr17:4710395-4726727	chr17:4210395-5226727	chr17:4657377-4673694	rs9915202	kgp10024037
PLEKHA4	chr19:49340353-49371884	chr19:48840353-49871884	chr19:54032166-54063670	kgp21466232	kgp7036888
PLK1	chr16:23690200-23701688	chr16:23190200-24201688	chr16:23597701-23609189	kgp6012631	kgp22747639
POLA2	chr11:65029431-65065088	chr11:64529431-65565088	chr11:64786007-64821664	rs637332	rs12800057
POLB	chr8:42195972-42229331	chr8:41695972-42729331	chr8:42315186-42348470	kgp20057794	kgp20541648
POLR2C	chr16:57496550-57505921	chr16:56996550-58005921	chr16:56054051-56063422	kgp12245826	rs3888264
POLR3F	chr20:18448032-18465286	chr20:17948032-18965286	chr20:18396032-18413286	kgp4834782	kgp4034265
PPARA	chr22:46546498-46639653	chr22:46046498-47139653	chr22:44925162-45018317	kgp1216941	kgp15069036
PPEF1	chrX:18709044-18846034	chrX:18209044-19346034	chrX:18618965-18755955	kgp22764965	kgp22802655
PPEF2	chr4:76781025-76823681	chr4:76281025-77323681	chr4:77000049-77042705	kgp3982074	kgp4693685
PPM1A	chr14:60712469-60765805	chr14:60212469-61265805	chr14:59782222-59835559	kgp19716116	kgp5849461
PPP1R13B	chr14:104200087-104313927	chr14:103700087-104813927	chr14:103269840-103383680	kgp19713395	kgp19494408
PPP1R14A	chr19:38741876-38747231	chr19:38241876-39247231	chr19:43433716-43439012	kgp7541975	kgp4659188
PPP3CA	chr4:101944586-102268628	chr4:101444586-102768628	chr4:102163609-102487376	kgp4575683	kgp7268908
PPYR1	chr10:47083533-47088320	chr10:46583533-47588320	chr10:46503539-46508326	kgp507194	rs11259820
PQBP1	chrX:48755194-48760422	chrX:48255194-49260422	chrX:48640138-48645364	rs28833838	rs2015487
PREI3	chr2:198364721-198418423	chr2:197864721-198918423	chr2:198072966-198126668	kgp9884304	kgp9480848
PRG2	chr11:57154833-57191532	chr11:56654833-57691532	chr19:763517-772952	kgp13043879	kgp12981403

Fig. 3-20

Tier 3 Gene	GeneRange(hg19)	GeneRange+500kb(hg19)	GeneRange(hg18)	StartSNP (GeneRange+500kb)	EndSNP (GeneRange+500 kb)
PRKACA	chr19:14202506-14228559	chr19:13702506-14728559	chr19:14063506-14089559	kgp6577295	kgp559477
PRKCB1	chr16:23847300-24231932	chr16:23347300-24731932	chr16:23754801-24139433	rs7190829	rs2343354
PRKCD	chr3:53195222-53226733	chr3:52695222-53726733	chr3:53170262-53201773	rs11715796	kgp8788109
PRKCG	chr19:54385466-54410901	chr19:53885466-54910901	chr19:59077278-59102713	kgp1393848	kgp11043930
PRKCI	chr3:169940219-170023770	chr3:169440219-170523770	chr3:171422913-171506464	kgp17942550	rs12485248
PRKCZ	chr1:1981908-2116834	chr1:1481908-2616834	chr1:1971768-2106694	kgp15756715	kgp907107
PRKG1	chr10:52750910-54058110	chr10:52250910-54558110	chr10:52420950-53725280	kgp22035660	rs7923443
PSCD2	chr19:48972465-48985571	chr19:48472465-49485571	chr19:53664277-53677383	rs16981057	rs5464
PSEN2	chr1:227058272-227083804	chr1:226558272-227583804	chr1:225124895-225150427	rs3219110	kgp1301981,rs3014274
PSG9	chr19:43757434-43773682	chr19:43257434-44273682	chr19:48449274-48465522	kgp21418993	kgp7929858
PSMA2	chr7:42956461-42971805	chr7:42456461-43471805	chr7:42922986-42938330	kgp13636285	kgp8523923
PSMD2	chr3:184017021-184026840	chr3:183517021-184526840	chr3:185499715-185509534	kgp4284536	rs11711955
PSPC1	chr13:20277008-20357159	chr13:19777008-20857159	chr13:19146895-19255083	kgp249471	kgp2992302
PTGIR	chr19:47123724-47128354	chr19:46623724-47628354	chr19:51815564-51820194	kgp21532737	rs184290
PTMAP7	chr2:232573235-232578250	chr2:232073235-233078250	chr2:232281479-232286494	kgp6878597	kgp14464906
PTP4A1	chr6:64231650-64293489	chr6:63731650-64793489	chr6:64289609-64351448	rs4710239	kgp357802
PTP4A3	chr8:142432006-142441620	chr8:141932006-142941620	chr8:142501188-142510802	rs12678285	kgp3296894
PTPN11	chr12:112856535-112947717	chr12:112356535-113447717	chr12:111340918-111432100	kgp22816522	rs1293743
PTPN12	chr7:77166772-77269388	chr7:76666772-77769388	chr7:77004770-77107322	kgp4690058	rs3807707
PTPN6	chr12:7055739-7070479	chr12:6555739-7570479	chr12:6926000-6940740	kgp18831609	kgp18845056
PTPRA	chr20:2844824-3019315	chr20:2344824-3519315	chr20:2792824-2967315	kgp725112	rs2853218

Fig. 3-21

Tier 3 Gene	GeneRange(hg19)	GeneRange+500kb(hg19)	GeneRange(hg18)	StartSNP (GeneRange+500kb)	EndSNP (GeneRange+500 kb)
PTPRJ	chr11:48002109-48192394	chr11:47502109-48692394	chr11:47958685-48148970	kgp11833163	kgp12755942
PTPRS	chr19:5158505-5340814	chr19:4658505-5840814	chr19:5109505-5291814	kgp6271833	kgp4407357
PTPRU	chr1:29563027-29653325	chr1:29063027-30153325	chr1:29435633-29525903	rs12068075	kgp9719744
RAB27A	chr15:55495163-55582013	chr15:54995163-56082013	chr15:53283091-53369293	kgp19829554	rs11631355
RAB3B	chr1:52373627-52456436	chr1:51873627-52956436	chr1:52157422-52228936	kgp22830492	rs10493168
RAB5A	chr3:19988571-20026667	chr3:19488571-20526667	chr3:19963762-20001647	rs1348231	kgp8738867
RAB8B	chr15:63481727-63559973	chr15:62981727-64059973	chr15:61268780-61347026	kgp20037308	rs17773778
RABAC1	chr19:42460832-42463528	chr19:41960832-42963528	chr19:47152675-47155311	kgp22776019	kgp2186225
RAC1	chr7:6414125-6443598	chr7:5914125-6943598	chr7:6380650-6410123	kgp13594313	kgp2338008
RACGAP1	chr12:50382944-50419307	chr12:49882944-50919307	chr12:48669211-48705574	rs12317050	kgp2525417
RAF1	chr3:12625099-12705700	chr3:12125099-13205700	chr3:12600099-12680700	kgp17997932	kgp3531880
RALB	chr2:120997639-121052286	chr2:120497639-121552286	chr2:120726883-120768756	rs17661862	kgp5177758
RASSF1	chr3:50367216-50378367	chr3:49867216-50878367	chr3:50342220-50353371	kgp8151957	kgp7341826
RBM23	chr14:23369853-23388396	chr14:22869853-23888396	chr14:22439693-22458236	rs3811239	kgp128686
RBM5	chr3:50126340-50156397	chr3:49626340-50656397	chr3:49952595-50112488	kgp22823256	rs375544
RCVRN	chr17:9801026-9808684	chr17:9301026-10308684	chr17:9741751-9749409	rs8082538	kgp2141837
REL	chr2:61108751-61150178	chr2:60608751-61650178	chr2:60962255-61003682	kgp8245960	kgp14294452
RELA	chr11:65421066-65430443	chr11:64921066-65930443	chr11:65177647-65186951	kgp6667058	kgp4478491
RELB	chr19:45504706-45541456	chr19:45004706-46041456	chr19:50196551-50233292	kgp9280266	kgp9663255
RFC5	chr12:118454505-118470042	chr12:117954505-118970042	chr12:116938892-116954422	rs11068526	kgp19024344
RGS10	chr10:121259338-121302222	chr10:120759338-121802222	chr10:121249328-121292212	kgp21619652	kgp5105745

Fig. 3-22

Tier 3 Gene	GeneRange(hg19)	GeneRange+500kb(hg19)	GeneRange(hg18)	StartSNP (GeneRange+500kb)	EndSNP (GeneRange+500 kb)
RGS13	chr1:192605267-192629440	chr1:192105267-193129440	chr1:190871904-190896012	rs11806786	kgp1816960
RGS14	chr5:176784843-176799599	chr5:176284843-177299599	chr5:176717449-176732205	rs1000144	kgp11311419
RGS16	chr1:182567757-182573548	chr1:182067757-183073548	chr1:180834380-180840171	kgp15787070	kgp4798391
RGS18	chr1:192127591-192154945	chr1:191627591-192654945	chr1:190394214-190421568	rs1338034	kgp6525246
RGS19	chr20:62704534-62711324	chr20:62204534-63211324	chr20:62174978-62181768	rs1630157	kgp19264714
RGS4	chr1:163038395-163046592	chr1:162538395-163546592	chr1:161305019-161313216	kgp15623644	kgp15384575
RGS5	chr1:163112088-163291581	chr1:162612088-163791581	chr1:161378720-161439496	kgp15331781	kgp2554099
RGS7	chr1:240938816-241520478	chr1:240438816-242020478	chr1:239005439-239587101	rs16839692	kgp15345284
RHO	chr3:129247481-129254187	chr3:128747481-129754187	chr3:130730171-130736877	kgp12236862	kgp11280524
RHOH	chr4:40198526-40246281	chr4:39698526-40746281	chr4:39874921-39922676	rs3912392	rs17513557
RIC8A	chr11:208529-215110	chr11:1-715110	chr11:198529-205110	kgp9815230	rs11246286
RIC8B	chr12:107168398-107283094	chr12:106668398-107783094	chr12:105692528-105807224	kgp7665070	kgp2084662
RIOK3	chr18:21032786-21063099	chr18:20532786-21563099	chr18:19286784-19317097	kgp4053645	kgp16177785
RIPK1	chr6:3064121-3115421	chr6:2564121-3615421	chr6:3009120-3060420	rs17208835	kgp17120238
RIPK2	chr8:90769974-90803292	chr8:90269974-91303292	chr8:90839109-90872433	rs7813237	rs2214416
RIT1	chr1:155867600-155881177	chr1:155367600-156381177	chr1:154134224-154147801	kgp10974682	rs12022607
RIT2	chr18:40323191-40695657	chr18:39823191-41195657	chr18:38577189-38949655	rs6507465	kgp3440940
RNF10	chr12:120972131-121015397	chr12:120472131-121515397	chr12:119456514-119499780	kgp19140786	kgp19017203
RNF11	chr1:51701944-51739119	chr1:51201944-52239119	chr1:51474532-51511707	kgp4558813	kgp7772065
RPL10	chrX:153627678-153632038	chrX:153127678-154132038	chrX:153279911-153283874	rs2071127	rs4074307
RPL12	chr9:130209952-130213711	chr9:129709952-130713711	chr9:129249775-129253505	kgp11622632	rs3802355

Fig. 3-23

Tier 3 Gene	GeneRange(hg19)	GeneRange+500kb(hg19)	GeneRange(hg18)	StartSNP (GeneRange+500kb)	EndSNP (GeneRange+500 kb)
RPL37A	chr2:217363519-217366188	chr2:216863519-217866188	chr2:217071764-217074433	kgp2247391	kgp7636371
RRAD	chr16:66955581-66959439	chr16:66455581-67459439	chr16:65513082-65516940	kgp16522328	kgp16305055
RTN4	chr2:55199326-55277734	chr2:54699326-55777734	chr2:55052830-55131238	kgp3749465	rs3748945
S100A8	chr1:153362507-153363664	chr1:152862507-153863664	chr1:151629131-151630173	rs6587709	kgp4686042
SAT1	chrX:23801274-23804327	chrX:23301274-24304327	chrX:23711224-23714248	kgp22758306	kgp22759648
SCN8A	chr12:51985019-52202299	chr12:51485019-52702299	chr12:50271286-50488566	rs7979705	kgp7295633
SDC1	chr2:20400557-20425194	chr2:19900557-20925194	chr2:20264038-20288675	kgp14253812	kgp8380770
SDC2	chr8:97505881-97624037	chr8:97005881-98124037	chr8:97575057-97693213	rs1421221	kgp1305908
SDC4	chr20:43953928-43977064	chr20:43453928-44477064	chr20:43387342-43410478	rs8116486	kgp19276986
SDCBP	chr8:59465727-59495419	chr8:58965727-59995419	chr8:59628281-59657973	rs954172	kgp20217944
SDCBP2	chr20:1290554-1373816	chr20:790554-1873816	chr20:1238620-1257838	kgp9852208	kgp10348674
SDPR	chr2:192699031-192712006	chr2:192199031-193212006	chr2:192407280-192420226	kgp6263901	kgp14266860
SELENBP1	chr1:151336779-151345164	chr1:150836779-151845164	chr1:149603403-149611788	rs12406660	rs6684312
SEMG1	chr20:43835637-43838414	chr20:43335637-44338414	chr20:43269087-43271823	rs6094023	rs6094202
SEMG2	chr20:43835637-43853099	chr20:43335637-44353099	chr20:43269087-43286513	rs6094023	rs6017667
SEPT4	chr17:56597610-56618179	chr17:56097610-57118179	chr17:53952614-53964410	kgp1250021	rs34058624
SETDB1	chr1:150898814-150937220	chr1:150398814-151437220	chr1:149165511-149203837	rs12759551	kgp1978717
SGOL1	chr3:20202084-20227724	chr3:19702084-20727724	chr3:20177088-20202687	kgp9539943	kgp18040639
SGOL2	chr2:201390864-201448818	chr2:200890864-201948818	chr2:201099186-201156750	kgp9074393	kgp14634946
SH2B3	chr12:111843751-111889427	chr12:111343751-112389427	chr12:110328134-110373810	kgp7682395	kgp10017505
SHC1	chr1:154934773-154946959	chr1:154434773-155446959	chr1:153201397-153213464	kgp11196367	kgp15752431

Fig. 3-24

Tier 3 Gene	GeneRange(hg19)	GeneRange+500kb(hg19)	GeneRange(hg18)	StartSNP (GeneRange+500kb)	EndSNP (GeneRange+500 kb)
SIRT2	chr19:39369194-39390502	chr19:38869194-39890502	chr19:44061039-44082201	kgp21526327	kgp9511717
SLC1A1	chr9:4490426-4587469	chr9:3990426-5087469	chr9:4480443-4577469	kgp7074545	kgp9946842
SLC6A9	chr1:44457171-44497134	chr1:43957171-44997134	chr1:44234741-44269721	rs6687571	rs6672462
SLC9A3R1	chr17:72744762-72765499	chr17:72244762-73265499	chr17:70256378-70277089	kgp14032523	kgp14006779
SMAD3	chr15:67358194-67487533	chr15:66858194-67987533	chr15:65145248-65274587	kgp1676807	kgp19813377
SMAD5	chr5:135468535-135518422	chr5:134968535-136018422	chr5:135496434-135546321	kgp5717445	kgp8569495
SMN2	chr5:70220767-70248842	chr5:69720767-70748842	chr5:70256523-70284594	rs28591114	kgp22633148
SMPD3	chr16:68392229-68482409	chr16:67892229-68982409	chr16:66949730-67039905	kgp2756941	kgp16310484
SNAP23	chr15:42787503-42825259	chr15:42287503-43325259	chr15:40575126-40612548	rs1668586	kgp19741111
SNAP25	chr20:10199476-10288066	chr20:9699476-10788066	chr20:10147476-10236065	kgp4923784	kgp19370207
SNAP91	chr6:84262604-84419127	chr6:83762604-84919127	chr6:84319331-84475831	kgp17413387	kgp16958869
SNTA1	chr20:31995762-32031698	chr20:31495762-32531698	chr20:31459423-31495359	kgp994844	kgp22753335
SNURF	chr15:25200069-25244225	chr15:24700069-25744225	chr15:22751162-22795318	kgp20028287	kgp5644000
SOX4	chr6:21593971-21598849	chr6:21093971-22098849	chr6:21701950-21706828	kgp3609791	rs9466264
SPAG1	chr8:101170262-101254132	chr8:100670262-101754132	chr8:101239438-101323306	kgp5198147	kgp20550876
SPG7	chr16:89574804-89624174	chr16:89074804-90124174	chr16:88102305-88151675	kgp3688149	rs3809643
SPP1	chr4:88896801-88904563	chr4:88396801-89404563	chr4:89115825-89123587	kgp20744622	kgp20764098
SPTBN1	chr2:54683453-54898583	chr2:54183453-55398583	chr2:54536957-54752087	kgp14832324	kgp12300457
SQSTM1	chr5:179233387-179265077	chr5:178733387-179765077	chr5:179170503-179197683	kgp10101186	kgp2553327
SRGAP3	chr3:9022277-9291311	chr3:8522277-9791311	chr3:8997277-9266311	kgp5324812	kgp18088153
STARD13	chr13:33677271-34250932	chr13:33177271-34750932	chr13:32575306-33148932	kgp1217969	kgp9105015

Fig. 3-25

Tier 3 Gene	GeneRange(hg19)	GeneRange+500kb(hg19)	GeneRange(hg18)	StartSNP (GeneRange+500kb)	EndSNP (GeneRange+500 kb)
STC2	chr5:172741725-172756506	chr5:172241725-173256506	chr5:172674331-172689112	kgp22378380	kgp10706002
STRN	chr2:37064840-37193615	chr2:36564840-37693615	chr2:36928975-37047119	kgp3533593	kgp9369923
STRN4	chr19:47222767-47250251	chr19:46722767-47750251	chr19:51914607-51941560	kgp21470253	rs4804031
STX4	chr16:31044415-31051485	chr16:30544415-31551485	chr16:30951916-30958986	kgp16259387	kgp7678241
STX5	chr11:62574331-62599563	chr11:62074331-63099563	chr11:62330944-62356136	kgp10937693	kgp568990
STXBP1	chr9:130374485-130454995	chr9:129874485-130954995	chr9:129414388-129494816	rs1768374	kgp4399986
STXBP3	chr1:109289284-109352148	chr1:108789284-109852148	chr1:109090807-109153671	rs6583070	rs17036360
SULT1E1	chr4:70706929-70725870	chr4:70206929-71225870	chr4:70741518-70760459	kgp22798798	kgp5241292
SUMO4	chr6:149721494-149722182	chr6:149221494-150222182	chr6:149763187-149763875	rs1871921	kgp17155476
SYT1	chr12:79257772-79845788	chr12:78757772-80345788	chr12:77781903-78367834	kgp11848377	kgp18913198
SYT9	chr11:7273180-7490276	chr11:6773180-7990276	chr11:7229756-7446846	rs7928685	kgp8567849
TANC1	chr2:159825145-160089170	chr2:159325145-160589170	chr2:159533391-159797416	rs4664962	kgp22743229
TANK	chr2:161993465-162092683	chr2:161493465-162592683	chr2:161701711-161800928	kgp7233899	rs1006427
TAOK2	chr16:29985187-30003582	chr16:29485187-30503582	chr16:29892722-29911082	rs257868	kgp2310172
TBCD	chr17:80709939-80901062	chr17:80209939-81401062	chr17:78303228-78494351	rs11653735	kgp10867492
TBCE	chr1:235530727-235612280	chr1:235030727-236112280	chr1:233597350-233678903	rs2673969	kgp15284682
TBK1	chr12:64845839-64895899	chr12:64345839-65395899	chr12:63132203-63182158	kgp18934034	kgp19122002
TCF1	chr5:134240810-134298336	chr5:133740810-134798336	chr5:134268709-134326235	kgp22161149	kgp4823163
TCF3	chr19:1609288-1652328	chr19:1109288-2152328	chr19:1560294-1603328	rs2302109	kgp2427498
TCF4	chr18:52889561-53303188	chr18:52389561-53803188	chr18:51040559-51454183	kgp10409423	rs1792746
TDGF1	chr3:46616044-46623952	chr3:46116044-47123952	chr3:46594216-46598956	kgp980076	kgp18003873

Fig. 3-26

Tier 3 Gene	GeneRange(hg19)	GeneRange+500kb(hg19)	GeneRange(hg18)	StartSNP (GeneRange+500kb)	EndSNP (GeneRange+500 kb)
TEP1	chr14:20833825-20881579	chr14:20333825-21381579	chr14:19905765-19951420	rs1780944	rs12435821
TERT	chr5:1253286-1295162	chr5:753286-1795162	chr5:1306286-1348162	kgp22831882	rs4975846
TGFA	chr2:70674411-70781147	chr2:70174411-71281147	chr2:70527924-70634613	kgp14279885	kgp4236793
TIAM1	chr21:32490735-32931290	chr21:31990735-33431290	chr21:31412606-31853161	rs1702403	rs1892577
TM4SF1	chr3:149086804-149095568	chr3:148586804-149595568	chr3:150569494-150578258	kgp18120845	kgp17746361
TMSB4X	chrX:12993225-12995346	chrX:12493225-13495346	chrX:12903145-12905267	kgp22760889	kgp22772999
TNFRSF14	chr1:2487804-2495267	chr1:1987804-2995267	chr1:2479150-2486613	rs2803309	kgp11439882
TNFRSF1A	chr12:6437922-6451283	chr12:5937922-6951283	chr12:6308183-6321522	kgp6731378,rs4764519	kgp19158534
TNFRSF1B	chr1:12227059-12269277	chr1:11727059-12769277	chr1:12149646-12191864	kgp15495881	rs3010872
TNIP2	chr4:2743386-2758103	chr4:2243386-3258103	chr4:2713184-2727859	kgp20948263	kgp5432833
TNNI2	chr11:1860232-1862910	chr11:1360232-2362910	chr11:1817480-1819484	kgp11231095	rs800123
TNNI3	chr19:55663135-55669100	chr19:55163135-56169100	chr19:60354947-60360912	rs13382124	kgp21397937
TNNT2	chr1:201328141-201346805	chr1:200828141-201846805	chr1:199594764-199613428	rs12733378	rs10920269
TOMM20	chr1:235272657-235292256	chr1:234772657-235792256	chr1:233339282-233358754	kgp8358331	kgp15139309
TOP2A	chr17:38544772-38574202	chr17:38044772-39074202	chr17:35798321-35827695	kgp7375263	kgp10420460
TP53	chr17:7571719-7590863	chr17:7071719-8090863	chr17:7512444-7531588	kgp12029669	kgp11286494
TRADD	chr16:67188088-67193812	chr16:66688088-67693812	chr16:65745589-65751313	kgp16482196	kgp16510307,rs28521023
TRAF1	chr9:123664670-123691451	chr9:123164670-124191451	chr9:122704492-122731300	kgp6551598	rs306777
TRAF6	chr11:36505316-36531863	chr11:36005316-37031863	chr11:36467298-36488398	kgp12764289	rs333778
TRBV21-1	chr7:142344427-142344887	chr7:141844427-142844887	chr7:142025416-142025876	kgp2155197	kgp9570297
TRIM2	chr4:154074269-154260474	chr4:153574269-154760474	chr4:154293719-154479918	rs6849505	rs6843172

Fig. 3-27

Tier 3 Gene	GeneRange(hg19)	GeneRange+500kb(hg19)	GeneRange(hg18)	StartSNP (GeneRange+500kb)	EndSNP (GeneRange+500 kb)
TRIM29	chr11:119981993-120008863	chr11:119481993-120508863	chr11:119487203-119514073	kgp12998914	rs7122702
TRIO	chr5:14143828-14509458	chr5:13643828-15009458	chr5:14196828-14562458	rs1445678	kgp8041369
TRPC1	chr3:142443265-142526729	chr3:141943265-143026729	chr3:143925955-144009419	rs9842771	rs7641069
TRPC3	chr4:122800182-122872909	chr4:122300182-123372909	chr4:123019881-123092359	kgp21231448	kgp5789583
TRPC4	chr13:38210772-38443939	chr13:37710772-38943939	chr13:37108794-37341935	kgp22792521	rs7338958
TRPV1	chr17:3468739-3512705	chr17:2968739-4012705	chr17:3415489-3459454	kgp8654960	rs9890881
TRPV4	chr12:110220891-110271212	chr12:109720891-110771212	chr12:108705276-108755595	kgp11365980	kgp19139284
TRPV6	chr7:142568959-142583490	chr7:142068959-143083490	chr7:142279081-142293599	kgp9647465	kgp2837315
TSC22D4	chr7:100064141-100076902	chr7:99564141-100576902	chr7:99902077-99914838	kgp5759639	kgp10599319
TSHR	chr14:81421868-81612646	chr14:80921868-82112646	chr14:80491621-80682399	kgp19546597	rs10134565
TSPAN6	chrX:99883794-99891794	chrX:99383794-100391794	chrX:99770450-99778450	kgp22794008	rs7059563
TTBK1	chr6:43211221-43255997	chr6:42711221-43755997	chr6:43319199-43363975	kgp17369454	kgp17498760
TTC1	chr5:159436179-159492550	chr5:158936179-159992550	chr5:159368757-159425128	kgp5018309	kgp22489460
TTK	chr6:80714321-80752244	chr6:80214321-81252244	chr6:80771077-80808958	kgp949561	kgp12311980
TTN	chr2:179390717-179672150	chr2:178890717-180172150	chr2:179098963-179380395	rs959775	rs6433773
TUB	chr11:8040790-8127654	chr11:7540790-8627654	chr11:8016755-8084228	kgp12365126	kgp1066384
TUBA8	chr22:18593452-18614498	chr22:18093452-19114498	chr22:16940685-16994498	rs1034470	kgp9877961
UBE2V2	chr8:48920994-48974454	chr8:48420994-49474454	chr8:49083547-49137007	kgp3293751	kgp20374954
ULK1	chr12:132379278-132407707	chr12:131879278-132907707	chr12:130945231-130973649	kgp7696078	kgp11815104
USP7	chr16:8985950-9057341	chr16:8485950-9557341	chr16:8893451-8964842	kgp79060	rs1035944
VAV1	chr19:6772721-6857371	chr19:6272721-7357371	chr19:6723721-6808371	kgp21410647	kgp21471951

Fig. 3-28

Tier 3 Gene	GeneRange(hg19)	GeneRange+500kb(hg19)	GeneRange(hg18)	StartSNP (GeneRange+500kb)	EndSNP (GeneRange+500kb)
VCL	chr10:75754950-75879914	chr10:75254950-76379914	chr10:75424956-75549920	rs7099640	kgp21840278
VDAC1	chr5:133307565-133340824	chr5:132807565-133840824	chr5:133335505-133368723	kgp22321002	kgp9499928
VIL2	chr6:159186773-159239340	chr6:158686773-159739340	chr6:159106761-159159328	rs9366083	kgp10633571
VIM	chr10:17270257-17279592	chr10:16770257-17779592	chr10:17310475-17319598	kgp1974218	kgp8572563
VTN	chr17:26694298-26697373	chr17:26194298-27197373	chr17:23718425-23721500	rs12602762	kgp2208161
WDR62	chr19:36545782-36596012	chr19:36045782-37096012	chr19:41237622-41287852	kgp5818871	kgp7464156
WDR91	chr7:134868589-134896316	chr7:134368589-135396316	chr7:134520524-134546811	kgp7394785	kgp4752834
WWC1	chr5:167719064-167899308	chr5:167219064-168399308	chr5:167651669-167829342	rs10454965	rs7724207
XK	chrX:37545132-37591383	chrX:37045132-38091383	chrX:37430051-37476322	kgp22781551	kgp22821350
YWHAB	chr20:43514343-43537161	chr20:43014343-44037161	chr20:42947757-42970575	rs4364072	rs2247619
YWHAE	chr17:1247833-1303556	chr17:747833-1803556	chr17:1194592-1250267	rs4968122	kgp1552188
YWHAG	chr7:75956107-75988342	chr7:75456107-76488342	chr7:75794051-75826252	kgp13357645	kgp7952605
YWHAZ	chr8:101930803-101965623	chr8:101430803-102465623	chr8:102000089-102034745	rs4075553	kgp4135753
ZNF24	chr18:32912177-32924426	chr18:32412177-33424426	chr18:31166175-31178424	kgp5227729	kgp15931312

Fig. 3-29

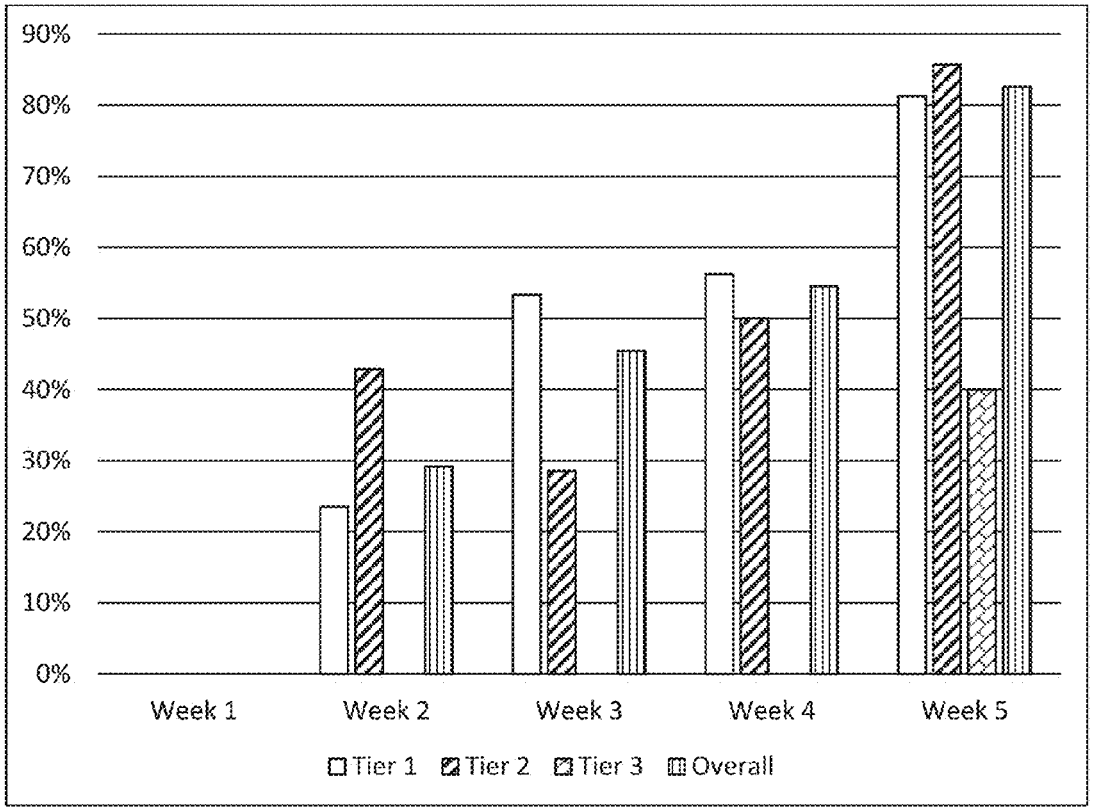

90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Week 1
Week 2
Week 3
Week 4
Week 5
Tier 1
Tier 2
Tier 3
Overall

FIG. 4

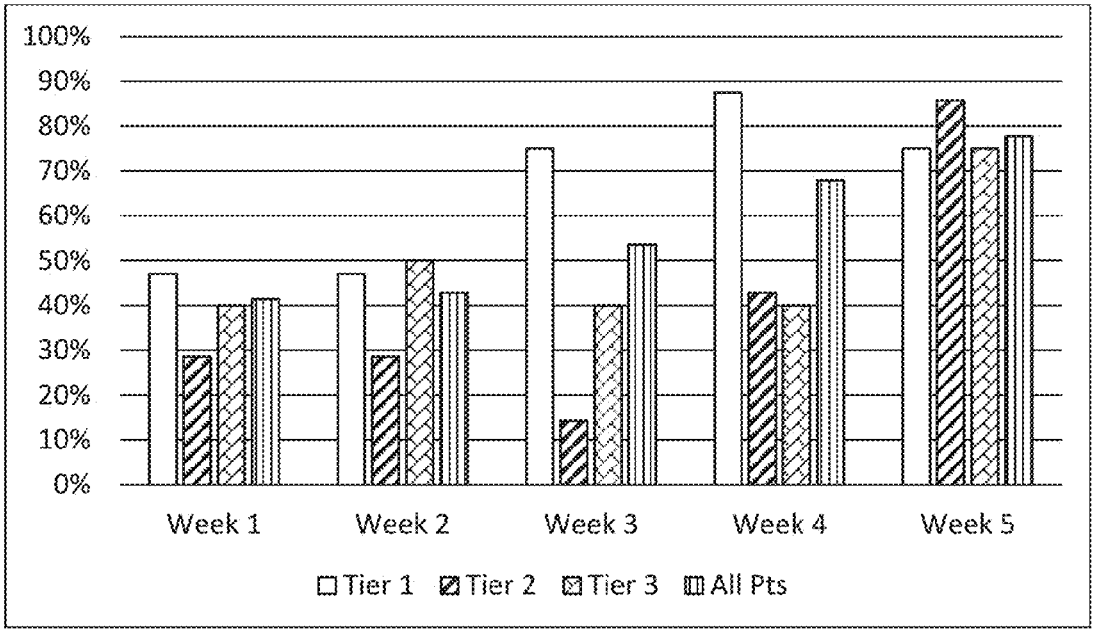

100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Week 1
Week 2
Week 3
Week 4
Week 5
Tier 1
Tier 2
Tier 3
All Pts

FIG. 5A

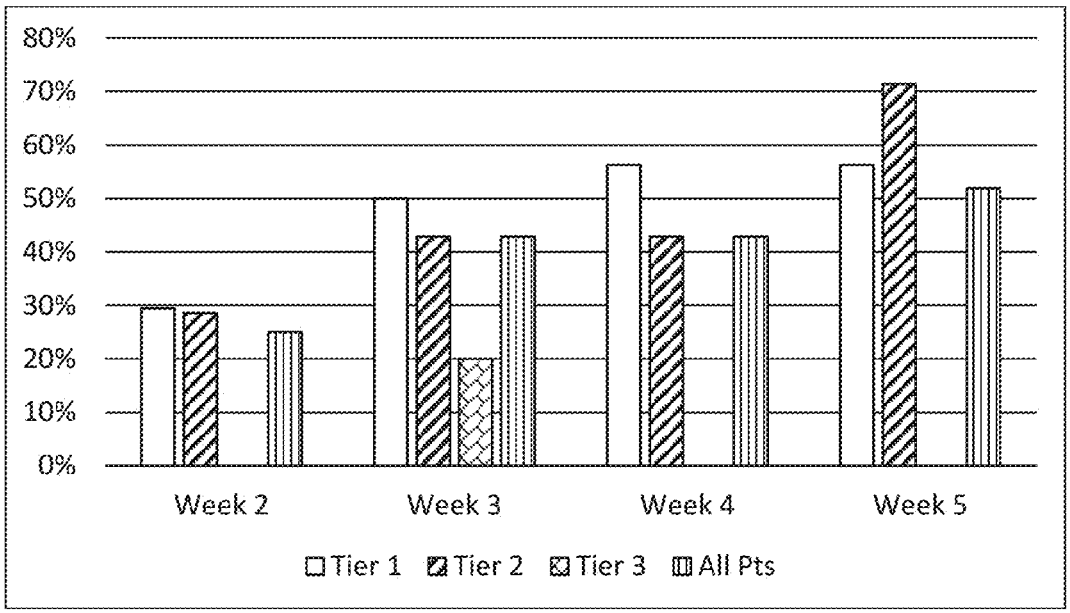

80%
70%
60%
50%
40%
30%
20%
10%
0%
Week 2
Week 3
Week 4
Week 5
Tier 1
Tier 2
Tier 3
All Pts

FIG. 5B

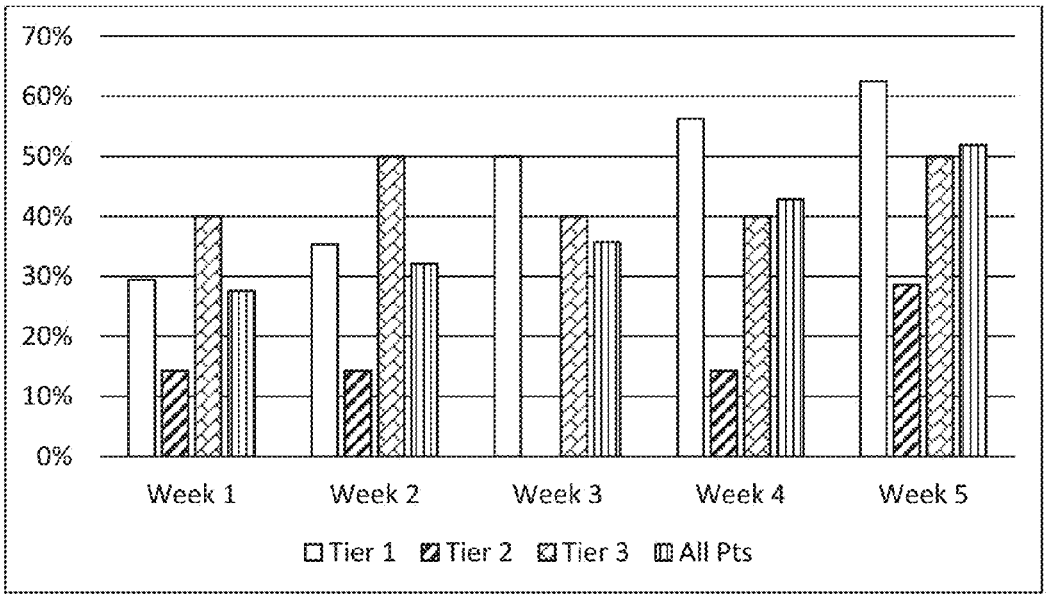

70%
60%
50%
40%
30%
20%
10%
0%
Week 1
Week 2
Week 3
Week 4
Week 5
Tier 1
Tier 2
Tier 3
All Pts

FIG. 6A

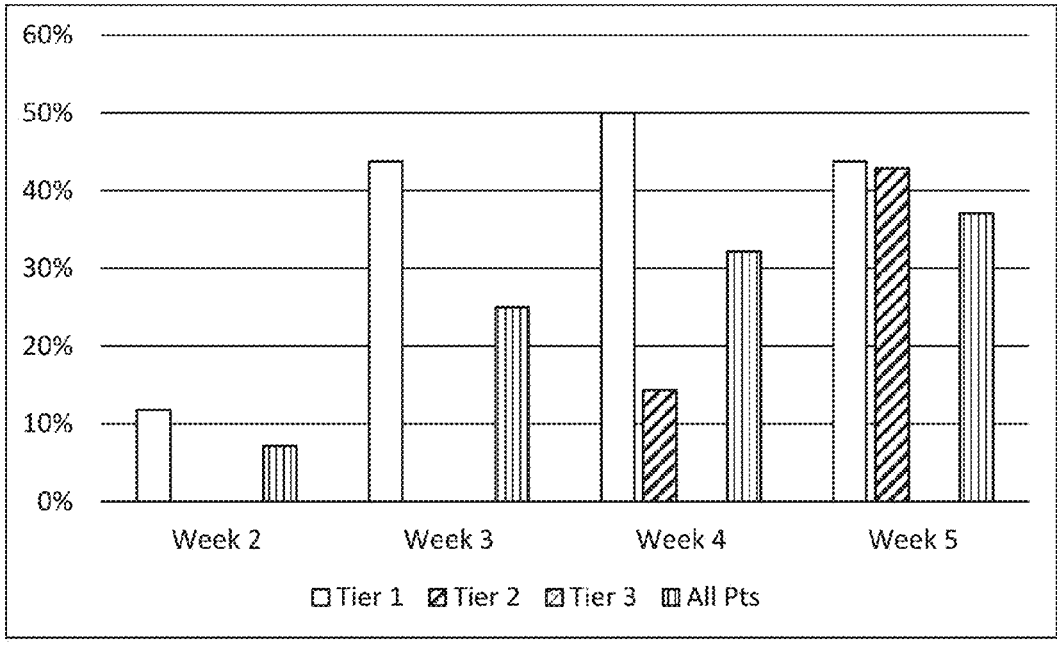

60%
50%
40%
30%
20%
10%
0%
Week 2
Week 3
Week 4
Week 5
Tier 1
Tier 2
Tier 3
All Pts

FIG. 6B

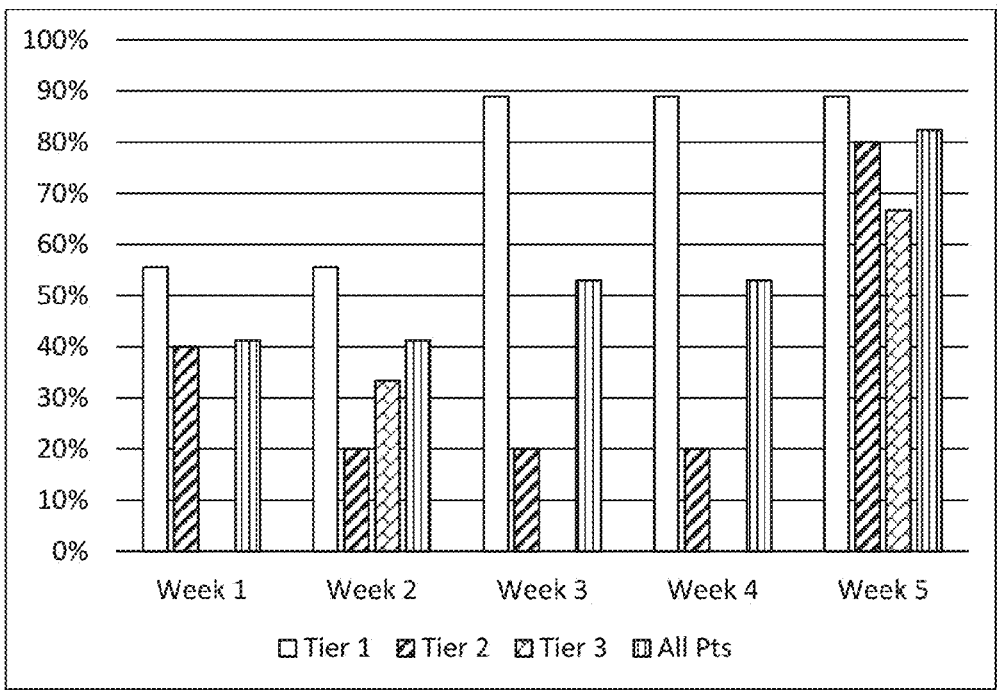

100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Week 1
Week 2
Week 3
Week 4
Week 5
Tier 1
Tier 2
Tier 3
All Pts

FIG. 7A

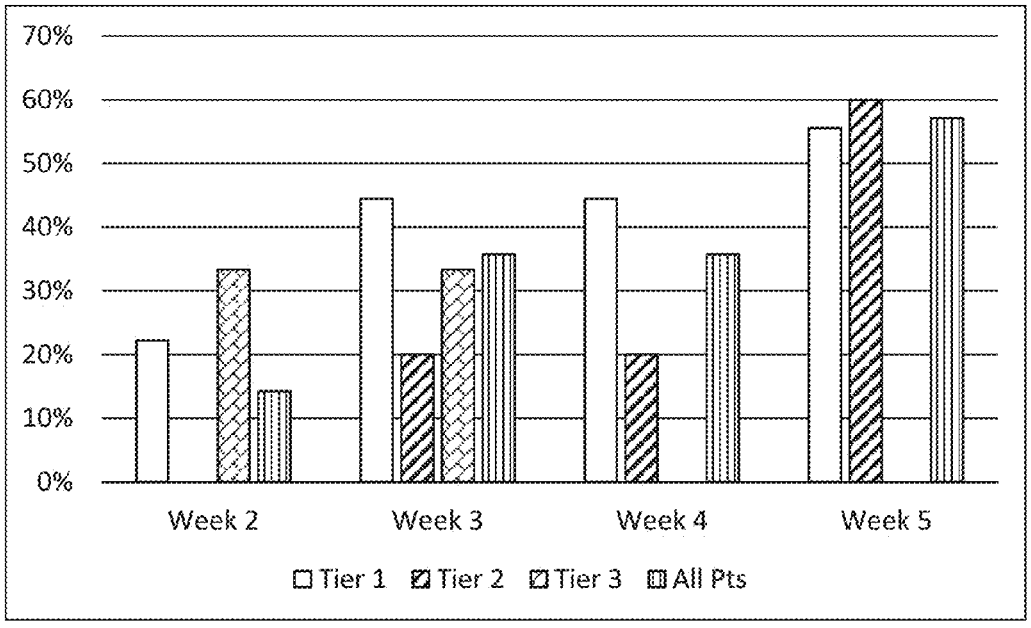

70%
60%
50%
40%
30%
20%
10%
0%
Week 2
Week 3
Week 4
Week 5
Tier 1
Tier 2
Tier 3
All Pts

FIG. 7B

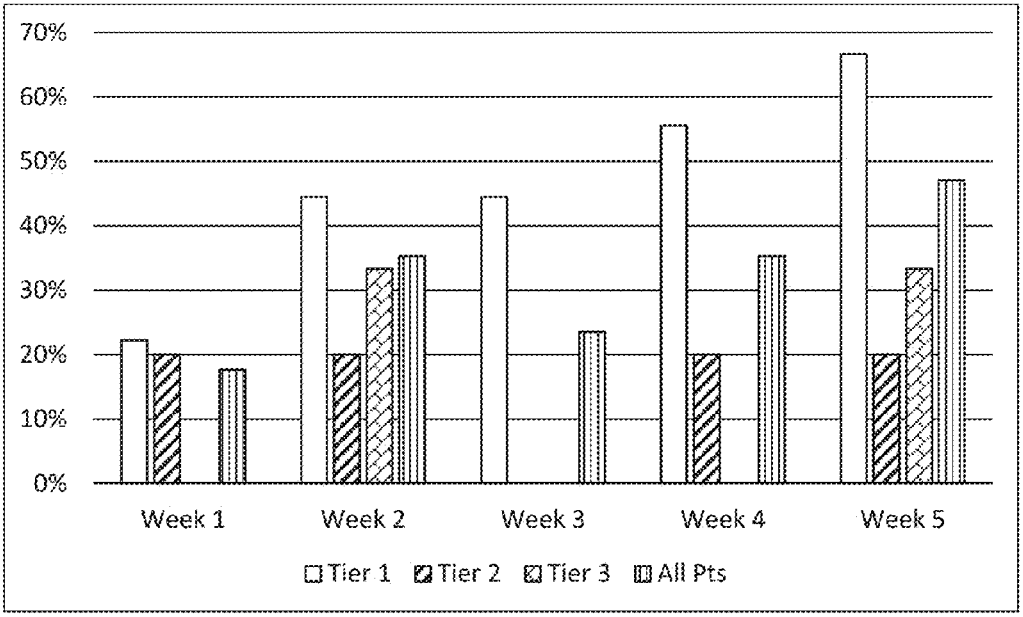

70%
60%
50%
40%
30%
20%
10%
0%
Week 1
Week 2
Week 3
Week 4
Week 5
Tier 1
Tier 2
Tier 3
All Pts

FIG. 8A

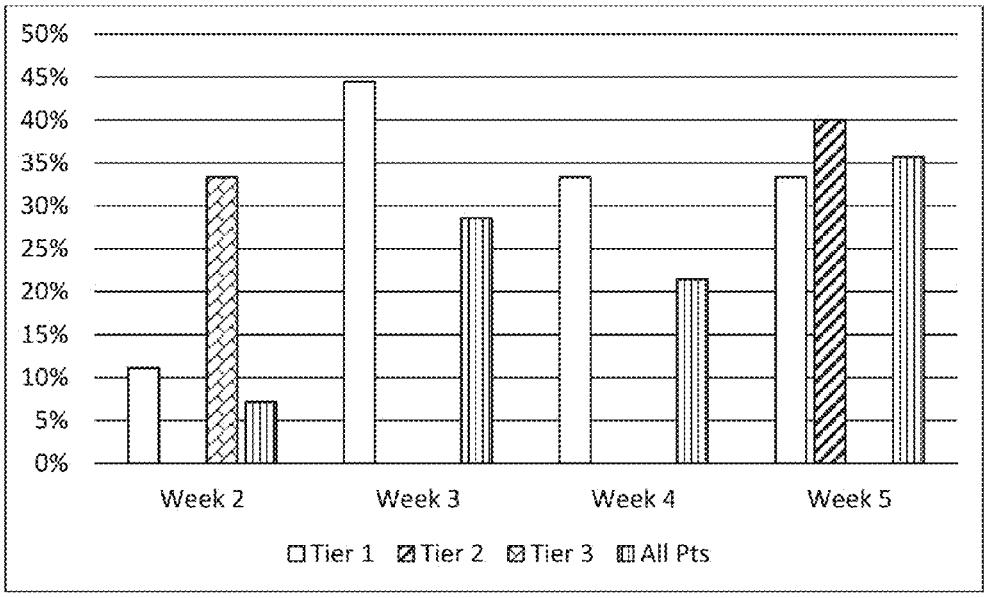

50%
45%
40%
35%
30%
25%
20%
15%
10%
5%
0%
Week 2
Week 3
Week 4
Week 5
Tier 1
Tier 2
Tier 3
All Pts

FIG. 8B

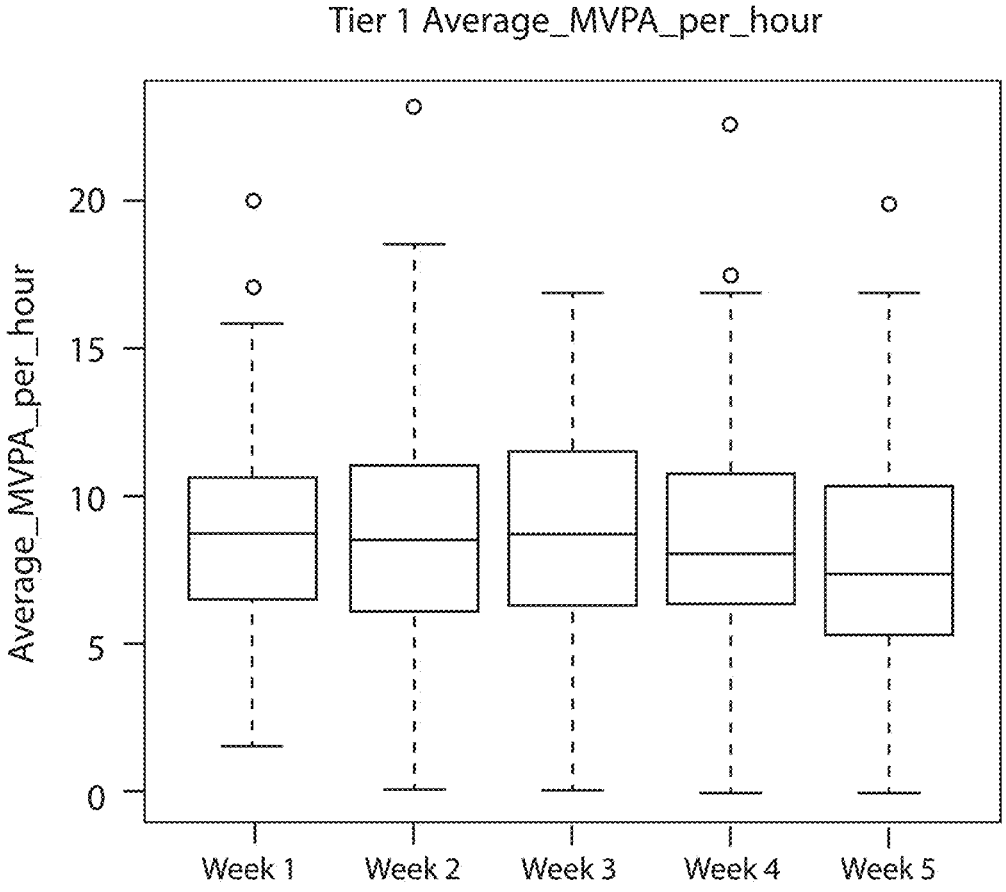

Tier 1 Average_MVPA_per_hour
Average_MVPA_per_hour
0
5
10
15
20
Week 1
Week 2
Week 3
Week 4
Week 5

Fig. 9A

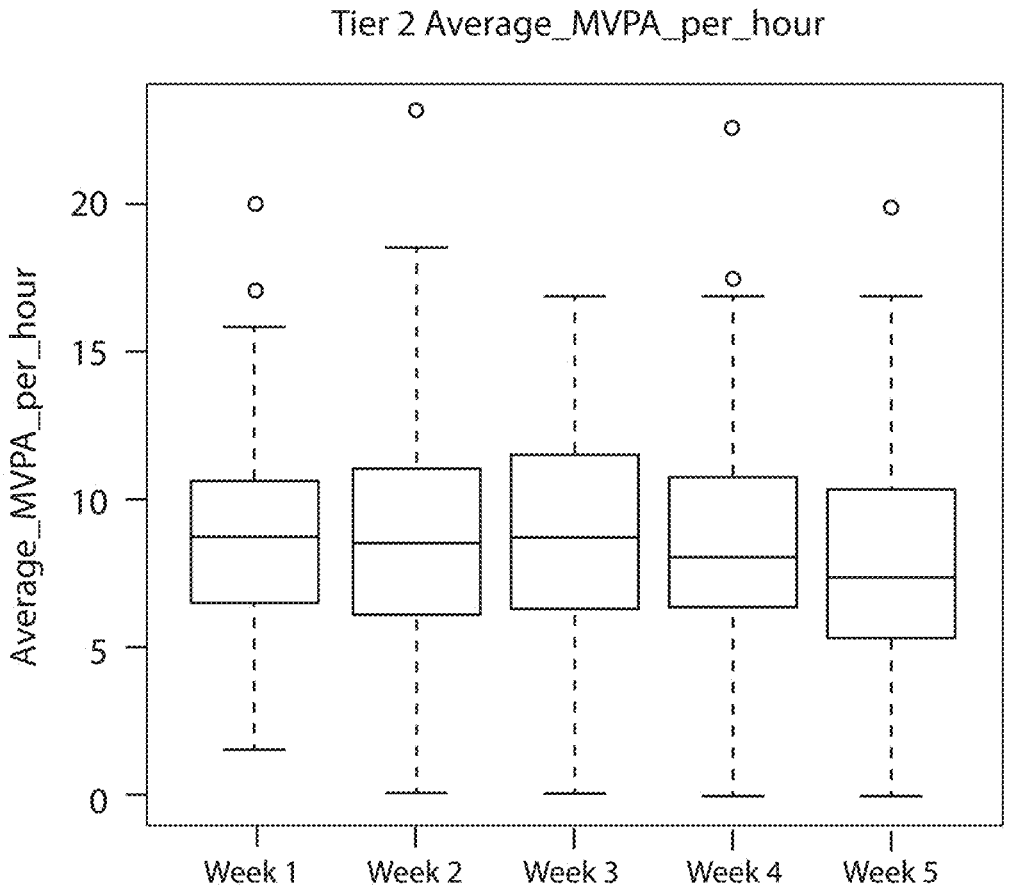

Tier 2 Average_MVPA_per_hour
Average_MVPA_per_hour
0
5
10
15
20
Week 1
Week 2
Week 3
Week 4
Week 5

Fig. 9B

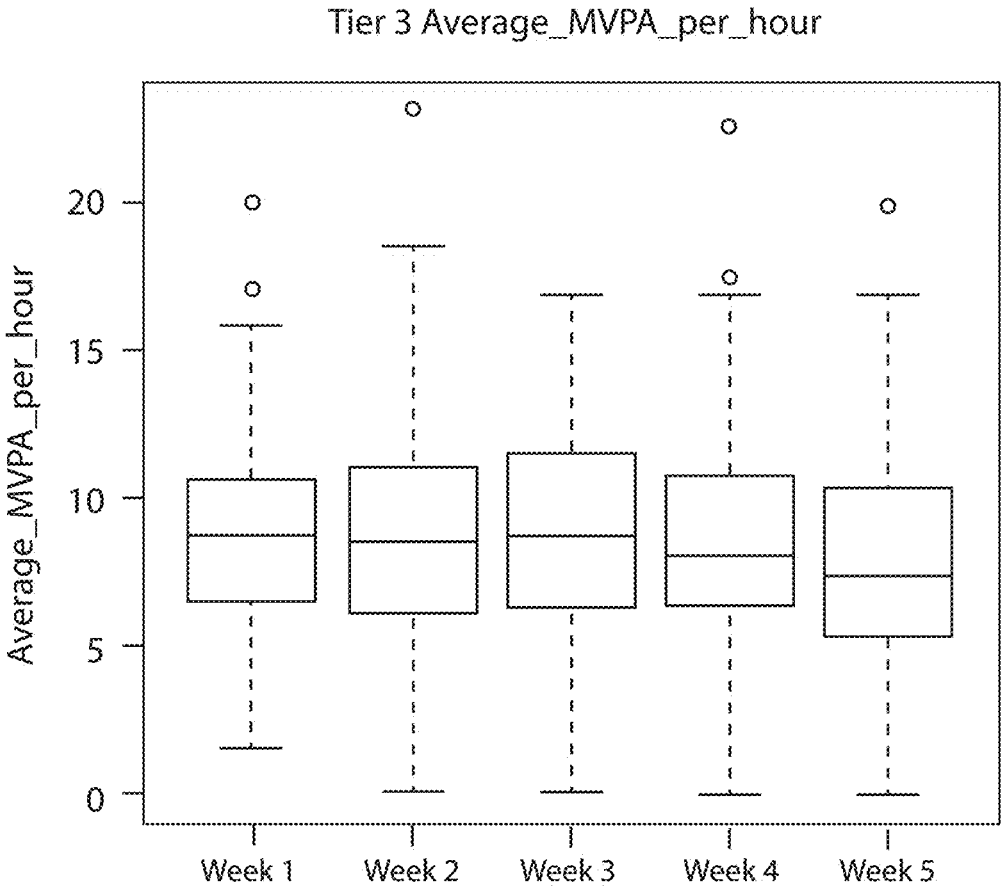

Tier 3 Average_MVPA_per_hour
Average_MVPA_per_hour
0
5
10
15
20
Week 1
Week 2
Week 3
Week 4
Week 5

Fig. 9C

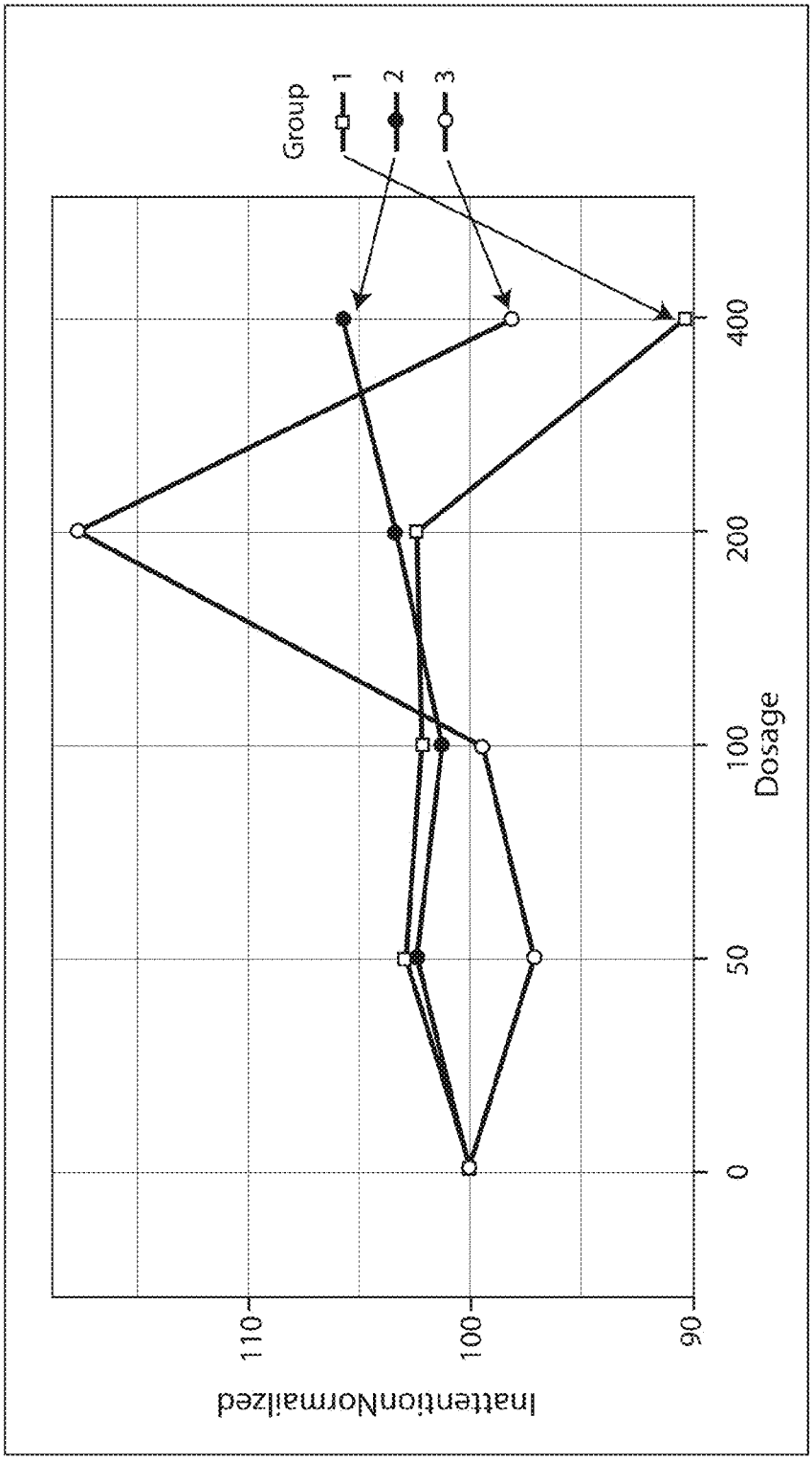

Group
1
2
3
InattentionNormalized
110
100
90
0
50
100
200
400
Dosage

Fig. 10

NONSELECTIVE METABOTROPIC GLUTAMATE RECEPTOR ACTIVATORS FOR TREATMENT OF ATTENTION DEFICIT DISORDER AND 22Q SYNDROME

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to the following four United States Provisional Patent Applications, each filed on Sep. 8, 2015: 62/215,628; 62/215,633; 62/215,636; and 62/215,673, each of which is incorporated herein by reference in its entirety.

FIELD

[0002] This application relates to treating attention deficit hyperactivity disorder (ADHD) and 22q syndrome with a nonselective activator of metabotropic glutamate receptors, for example, in subjects having a genetic alteration in at least one metabotropic glutamate receptor (mGluR) network gene.

BACKGROUND

[0003] Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder that may cause significant impairment in childhood and later life. Symptoms of ADHD include inattentiveness, hyperactivity, and impulsivity.

[0004] We previously conducted a large-scale, genome-wide study comparing copy number variations (CNVs) in about 3500 ADHD cases compared to about 13,000 controls, and found that CNVs in genes coding for metabotropic glutamate receptors (mGluR proteins or GRM genes) as well as CNVs in genes coding for proteins that interact with mGluRs occur significantly more frequently in ADHD cases compared to controls. (See WO 2012/027491 and US 2013/0203814; Elia et al., Nature Genetics, 44(1): 78-84 (2012).) The frequency of each individual genetic alteration appears to be quite rare. But collectively, about 11% or more of ADHD cases compared to about 1% of controls have at least one genetic alteration in a gene coding for an mGluR network protein. Thus, ADHD patients are about 10 times more likely than control individuals to have a genetic alteration affecting one or more mGluR network genes. Furthermore, a network analysis of the mGluR pathway in the European American population of approximately 1000 cases and 4000 controls showed that copy number variations (CNVs) in genes coding for proteins involved in mGluR signaling pathways and their interacting proteins impact about 20% of ADHD cases compared to controls.

[0005] There is no cure for ADHD, but the symptoms can be managed by combinations of behavior therapy and medications. Currently approved therapeutics for ADHD include several stimulant and non-stimulant drugs. Current medications are not ideal, especially stimulants, because they have a number of possibly harmful side effects and have short half-lives of activity. Moreover, stimulants are often misused and abused by qualifying and non-qualifying patients alike. Hence, additional ADHD medications are needed. In addition, given the genetic heterogeneity of ADHD patients, tailoring certain medication schemes to patients based on their underlying genetic profile may also improve ADHD treatment.

[0006] The inventors have conducted a clinical trial testing a nonselective activator of mGluR proteins called NFC-1 or fasoracetam monohydrate in pediatric ADHD patients who have at least one genetic alteration in a gene coding for an mGluR network protein.

[0007] This trial also included ADHD patients who have 22q syndromes, which are characterized by either a deletion (22q deletion syndrome) or duplication (22q duplication syndrome) in the 22q11.2 region of chromosome 22. Those syndromes may occur in at least about 1 out of every 2000-4000 children and may involve disruptions in as many as 30-40 genes. Among the genes that may be affected is RANBP1, an mGluR network gene. Children with a deletion or duplication at 22q11.2 have a higher than average rate of psychiatric disorders including ADHD, autism spectrum (ASD), and anxiety disorder, and a significant percentage may develop psychoses such as schizophrenia later in life. Children with a deletion or duplication of that region may also suffer from various intellectual disabilities.

[0008] Treatment of psychiatric symptoms in 22q syndrome patients may be complicated due to the physical abnormalities of these patients, including cardiac anomalies. For example, it may be necessary to avoid use of otherwise widely-prescribed stimulant drugs due to their negative side effects in the 22q syndrome population. Thus, improved therapeutic treatments are particularly needed for patients with ADHD, ASD, anxiety disorder or other conditions who have an underlying 22q genetic syndrome.

SUMMARY

[0009] Provided herein are methods of treating attention deficit hyperactivity disorder (ADHD) in a subject comprising administering a therapeutically effective amount of a nonselective metabotropic glutamate receptor (mGluR) activator to a subject, thereby treating ADHD.

[0010] Also provided are methods of treating attention deficit hyperactivity disorder (ADHD) in a subject comprising administering a therapeutically effective amount of a nonselective metabotropic glutamate receptor (mGluR) activator to a subject having at least one genetic alteration in an mGluR network gene, thereby treating ADHD.

[0011] Further provided herein are methods of treating ADHD in a subject comprising administering a nonselective mGluR activator to a subject with ADHD in an amount or dosage regime shown to be effective to result in a clinical general impression—improvement (CGI-I) score of 1 or 2 after at least four weeks of treatment and/or an improvement of at least 25%, such as at least 30%, at least 35%, or at least 40%, in an ADHD rating scale score after at least four weeks of treatment in a majority of subjects of at least one clinical trial.

[0012] In some embodiments, the subject has genetic alterations in at least one mGluR network gene. In some embodiments, the subject has genetic alterations in at least two mGluR network genes.

[0013] In some embodiments, the subject is a pediatric or adolescent subject, such as a subject between the ages of 5 and 17, 8 and 17, 5 and 12, 5 and 8, 8 and 12, 12 and 18, 13 and 18, or 12 and 17. In other embodiments, the subject is an adult.

[0014] In some embodiments, the nonselective mGluR activator is fasoracetam, such as fasoracetam monohydrate (NFC-1).

[0015] In some embodiments where the activator is fasoracetam, the fasoracetam is administered at a dose of 50-400 mg, such as 100-400 mg, or 100-200 mg, or 200-400 mg, or

100 mg, or 200 mg, or 300 mg, or 400 mg, and the dose is administered once, twice, or three times daily. In some embodiments, the fasoracetam is administered at a dose of 100 mg, 200 mg, 300 mg, or 400 mg twice daily, such as 100-200 mg twice daily.

[0016] In some embodiments, of the ADHD treatment methods above, the activator is administered in combination with a stimulant, such as methylphenidate, dexmethylphenidate, amphetamine, dextroamphetamine, or lisdexamphetamine; and/or in combination with a nonstimulant, such as atomoxetine, clonidine, or guanfacine; and/or in combination with an antidepressant, such as fluoxetine, escitalopram, bupropion, mirtazapine, amitriptyline, imipramine, venlafaxine, sertraline, paroxetine, tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, norepinephrine and dopamine reuptake inhibitors, or monoamine oxidase inhibitors; and/or in combination with an anxiolytic, such as barbiturates, pregabalin, or benzodiazepines, including chlordiazepoxide, clorazepate, diazepam, flurazepam, halazepam, prazepam, lorazepam, lormetazepam, oxazepam, temazepam, clonazepam, flunitrazepam, nimetazepam, nitrazepam, adinazolam, alprazolam, estazolam, triazolam, climazolam, loprazolam, or midazolam; and/or in combination with an anti-psychotic, such as aripiprazole or risperidone; and/or in combination with a beta blocker, such as acebutolol, atenolol, betaxolol, bisoprolol, esmolol, nebivolol, metoprolol, cartelol, penbutolol, pindolol, carvedilol, labetalol, levobunolol, metipranolol, nadolol, propranolol, sotalol, or timolol.

[0017] In some embodiments, the activator is administered in combination with non-pharmaceutical therapy, such as brain stimulation, for example vagus nerve stimulation, repetitive transcranial magnetic stimulation, magnetic seizure therapy, and/or deep brain stimulation.

[0018] In some embodiments, the ADHD subject has at least one co-morbid phenotype or condition such as oppositional defiant disorder (ODD), anxiety disorder, conduct disorder, Tourette's syndrome, autism, difficulty controlling anger, disruptive behavior, obsessive compulsive disorder (OCD), dermatillomania, a developmental disorder, or a movement disorder. In some embodiments, the ADHD subject has 22q deletion or duplication syndrome. In some embodiments, the subject does not have at least one or does not have any of ODD, anxiety disorder, conduct disorder, Tourette's syndrome, autism, 22q deletion or duplication syndrome, difficulty controlling anger, disruptive behavior, obsessive compulsive disorder (OCD), dermatillomania, a developmental disorder, or a movement disorder. In some embodiments, the subject has ODD. In some such embodiments, the method treats ODD in the subject, for example by reducing symptoms of argumentativeness and defiance, vindictiveness, and/or anger and irritability. In some embodiments, the ADHD subject has a co-morbid phenotype such as a mood disorder or sleep disorder such as insomnia. In some cases, the method treats the mood or sleep disorder, such as by reducing its symptoms. In some embodiments, the subject has a co-morbid symptom such as difficultly controlling anger and/or disruptive behavior. In some cases, the method reduces one or both of those symptoms. In some embodiments, the subject has co-morbid symptoms of anxiety and in some cases, the method reduces anxiety symptoms. In some embodiments, the subject has OCD and in some cases, the method reduces OCD symptoms. In some cases, the subject has co-morbid symptoms of dermatillomania, such as excessive skin picking, and the method reduces those symptoms. In some embodiments, the subject has one or more co-morbid developmental disorders, and in some cases, the method reduces the severity of symptoms related to the developmental disorders.

[0019] In some embodiments, the methods may reduce behavioral symptoms of ADHD such as inattentiveness, hyperactivity, and/or impulsiveness. In some embodiments, the methods also comprise assessing symptoms such as inattentiveness, hyperactivity, and/or impulsiveness during or after administration, for example, to determine if one or more of those symptoms have been reduced in the subject. In some methods, such assessment may be performed based on an ADHD rating scale or based on a clinical global impression (CGI) scale, e.g. a CGI-severity or CGI-improvement scale. For example, in some embodiments, the methods further comprise obtaining a clinical global impression of severity or improvement for the subject during or after administration. In some embodiments, the methods may improve clinical global improvement scores and/or ADHD rating scale scores in the subject. In some cases, symptoms may be reduced after at least 1 week, at least 2 weeks, at least 3 weeks, or at least 4 weeks of treatment with the activator.

[0020] In some embodiments of the above ADHD treatment methods, the subject has at least one genetic alteration in an mGluR network gene, such as a point mutation, insertion, deletion, or copy number variation (CNV). In some embodiments, the subject has a genetic alteration in two or more mGluR network genes. In some embodiments, the genetic alteration is detected by a process comprising a genetic test comprising obtaining a sample from the subject, optionally isolating nucleic acid from the sample, optionally amplifying the nucleic acid, and analyzing the nucleic acid for a genetic alteration in at least one mGluR network gene.

[0021] In some embodiments, the treatment method further comprises obtaining results of the genetic test prior to initial administration of the activator. In some embodiments, the genetic test comprises analyzing the nucleic acid for a CNV or SNV in at least 5, 6, 7, 8, 9, 10, 15, 20, 30, 40, 50, 60, 70, or all Tier 1 mGluR network genes (FIG. **1** herein).

[0022] In some embodiments, the genetic test comprises analyzing the nucleic acid for a CNV or SNV in at least 5, 10, 20, 30, 50, 100, 150, 175, or all Tier 2 mGluR network genes (FIG. **2**). In some embodiments, the method comprises analyzing the nucleic acid for a CNV or SNV in at least 5, 10, 20, 50, 100, 200 300, 400, 500, or all Tier 3 mGluR network genes (FIG. **3**). In some embodiments, the genetic test does not assess CNVs or SNVs in one or more of GRM1, GRM2, GRM3, GRM4, GRM5, GRM6, GRM7 or GRM8. In some embodiments, the subject does not have a CNV or SNV in one or more of GRM1, GRM2, GRM3, GRM4, GRM5, GRM6, GRM7 or GRM8.

[0023] Further provided herein is a method of treating ADHD in a subject comprising administering fasoracetam to the subject at a dose of 50-400 mg, such as 100-400 mg, or 100-200 mg, or 200-400 mg, or 100 mg, or 200 mg, or 300 mg, or 400 mg, wherein the dose is administered once, twice, or three times daily, thereby treating ADHD. In some such embodiments, the fasoracetam is administered at a dose of 100 mg, 200 mg, 300 mg, or 400 mg twice daily, such as 100-200 mg twice daily.

[0024] In some embodiments of the above ADHD treatment methods, the subject has at least one genetic alteration in an mGluR network gene, such as a point mutation, insertion, deletion, single nucleotide variation (SNV) or copy number variation (CNV). In some embodiments, the subject has a genetic alteration in two or more mGluR network genes. In some embodiments, the genetic alteration is detected by a process comprising a genetic test comprising obtaining a sample from the subject, optionally isolating nucleic acid from the sample, optionally amplifying the nucleic acid, and analyzing the nucleic acid for a genetic alteration in at least one mGluR network gene.

[0025] In some embodiments, the treatment method further comprises obtaining results of the genetic test prior to initial administration of the activator. In some embodiments, the genetic test comprises analyzing the nucleic acid for a CNV or SNV in at least 5, 6, 7, 8, 9, 10, 15, 20, 30, 40, 50, 60, 70, or all Tier 1 mGluR network genes (FIG. **1** herein). In some embodiments, the genetic test comprises analyzing the nucleic acid for a CNV or SNV in at least 5, 10, 20, 30, 50, 100, 150, 175, or all Tier 2 mGluR network genes (FIG. **2**).

[0026] In some embodiments, the method comprises analyzing the nucleic acid for a CNV or SNV in at least 5, 10, 20, 50, 100, 200 300, 400, 500, or all Tier 3 mGluR network genes (FIG. **3**). In some embodiments, the genetic test does not assess CNVs or SNVs in one or more of GRM1, GRM2, GRM6, GRM7 or GRM8.

[0027] In some embodiments, the ADHD subject has a genetic alteration, such as a CNV, in a Tier 1 or Tier 2 mGluR network gene but does not have a genetic alteration, such as a CNV, in a Tier 3 mGluR network gene. In some embodiments, the test utilizes a solid support, microarray, or chip containing appropriate probes to detect the presence of CNVs and/or SNVs in the genes.

[0028] In some embodiments, the subject is a pediatric or adolescent subject, such as a subject between the ages of 5 and 17, 8 and 17, 5 and 12, 5 and 8, 8 and 12, 12 and 18, 13 and 18, or 12 and 17. In other embodiments, the subject is an adult.

[0029] In some embodiments, the fasoracetam is administered in combination with a stimulant, such as methylphenidate, dexmethylphenidate, amphetamine, dextroamphetamine, or lisdexamphetamine; and/or in combination with a nonstimulant, such as atomoxetine, clonidine, or guanfacine; and/or in combination with an antidepressant, such as fluoxetine, escitalopram, bupropion, mirtazapine, amitriptyline, imipramine, venlafaxine, sertraline, paroxetine, tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, norepinephrine and dopamine reuptake inhibitors, or monoamine oxidase inhibitors; and/or in combination with an anxiolytic, such as barbiturates, pregabalin, or benzodiazepines, including chlordiazepoxide, clorazepate, diazepam, flurazepam, halazepam, prazepam, lorazepam, lormetazepam, oxazepam, temazepam, clonazepam, flunitrazepam, nimetazepam, nitrazepam, adinazolam, alprazolam, estazolam, triazolam, climazolam, loprazolam, or midazolam; and/or in combination with an anti-psychotic, such as aripiprazole or risperidone; and/or in combination with a beta blocker, such as acebutolol, atenolol, betaxolol, bisoprolol, esmolol, nebivolol, metoprolol, cartelol, penbutolol, pindolol, carvedilol, labetalol, levobunolol, metipranolol, nadolol, propranolol, sotalol, or timolol.

[0030] In some embodiments, the fasoracetam is administered in combination with non-pharmaceutical therapy, such as brain stimulation, for example vagus nerve stimulation, repetitive transcranial magnetic stimulation, magnetic seizure therapy, and/or deep brain stimulation.

[0031] In some embodiments, the ADHD subject has at least one co-morbid phenotype or condition such as oppositional defiant disorder (ODD), anxiety disorder, conduct disorder, Tourette's syndrome, autism, difficulty controlling anger, disruptive behavior, 22q deletion or duplication syndrome, difficulty controlling anger, disruptive behavior, obsessive compulsive disorder (OCD), dermatillomania, a developmental disorder, or a movement disorder. In some embodiments, the subject does not have at least one or does not have any co-morbid phenotype such as ODD, anxiety disorder, conduct disorder, Tourette's syndrome, autism, difficulty controlling anger, disruptive behavior, 22q deletion or duplication syndrome, difficulty controlling anger, disruptive behavior, obsessive compulsive disorder (OCD), dermatillomania, a developmental disorder, or a movement disorder.

[0032] In some embodiments, the subject has ODD. In some such embodiments, the method treats ODD in the subject, for example by reducing symptoms of argumentativeness and defiance, vindictiveness, and/or anger and irritability. In some embodiments, the subject has ODD and ADHD.

[0033] In some embodiments, the ADHD subject has a co-morbid phenotype such as a mood disorder or sleep disorder such as insomnia. In some cases, the method treats the mood or sleep disorder, such as by reducing its symptoms. In some embodiments, the subject has co-morbid symptoms of anxiety and in some cases, the method reduces anxiety symptoms. In some embodiments, the subject has OCD and in some cases, the method reduces OCD symptoms. In some cases, the subject has co-morbid symptoms of dermatillomania, such as excessive skin picking, and the method reduces those symptoms. In some embodiments, the subject has one or more co-morbid developmental disorders, and in some cases, the method reduces the severity of symptoms related to the developmental disorders.

[0034] For example, in some embodiments, the methods may reduce behavioral symptoms of ADHD such as inattentiveness, hyperactivity, and/or impulsiveness. In some embodiments, the methods also comprise assessing symptoms such as inattentiveness, hyperactivity, and/or impulsiveness during or after administration, for example, to determine if one or more of those symptoms have been reduced in the subject. In some methods, such assessment may be performed based on an ADHD rating scale or based on a clinical global impression (CGI) scale, e.g. a CGI-severity or CGI-improvement scale. For example, in some embodiments, the methods further comprise obtaining a clinical global impression of severity or improvement for the subject during or after administration. In some cases, symptoms may be reduced after at least 1 week, at least 2 weeks, at least 3 weeks, or at least 4 weeks of treatment with the activator.

[0035] In some embodiments, the methods may improve clinical global improvement scores and/or ADHD rating scale scores in the subject. For example, in any of the above ADHD treatment methods, the subject may have one or more of the following changes in symptoms after at least one, two, three, or four weeks of treatment with the activa-

tor: (a) the subject has symptoms of anger control and the anger control symptoms are reduced; (b) the subject has symptoms of disruptive behavior and the disruptive behavior symptoms are reduced; (c) the subject's CGI-I is reduced by at least 1 or by at least 2; (d) the subject's CGI-I score after one, two, three, or four weeks of treatment is 1 or 2; (e) the subject's CGI-S score after one, two, three, or four weeks of treatment is 1; (f) the subject's ADHD Rating Scale score is reduced by at least 25%, such as at least 30%, at least 35%, or at least 40%; (g) the subject has symptoms of inattentiveness and the inattentiveness symptoms are reduced; (h) the subject has symptoms of hyperactivity and the hyperactivity symptoms are reduced; (i) the subject has symptoms of impulsiveness and the impulsiveness symptoms are reduced; (j) the subject has symptoms of ODD such as anger and irritability, argumentation and defiance, and/or vindictiveness and the ODD symptoms are reduced; (k) the subject has symptoms of conduct disorder and the conduct disorder symptoms are reduced; (1) the subject has symptoms of anxiety and the anxiety symptoms are reduced; (m) the subject has symptoms of Tourette's syndrome, and the Tourette's syndrome symptoms are reduced; (n) the subject has symptoms of autism, and the autism symptoms are reduced; and (o) the subject has symptoms of movement disorder and the movement disorder symptoms are reduced.

[0036] In some embodiments where the ADHD subject has at least one genetic alteration in an mGluR network gene, the genetic alteration is detected by a process comprising a genetic test comprising obtaining a sample from the subject, optionally isolating nucleic acid from the sample, optionally amplifying the nucleic acid, and analyzing the nucleic acid for a genetic alteration in at least one mGluR network gene.

[0037] In some embodiments, the treatment method further comprises obtaining results of the genetic test prior to initial administration of the activator. In some embodiments, the genetic test comprises analyzing the nucleic acid for a CNV or SNV in at least 5, 6, 7, 8, 9, 10, 15, 20, 30, 40, 50, 60, 70, or all Tier 1 mGluR network genes (FIG. **1** herein).

[0038] In some embodiments, the genetic test comprises analyzing the nucleic acid for a CNV or SNV in at least 5, 10, 20, 30, 50, 100, 150, 175, or all Tier 2 mGluR network genes (FIG. **2**). In some embodiments, the method comprises analyzing the nucleic acid for a CNV or SNV in at least 5, 10, 20, 50, 100, 200 300, 400, 500, or all Tier 3 mGluR network genes (FIG. **3**).

[0039] In some embodiments, the genetic test does not assess CNVs or SNVs in one or more of GRM1, GRM2, GRM3, GRM4, GRM5, GRM6, GRM7 or GRM8. In some embodiments, the subject does not have a CNV or SNV in one or more of GRM1, GRM2, GRM3, GRM4, GRM5, GRM6, GRM7 or GRM8. In some embodiments, the ADHD subject has a genetic alteration, such as a CNV, in a Tier 1 or Tier 2 mGluR network gene but does not have a genetic alteration, such as a CNV, in a Tier 3 mGluR network gene.

[0040] Also provided herein are methods of treating 22q syndrome in a subject comprising administering an effective amount of a nonselective metabotropic glutamate receptor (mGluR) activator to a subject with 22q syndrome, thereby treating 22q syndrome. In some embodiments, the subject has a genetic alteration, such as a point mutation, insertion, deletion, or copy number variation (CNV) in the gene RANBP1. For example, the subject may have a deletion or a duplication at 22q11.2, i.e. a 22q deletion or 22q duplication syndrome. In some embodiments, provided methods comprise treating 22q deletion syndrome in a subject comprising administering an effective amount of a nonselective metabotropic glutamate receptor (mGluR) activator to a subject with 22q deletion syndrome, thereby treating 22q deletion syndrome.

[0041] In some embodiments, provided methods comprise treating 22q duplication syndrome in a subject comprising administering an effective amount of a nonselective metabotropic glutamate receptor (mGluR) activator to a subject with 22q duplication syndrome, thereby treating 22q deletion syndrome. In some embodiments, the subject has a genetic alteration in RANBP1 and in at least one further mGluR network gene, such as a Tier 1, Tier 2, or Tier 3 gene as disclosed herein in FIGS. **1-3**. In some embodiments, the subject does not have a CNV or a single nucleotide variation (SNV) in one or more of GRM1, GRM2, GRM3, GRM4, GRM5, GRM6, GRM7 or GRM8.

[0042] In some embodiments, the 22q syndrome subject has attention deficit hyperactivity disorder (ADHD), and treating the subject may comprise treating the ADHD, such as alleviating at least one ADHD symptom in the subject, including include inattentiveness, hyperactivity, and impulsivity. In some embodiments, the subject is a pediatric or adolescent subject, such as a subject between the ages of 5 and 17, 8 and 17, 5 and 12, 5 and 8, 8 and 12, 12 and 18, 13 and 18, or 12 and 17. In other embodiments, the subject is an adult.

[0043] In some embodiments, the nonselective mGluR activator is fasoracetam, such as fasoracetam monohydrate (NFC-1).

[0044] In some embodiments where the activator is fasoracetam, the fasoracetam is administered at a dose of 50-400 mg, such as 100-400 mg, or 100-200 mg, or 200-400 mg, or 100 mg, or 200 mg, or 300 mg, or 400 mg, and is administered once, twice, or three times daily. In some embodiments, the fasoracetam is administered at a dose of 100 mg, 200 mg, 300 mg, or 400 mg twice daily, such as 100-200 mg twice daily.

[0045] In some embodiments, the activator is administered in combination with another pharmaceutical agent, such as a stimulant, such as methylphenidate, dexmethylphenidate, amphetamine, dextroamphetamine, or lisdexamphetamine; and/or in combination with a nonstimulant, such as atomoxetine, clonidine, or guanfacine; and/or in combination with an antidepressant, such as fluoxetine, escitalopram, bupropion, mirtazapine, amitriptyline, imipramine, venlafaxine, sertraline, paroxetine, tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, norepinephrine and dopamine reuptake inhibitors, or monoamine oxidase inhibitors; and/or in combination with an anxiolytic, such as barbiturates, pregabalin, or benzodiazepines, including chlordiazepoxide, clorazepate, diazepam, flurazepam, halazepam, prazepam, lorazepam, lormetazepam, oxazepam, temazepam, clonazepam, flunitrazepam, nimetazepam, nitrazepam, adinazolam, alprazolam, estazolam, triazolam, climazolam, loprazolam, or midazolam; and/or in combination with an anti-psychotic, such as aripiprazole or risperidone; and/or in combination with a beta blocker, such as acebutolol, atenolol, betaxolol, bisoprolol, esmolol, nebivolol, metoprolol, cartelol, penbutolol, pindolol, carvedilol, labetalol, levobunolol, metipranolol, nadolol, propranolol, sotalol, or timolol.

[0046] In some embodiments, the activator is administered in combination with non-pharmaceutical therapy, such as brain stimulation, for example vagus nerve stimulation, repetitive transcranial magnetic stimulation, magnetic seizure therapy, and/or deep brain stimulation.

[0047] In some embodiments, the 22q deletion and/or duplication syndrome subject may have at least one co-morbid phenotype or condition such as oppositional defiant disorder (ODD), anxiety disorder, conduct disorder, Tourette's syndrome, autism, difficulty controlling anger, disruptive behavior, obsessive compulsive disorder (OCD), dermatillomania, a developmental disorder, or a movement disorder. In some embodiments, the subject does not have at least one of oppositional defiant disorder (ODD), anxiety disorder, conduct disorder, Tourette's syndrome, autism, difficulty controlling anger, disruptive behavior, obsessive compulsive disorder (OCD), dermatillomania, a developmental disorder, or a movement disorder, or in some embodiments, does not have any of those co-morbid conditions.

[0048] In some embodiments, wherein the 22q deletion and/or duplication subject has ADHD, the subject does not have at least one of ODD, conduct disorder, anxiety disorder, Tourette's syndrome, autism, difficulty controlling anger, disruptive behavior, obsessive compulsive disorder (OCD), dermatillomania, a developmental disorder, or a movement disorder. In some embodiments, the subject does not have any of ODD, conduct disorder, anxiety disorder, Tourette's syndrome, autism, difficulty controlling anger, disruptive behavior, obsessive compulsive disorder (OCD), dermatillomania, a developmental disorder, or a movement disorder. In some embodiments, the 22q deletion and/or duplication subject also has a mood disorder or a sleep disorder such as insomnia. In some such embodiments, the method treats the mood disorder or sleep disorder by, for example, reducing its symptoms. In some embodiments, the subject has ODD. In some such embodiments, the method treats ODD in the subject, for example by reducing symptoms of argumentativeness and defiance, vindictiveness, and/or anger and irritability. In some embodiments, the subject has co-morbid symptoms of anxiety and in some cases, the method reduces anxiety symptoms. In some embodiments, the subject has OCD and in some cases, the method reduces OCD symptoms. In some cases, the subject has co-morbid symptoms of dermatillomania, such as excessive skin picking, and the method reduces those symptoms. In some embodiments, the subject has one or more co-morbid developmental disorders, and in some cases, the method reduces the severity of symptoms related to the developmental disorders.

[0049] The 22q syndrome may be diagnosed in the subject by tests currently used to determine the presence of a 22q deletion or duplication. In some embodiments, a subject is diagnosed by a process comprising a genetic test to detect the presence or absence of a deletion or duplication at 22q11.2 and/or for the presence or absence of a genetic alteration in RANBP1 in a sample from the subject. In some embodiments, the method of treatment comprises obtaining results of a genetic test for 22q (such as for presence or absence of a deletion or duplication at 22q11.2 and/or for the presence or absence of a genetic alteration in RANBP1 in a sample from the subject) prior to initial administration of the activator. In some embodiments, the activator is administered in an amount or dosage regime shown to be effective to result in a clinical general impression-improvement (CGI-I) score of 1 or 2 after four weeks of treatment and/or an improvement of at least 25%, such as at least 30%, at least 35%, or at least 40%, in an ADHD rating scale score after four weeks of treatment in a majority of subjects of at least one clinical trial. In any of the above embodiments, the 22q syndrome may in some cases be deemed treated if neurobehavioral, neuropsychiatric and neurodevelopmental symptoms associated with 22q deletion and/or duplication syndrome are alleviated. Such symptoms include but are not limited to, improvements in memory, attention, cognition, anxiety, and stabilization or reversal of mood disorder, autism spectrum disorder, psychosis and hyperactivity. In any of the above embodiments, the 22q deletion and/or duplication syndrome may in some cases be deemed treated if at least one symptom of ADHD is improved in the subject. For example, in some embodiments, the methods may reduce behavioral symptoms such as inattentiveness, hyperactivity, and/or impulsiveness. In some embodiments, the methods also comprise assessing symptoms such as inattentiveness, hyperactivity, and/or impulsiveness as well as anger control and/or disruptive behaviors during or after administration, for example, to determine if one or more of those symptoms have been reduced in the subject. In some methods, such assessment may be performed based on an ADHD rating scale or based on a clinical global impression (CGI) scale, e.g. a CGI-severity or CGI-improvement scale. For example, in some embodiments, the methods further comprise obtaining a clinical global impression of severity or improvement for the subject during or after administration. In some embodiments, the methods may improve clinical global improvement scores and/or ADHD rating scale scores in the subject. For example, in any of the above 22q deletion and/or duplication syndrome treatment methods, the subject may have one or more of the following changes in symptoms after at least one, two, three, or four weeks of treatment with the activator: (a) the subject has symptoms of anger control and the anger control symptoms are reduced; (b) the subject has symptoms of disruptive behavior and the disruptive behavior symptoms are reduced; (c) the subject's CGI-I is reduced by at least 1 or by at least 2; (d) the subject's CGI-I score after one, two, three, or four weeks of treatment is 1 or 2; (e) the subject's CGI-S score after one, two, three, or four weeks of treatment is 1; (f) the subject's ADHD Rating Scale score is reduced by at least 25%, such as at least 30%, at least 35%, or at least 40%; (g) the subject has symptoms of inattentiveness and the inattentiveness symptoms are reduced; (h) the subject has symptoms of hyperactivity and the hyperactivity symptoms are reduced; (i) the subject has symptoms of impulsiveness and the impulsiveness symptoms are reduced; (j) the subject has symptoms of ODD such as anger and irritability, argumentation and defiance, and/or vindictiveness and the ODD symptoms are reduced; (k) the subject has symptoms of conduct disorder and the conduct disorder symptoms are reduced; (1) the subject has symptoms of anxiety and the anxiety symptoms are reduced; (m) the subject has symptoms of Tourette's syndrome, and the Tourette's syndrome symptoms are reduced; (n) the subject has symptoms of autism, and the autism symptoms are reduced; and (o) the subject has symptoms of movement disorder and the movement disorder symptoms are reduced.

[0050] Additional objects and advantages will be set forth in part in the description which follows, and in part will be

obvious from the description, or may be learned by practice. The objects and advantages will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims.

[0051] It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the claims.

[0052] The accompanying drawings, which are incorporated in and constitute a part of this specification, illustrate one (several) embodiment(s) and together with the description, serve to explain the principles described herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0053] FIGS. **1-1** to **1-4** show the mGluR network genes included in the Tier 1 gene set. These genes have 2 degrees of protein-protein interaction with mGluR genes (GRM1-8) based on the Cytoscape Human Interactome, which is software for integrating biomolecular interaction networks with high-throughput data (as described in Shannon P (2003) Genome Research 13:2498-2504). The Tier 1 gene set includes 76 genes. The exact location for each gene in Tier 1 is listed in both the Human Genome version 18 (hg18) and Human Genome version 19 (hg19). In addition, the exact gene location plus 500 kilobase (i.e., the range from 500 kilobase before and 500 kilobase after the gene of interest) is listed for hg19. The start single nucleotide polymorphism (StartSNP) (i.e., the SNP located 500 kilobases before the gene of interest) and the EndSNP (i.e., the SNP located 500 kilobases after the gene of interest) are also listed. Genes of the mGluRs themselves are noted as "GRM." The expanded regions (i.e., 500 kg up and down stream) frequently harbor regulatory elements and if impacted by a CNV, can have the same impact on the gene expression and function as a CNV residing in the gene sequence itself.

[0054] FIGS. **2-1** to **2-10** show the mGluR network genes included in the Tier 2 gene set. These genes have 2 degrees of protein-protein interaction with mGluR genes (GRM1-8) based on the Cytoscape Human Interactome but exclude genes from Tier 1. The Tier 2 gene set includes 197 genes. The exact location for each gene in Tier 2 is listed in both the Human Genome version 18 (hg18) and Human Genome version 19 (hg19). In addition, the exact gene location plus 500 kilobase (i.e., the range from 500 kilobase before and 500 kilobase after the gene of interest) is listed for hg19. The start single nucleotide polymorphism (StartSNP) (i.e., the SNP located 500 kilobases before the gene of interest) and the EndSNP (i.e., the SNP located 500 kilobases after the gene of interest) in hg19 are also listed.

[0055] FIGS. **3-1** to **3-29** show genes within the Tier 3 gene set. Genes with reciprocal gene querying with 2 degrees of protein-protein interaction with mGluR genes based on Cytoscape Human Interactome are included. Genes contained within Tiers 1 and 2 are excluded from Tier 3. The Tier 3 gene set includes 599 genes. The exact location for each gene in Tier 3 is listed in both the Human Genome version 18 (hg18) and Human Genome version 19 (hg19). In addition, the exact gene location plus 500 kilobase (i.e., the range from 500 kilobase before and 500 kilobase after the gene of interest) is listed for hg19. The StartSNP (i.e., the SNP located 500 kilobases before the gene of interest) and the EndSNP (i.e., the SNP located 500 kilobases after the gene of interest) in hg19 are also listed.

[0056] FIG. **4** shows the percentages of subjects the Phase Ib clinical trial described in Example 1 considered to be responders to NFC-1 based on having a clinical global impression-improvement (CGI-I) score of 1 or 2 (much improved or very much improved) at each week of the dose escalation phase of the clinical trial from week 1 (placebo baseline) to week 5, both based on the overall study population and based on genetic Tier (1, 2, or 3).

[0057] FIGS. **5***a* and **5***b* show the percent of clinical trial subjects showing improvement in Vanderbilt ADHD scores each week compared to either pre-study baseline (FIG. **5***a*) or placebo baseline (week 1) (FIG. **5***b*) both by genetic Tier and by the overall study population. An at least 25% decrease in Vanderbilt ADHD score is considered responsive and an improvement.

[0058] FIGS. **6***a* and **6***b* show the percent of clinical trial subjects showing robust improvement in Vanderbilt ADHD scores each week compared to either pre-study baseline (FIG. **6***a*) or placebo baseline (week 1) (FIG. **6***b*) both by genetic tier and by the overall study population. An at least 40% decrease in Vanderbilt ADHD score is considered a robust improvement.

[0059] FIGS. **7***a* and **7***b* show the percent of clinical trial subjects who completed the full dose escalation to 400 mg twice daily NFC-1 at week 5 that showed improvement in Vanderbilt ADHD scores each week compared to either pre-study baseline (FIG. **7***a*) or placebo baseline (week 1) (FIG. **7***b*) both by genetic tier and by the overall study population. An at least 25% decrease in Vanderbilt ADHD score is considered an improvement.

[0060] FIGS. **8***a* and **8***b* show the percent of clinical trial subjects who completed the full dose escalation to 400 mg twice daily NFC-1 at week 5 that showed robust improvement in Vanderbilt ADHD scores each week compared to either pre-study baseline (FIG. **8***a*) or placebo baseline (week 1) (FIG. **8***b*) both by genetic tier and by the overall study population. An at least 40% decrease in Vanderbilt ADHD score is considered a robust improvement.

[0061] FIGS. **9***a*, **9***b*, and **9***c* show results from actigraphy tests in the subjects of the clinical trial by genetic tier group. The observed reduction in moderate to vigorous physical activity (MVPA) from week 1 (placebo) to week 5 for genetic Tier-1 (FIG. **9***a*); genetic Tier-2 (FIG. **9***b*); and genetic Tier-3 (FIG. **9***c*) was most prominent in 400 mg bid dose group.

[0062] FIG. **10** shows that clinical trial subjects in the Tier-1 genetic group had significant improvement in the QUOTIENT® ADHD test's measure of inattention between week 1 (placebo) and week 5 (400 mg twice daily) as shown by reduction in inattention in the Tier-1 group ($P<0.05$) from a normalized inattention value of just over 100 to about 90 between weeks 4 (200 mg twice daily) and 5 (400 mg twice daily) of the dose escalation.

DESCRIPTION OF THE EMBODIMENTS

I. Definitions

[0063] In addition to definitions included in this subsection, further definitions of terms are interspersed throughout the text.

[0064] In this invention, "a" or "an" means "at least one" or "one or more," etc., unless clearly indicated otherwise by context. The term "or" means "and/or" unless stated other-

wise. In the case of a multiple-dependent claim, however, use of the term "or" refers back to more than one preceding claim in the alternative only.

[0065] An "mGluR" or metabotropic glutamate receptor refers to one of eight glutamate receptors expressed in neural tissue named mGluR1, mGluR2, mGluR3, mGluR4, mGluR5, mGluR6, mGluR7, and mGluR8. Their genes are abbreviated GRM1 to GRM8. The mGluR proteins are G-protein-coupled receptors. They are typically placed into three sub-groups, Group I receptors including mGluR1 and mGluR5 are classed as slow excitatory receptors. Group II includes mGluR2 and mGluR3. Group III includes mGluR4, mGluR6, mGluR7, and mGluR8. Groups II and III are classed as slow inhibitory receptors. The mGluRs are distinguished from the ionotropic GluRs or iGluRs, which are ion channel-associated glutamate receptors and are classed as fast excitatory receptors.

[0066] An "mGluR network gene," for purposes of this invention, comprises not only the mGluR genes GRM1, GRM2, GRM3, GRM4, GRM5, GRM6, GRM7, and GRM8, but also each of the other genes listed herein in FIGS. **1-3** as well as the regions of DNA that regulate the genes listed in FIGS. **1-3**. In addition, "mGluR network proteins" are the proteins encoded by the mGluR network genes.

[0067] The mGluR network genes are grouped into three subsets: Tier 1, Tier 2, and Tier 3. (See FIGS. **1-3**.) Tier 1 mGluR network genes, shown in FIG. **1**, comprise 76 genes, including some GRM genes themselves as well as a number of other genes. The Tier 2 mGluR network genes, shown in FIG. **2**, comprise 197 genes, and exclude the Tier 1 genes.

[0068] Tiers 1 and 2 together are included in the "primary mGluR network." The "primary network" of mGluR genes also includes the genes 4-Sep, LOC642393, and LOC653098, for a total of 276 genes. There are presently technical difficulties in assessing the 4-Sep, LOC642393, and LOC653098 genes. Thus, they are not included in Tiers 1 and 2, although they are included in the primary network of genes of the present invention. The genes of Tier 1 and Tier 2 differ in that alterations in Tier 1 genes had been documented in previous genotyping studies of subjects suffering from mental disorders.

[0069] Tier 3 mGluR network genes, shown in FIG. **3**, comprise 599 genes that are in the distal part of the mGluR network based on the merged human interactome provided by the Cytoscape Software (Shannon P et al. (2003) Genome Research 13:2498-2504), and exclude the Tier 1 and Tier 2 genes. The Tier 3 genes are thus part of the "distal mGluR network." In addition to the Tier 3 genes, the genes LOC285147, LOC147004, and LOC93444 are included in the "distal mGluR network," although they were not assessed in the present study and are not included in Tier 3 due to technical difficulties.

[0070] A "genetic alteration" as used herein means any alteration in the DNA of a gene, or in the DNA regulating a gene, that, for example, may result in a gene product that is functionally changed as compared to a gene product produced from a non-altered DNA. A function change may be differing expression levels (up-regulation or down-regulation) or loss or change in one or more biological activities, for example. A genetic alteration includes without limitation, copy number variations (CNVs), single nucleotide variations (SNVs) (also called single nucleotide polymorphisms (SNPs) herein), frame shift mutations, or any other base pair substitutions, insertions, and deletions.

[0071] A "copy number variation" or "CNV" is a duplication or deletion of a DNA segment encompassing a gene, genes, segment of a gene, or DNA region regulating a gene, as compared to a reference genome. In some embodiments, a CNV is determined based on variation from a normal diploid state. In some embodiments, a CNV represents a copy number change involving a DNA fragment that is 1 kilobase (kb) or larger. CNVs described herein do not include those variants that arise from the insertion/deletion of transposable elements (e.g., 6-kb KpnI repeats). The term CNV therefore encompasses terms such as large-scale copy number variants (LCVs; Iafrate et al. 2004), copy number polymorphisms (CNPs; Sebat et al. 2004), and intermediate-sized variants (ISVs; Tuzun et al. 2005), but not retrotransposon insertions.

[0072] A "CNV deletion" or "deletion CNV" or similar terms refer to a CNV in which a gene or gene segment is deleted. A "CNV duplication" or "duplication CNV" or similar terms refer to a CNV in which a gene or gene segment is present in at least two, and possibly more than two, copies in comparison with the single copy found in a normal reference genome.

[0073] A "sample" refers to a sample from a subject that may be tested, for example, for presence of a CNV in one or more mGluR network proteins, as described herein. The sample may comprise cells, and it may comprise body fluids, such as blood, serum, plasma, cerebral spinal fluid, urine, saliva, tears, pleural fluid, and the like.

[0074] As used herein "22q syndrome" and "22q11.2 syndrome" are used interchangeably.

[0075] The terms "pediatric subject" or "pediatric patient" are used interchangeably to refer to a human less than 18 years of age. An "adult patient" or "adult subject" refers to a human 18 years of age or older. An "adolescent patient" or "adolescent subject" is typically about 12 to 18, such as 12 to 17 or 13 to 18, years old.

II. Attention Deficit Hyperactivity Disorder (ADHD)

[0076] The term "attention deficit hyperactivity disorder" or ADHD refers to a heterogeneous disorder that may be characterized at least in part by inattentiveness, hyperactivity, and impulsiveness. Symptoms of ADHD include difficulty staying focused and paying attention, difficulty controlling behavior, and hyperactivity. According to the Diagnostic and Statistical Manual of Mental Disorders, 5th Ed., (DSM-5), a physician may diagnose ADHD when a subject shows a persistent pattern of inattentiveness or hyperactivity-impulsiveness that interferes with the subject's functioning or development. ADHD may occur in at least 5% of the population and may be diagnosed in both adult and pediatric subjects.

[0077] There are three classes of ADHD: predominantly hyperactive-impulsive, predominantly inattentive, and combined hyperactive-impulsive and inattentive. Predominantly hyperactive-impulsive patients have more pronounced hyperactivity-impulsivity than inattention. Predominantly inattentive patients lack attention, but they have fewer symptoms of hyperactivity-impulsivity; these patients may be able to sit quietly in classroom setting but are not paying attention to the task that they are supposed to be performing. Combined hyperactive-impulsive and inattentive patients

have significant symptoms of both inattention and hyperactivity-impulsivity. Combined ADHD is the most common type in children. Each of the methods described herein encompass treatment of all classes of ADHD.

[0078] ADHD is a heterogeneous condition and may result from a combination of factors, such as genes, environmental factors, and/or brain injuries. In addition, ADHD patients are significantly more likely than normal individuals to have a genetic alteration such as a CNV in at least one mGluR network gene. (See WO 2012/027491 and US 2013/0203814; Elia et al., Nature Genetics, 44(1): 78-84 (2012).)

[0079] Currently approved therapeutics for ADHD include stimulant drugs, such as methylphenidate and amphetamines, as well as non-stimulant drugs, such as atomoxetine. Antidepressants may also be given in some cases, such as serotonin selective uptake inhibitors, e.g. fluoxetine, sertraline, and citalopram, as well as clonidine and guanfacine. These medications, however, may have a number of possible side effects and some also have short half-lives of activity.

[0080] Some subjects with ADHD may have one or more co-morbid disorders such as oppositional defiant disorder (ODD), anxiety disorder, a mood disorder, a phobia, obsessive compulsive disorder (OCD), depression, conduct disorder, Tourette's syndrome, autism, or a movement disorder. In other cases, an ADHD subject does not have any of ODD, anxiety disorder, a mood disorder, a phobia, obsessive compulsive disorder (OCD), depression, conduct disorder, Tourette's syndrome, autism, or a movement disorder. Some subjects with ADHD may also show mood disorders or sleep disorders such as insomnia.

[0081] About 40% of pediatric ADHD patients, for example, also have ODD, and some ADHD medications are believed to improve ODD symptoms as part of treating ADHD. According to the DSM-5, a subject may be diagnosed with ODD if the subject shows at least four symptoms indicative of an angry and irritable mood, argumentative and defiant behavior, or vindictiveness that occur with at least one non-sibling individual, that cause significant problems at work, school, or at home, and that persist for at least six months. Symptoms indicative of an angry and irritable mood include: often loses temper, is often touchy or easily annoyed by others, is often angry and resentful. Symptoms indicative of argumentative and defiant behavior include: often argues with adults or people in authority, often actively defies or refuses to comply with adults' requests or rules, often deliberately annoys people, and often blames others for his/her own mistakes or misbehavior. Symptoms indicative of vindictiveness include: is often spiteful or vindictive, and has shown spiteful or vindictive behavior at least twice within the past six months. The symptoms must occur on their own and not as part of the course of another mental health problem such as substance abuse, depression, or bi-polar disorder. Individuals 5 years and older may be diagnosed with ODD if the symptoms occur at least once per week for at least six months. Accordingly, a subject with "ODD" is defined herein as one who has been diagnosed as having ODD based on the above DSM-5 criteria.

[0082] Subjects with ADHD may also show a variety of additional behavioral phenotypes such as difficulty controlling anger and disruptive behaviors whether or not the subjects have been diagnosed with a co-morbid disorder.

[0083] Other co-morbid disorders that an ADHD subject may suffer from include obsessive compulsive disorder (OCD), a developmental disorder, or dermatillomania. "Developmental disorders" herein include, for example, those classified under the International Classification of Diseases 9th Ed. (World Health Organization) under codes 299.80, 299.90, 315.2, 315.39, 315.4, 315.5, 315.8, and 315.9, and may affect behaviors such as learning, coordination, and speech. "Dermatillomania" is also called skin picking disorder or excoriation, and is a disorder involving excessive picking at one's own skin to the extent of causing damage, and includes picking at normal skin as well as at real or imagined skin defects such as moles, freckles, or acne.

III. 22q Syndromes

[0084] The terms "22q syndrome" or "22q11 syndrome" or "22q11.2 syndrome" are used interchangeably herein to refer to subjects whose genomes have a CNV in the q11.2 region of chromosome 22 that includes the RANBP1 mGluR network gene locus. RANBP1 encodes a protein that interacts with mGluR3. A subject with "22q deletion syndrome" or "22qDS" or "22q11.2DS" has a deletion in that region of the chromosome while a subject with "22q duplication syndrome" or "22qDupS" or "22q11.2DupS" has a duplication in that region.

[0085] Deletion of a small piece of chromosome 22 at q11.2 that includes the RANBP1 mGluR network gene locus is called "22q deletion syndrome" or "22q11.2DS." A 22q deletion frequently involves loss of approximately 30 to 40 genes including RANBP1 and may be characterized by heart defects, cleft palate, and distinctive facial features, as well as a low intellectual level. About 37% of children with 22q11.2DS are also diagnosed with ADHD. Children with 22q11.2DS also have high rates of autism spectrum (ASD) and anxiety disorder, and a significant percentage may develop psychoses such as schizophrenia later in life. 22q11.2DS occurs in about 1 out of every 2000-4000 people, although this may be an under-estimate as mild cases may not always be diagnosed. Before the genetic basis of 22q11.2DS was understood, different groupings of symptoms of 22q11.2DS were previously called DiGeorge syndrome, velocardiofacial syndrome, and conotruncal anomaly face syndrome.

[0086] Duplication at position q11.2 on chromosome 22, including the RANBP1 locus, is called "22q duplication syndrome," "22q11.2 duplication syndrome" or "22q11.2DupS," and may be characterized by intellectual/learning disability, delayed psychomotor development, growth retardation, and muscular hypotonia. The piece of chromosome 22 that is duplicated in 22q.11.2DupS if often the same one that is frequently deleted in 22q11.2DS, involving 30-40 genes. The incidence of 22q11.2DupS in patients referred for genomic microarray analysis to investigate developmental delays or intellectual disability is about 1 in 300-700.

[0087] Available diagnostic tests for 22q11.2DS include targeted variant analysis (which looks for variants in a panel of targets), fluorescence in situ hybridization (FISH), and sequence coding of the entire coding region. Available diagnostic tests for 22q11.2DupS include chromosomal microarray and FISH methodology

IV. The mGluR Network Genes

[0088] In some embodiments herein, ADHD patients may be evaluated prior to treatment for a genetic alteration in one or more of the Tier 1, 2, and/or 3 mGluR network genes, such as single gene or a panel of such genes. In some

embodiments, the genetic alteration is a copy number variation (CNV), resulting from a duplication or other multiplication of one or both copies of the gene or a deletion of one or both copies of the gene. A CNV deletion or duplication can alter the expression of a resulting gene product contained within the CNV because of the change in copy number of this gene, and may therefore contribute to a disease phenotype. However, a CNV deletion or duplication may also have no effect on relative expression of gene products in any tissue (see Henrichsen C N et al. (2009) Human Molecular Genetics, 2009, Vol. 18(1):R1-R8). A CNV deletion or duplication may also affect the expression of genes located in the vicinity of the CNV, such that expression of genes outside of the actual CNV may also be affected. A CNV can also influence gene expression through perturbation of transcript structure; for example, a duplication CNV may lead to an increase in copy number but may actually lead to a decrease in gene product due to interference with normal transcription.

[0089] In some embodiments, ADHD patients are treated who have at least one genetic alteration, such as at least one CNV in an mGluR network gene, such as in a Tier1, Tier2, and/or Tier3 gene as shown in FIGS. **1-3**. In some embodiments, the patient has a genetic alteration, such as a CNV, such as a deletion or duplication that includes the gene RANBP1, a gene that may be deleted or duplicated in 22q syndromes.

[0090] In some embodiments, gene sets or panels of mGluR network genes are used for analyzing samples from patients with suspected ADHD or 22q deletion and/or duplication syndromes. In some embodiments, the presence of genetic alterations such as CNV duplications or deletions within these gene sets or panels is determined. In some embodiments, genetic alterations such as CNVs in the Tier 1 genes shown in FIG. **1** are determined. In some embodiments a panel of at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, or all of the Tier 1 genes is evaluated for the presence of genetic alterations such as CNVs. Within those embodiments, in some embodiments the panel includes specific genes such as RANBP1 or GRM1-8. Within any such panel of genes, any individual, specific Tier 1 genes may also be excluded from the panel. For instance, in some embodiments, one or more of the GRM1-8 genes are not included in the panel.

[0091] In some embodiments, the Tier 2 genes as shown in FIG. **2** are analyzed for the presence of genetic alterations such as CNVs, optionally in addition to evaluation of the above Tier 1 evaluations or in addition to evaluations of subsets of the Tier 1 genes as described above. In some embodiments, at least 50 Tier 2 genes are evaluated, while in some embodiments, at least 10, 20, 30, 50, 100, 150, or all of the Tier 2 genes are evaluated. Individual, specific Tier 2 genes may be excluded from the gene set for evaluation in some embodiments.

[0092] In some embodiments, the 599 Tier 3 genes shown in FIG. **3** are evaluated for genetic alterations such as CNVs, optionally in addition to evaluation of the above Tier 1 and/or Tier 2 evaluations or in addition to evaluations of subsets of the Tier 1 and/or Tier 2 genes as described above. Tier 3 genes are considered a wide range of potential interactors with the mGluR network, and genes contained within Tier 3 are not contained in Tier 1 and Tier 2. In some embodiments, at least 10, 20, 50, 100, 200, 300, 400, 500 or all of the Tier 3 genes are included in a panel to evaluate genetic alterations.

V. Evaluation of Genetic Alterations in mGluR Network Genes

[0093] Any biological sample may be used to determine the presence or absence of mGluR network gene alterations, including, but not limited to, blood, urine, serum, gastric lavage, CNS fluid, any type of cell (such as brain cells, white blood cells, mononuclear cells) or body tissue. Any biological source material whereby DNA can be extracted may be used to determine the presence or absence of mGluR network gene alterations. Samples may be freshly collected, or samples may have been previously collected for any use/purpose and stored until the time of testing for genetic alterations. DNA that was previously purified for a different purpose may also be used.

[0094] Various methods for determining genetic alterations are known, including the following:

A. Single Nucleotide Variation (SNV)/Single Nucleotide Polymorphism (SNP) Genotyping

[0095] Determining whether a patient has a genetic alteration, such as a CNV, in a mGluR network gene may be done by SNV/SNP Genotyping, using a SNV/SNP genotyping array such as those commercially available from Illumina or Affymetrix. A "single nucleotide variation (SNV)," also interchangeably referred to as a "single nucleotide polymorphism (SNP)" herein, refers to a change in which a single base in the DNA differs from the usual base at that position. Millions of SNVs have been cataloged in the human genome. Some SNVs are normal variations in the genome, while others are associated with disease. While specific SNVs may be associated with disease states or susceptibility, high-density SNV genotyping can also be undertaken, whereby sequencing information on SNVs is used to determine the unique genetic makeup of an individual.

[0096] In SNV genotyping, SNVs can be determined by hybridizing complementary DNA probes to the SNV site. A wide range of platforms can be used with SNV genotyping tools to accommodate varying sample throughputs, multiplexing capabilities, and chemistries. In high-density SNV arrays, hundreds of thousands of probes are arrayed on a small chip, such that many SNVs can be interrogated simultaneously when target DNA is processed on the chip. By determining the amount of hybridization of target DNA in a sample to a probe (or redundant probes) on the array, specific SNV alleles can be determined. Use of arrays for SNV genotyping allows the large-scale interrogation of SNVs.

[0097] When analyzing CNVs, after SNVs have been analyzed, a computer program can be used to manipulate the SNV data to arrive at CNV data. PennCNV or a similar program, can then be used to detect signal patterns across the genome and identify consecutive genetic markers with copy number changes. (See Wang K, et al. (June 2008) Cold Spring Harb Protoc). PennCNV allows for kilobase-resolution detection of CNVs. (See Wang K, et al. (November 2007) Genome Res. 17(11):1665-74).

[0098] In CNV analysis, the SNV genotyping data is compared with the behavior of normal diploid DNA. The software uses SNV genotyping data to determine the signal

intensity data and SNV allelic ratio distribution and to then use these data to determine when there is deviation from the normal diploid condition of DNA that indicates a CNV. This is done in part by using the log R Ratio (LRR), which is a normalized measure of the total signal intensity for the two alleles of the SNV (Wang 2008). If the software detects regions of contiguous SNVs with intensity (LRR) trending below 0, this indicates a CNV deletion. If the software instead detects regions of contiguous SNVs with intensity (LRR) trending above 0, this indicates a CNV duplication. If no change in LRR is observed compared to the behavior of diploid DNA, the sequence is in the normal diploid state with no CNV present. The software also uses B allele frequency (BAF), a normalized measure of the allelic intensity ratio of two alleles that changes when alleles are lost or gained as with a CNV deletion or duplication. For example, a CNV deletion is indicated by both a decrease in LRR values and a lack of heterozygotes in BAF values. In contrast, a CNV duplication is indicated by both an increase in LRR values and a splitting of the heterozygous genotype BAF clusters into two distinct clusters. The software automates the calculation of LRR and BAF to detect CNV deletions and duplications for whole-genome SNV data. The simultaneous analysis of intensity and genotype data accurately defines the normal diploid state and determines CNVs.

[0099] Array platforms such as those from Illumina, Affymetrix, and Agilent may be used in SNV Genotyping. Custom arrays may also be designed and used based on the data described herein.

B. Comparative Genomic Hybridization

[0100] Comparative genomic hybridization (CGH) is another method that may be used to evaluate genetic alterations such as CNVs. CGH is a molecular cytogenetic method for analyzing genetic alterations such as CNVs in comparison to a reference sample using competitive fluorescence in situ hybridization (FISH). DNA is isolated from a patient and a reference source and independently labeled with fluorescent molecules (i.e., fluorophores) after denaturation of the DNA. Hybridization of the fluorophores to the resultant samples are compared along the length of each chromosome to identify chromosomal differences between the two sources. A mismatch of colors indicates a gain or loss of material in the test sample in a specific region, while a match of the colors indicates no difference in genetic alterations such as copy number between the test and reference samples at a particular region. In certain embodiments, the fluorophores are not naturally occurring.

C. Whole Genome Sequencing, Whole Exome Sequencing, and Targeted Sequencing

[0101] Whole genome sequencing, whole exome sequencing, or targeted sequencing may also be used to analyze genetic alterations such as CNVs. Whole genome sequencing (also known as full genome sequencing, complete genome sequencing, or entire genome sequencing) involves sequencing of the full genome of a species, including genes that do or do not code for proteins. Whole exome sequencing, in contrast, is sequencing of only the protein-coding genes in the genome (approximately 1% of the genome). Targeted sequencing involves sequencing of only selected parts of the genome.

[0102] A wide range of techniques would be known to those skilled in the art to perform whole genome, whole exome, or targeted sequencing with DNA purified from a subject. Similar techniques could be used for different types of sequencing. Techniques used for whole genome sequencing include nanopore technology, fluorophore technology, DNA nanoball technology, and pyrosequencing (i.e., sequencing by synthesis). In particular, next-generation sequencing (NGS) involves sequencing of millions of small fragments of DNA in parallel followed by use of bioinformatics analyses to piece together sequencing data from the fragments.

[0103] As whole exome sequencing does not need to sequence as large an amount of DNA as whole genome sequencing, a wider range of techniques are may be used. Methods for whole exome sequencing include polymerase chain reaction methods, NGS methods, molecular inversion probes, hybrid capture using microarrays, in-solution capture, and classical Sanger sequencing. Targeted sequencing allows for providing sequence data for specific genes rather than whole genomes and can use any of the techniques used for other types of sequencing, including specialized microarrays containing materials for sequencing genes of interest.

D. Other Methods for Determining Genetic Alterations

[0104] Proprietary methodologies, such as those from BioNano or OpGen, using genome mapping technology can also be used to evaluate genetic alterations such as CNVs.

[0105] Standard molecular biology methodologies such as quantitative polymerase chain reaction (PCR), droplet PCR, and TaqMan probes (i.e., hydrolysis probes designed to increase the specificity of quantitative PCR) can be used to assess genetic alterations such as CNVs. Fluorescent in situ hybridization (FISH) probes may also be used to evaluate genetic alterations such as CNVs. The analysis of genetic alterations such as CNVs present in patients is not limited by the precise methods whereby the genetic alterations such as CNVs are determined

VI. Treatment of ADHD and 22q Syndromes with Nonselective mGluR Activators

[0106] In some embodiments, a subject with ADHD is treated with a nonselective mGluR activator. In other embodiments, a subject with 22q deletion and/or duplication syndrome is treated with a nonselective mGluR activator. In still other embodiments, a subject with ADHD and a 22q deletion and/or duplication syndrome is treated with a nonselective mGluR activator. The terms "subject" and "patient" are used interchangeably to refer to a human. The terms "pediatric subject" or "pediatric patient" are used interchangeably to refer to a human less than 18 years of age. In some embodiments, the subject may be between 6 and 17 years old, such as between 12 and 17 years old or between 6 and 12 years old. The terms "adult subject" or "adult patient" refer to a human of at least 18 years of age. An "adolescent" subject, for example, may be between 12 and 18, such as 12-17, 13-17, or 13-18 years old.

[0107] The term "treatment," as used herein, covers any administration or application of a therapeutic for disease in a subject, and includes inhibiting the disease, arresting its development, relieving one or more symptoms of the disease, or preventing reoccurrence of one or more symptoms

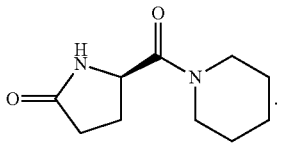
of the disease. For example, treatment of 22q deletion and/or duplication syndrome subjects may comprise alleviating neurobehavioral, neuropsychiatric and neurodevelopmental symptoms associated with 22q deletion and/or duplication syndrome. Such symptoms include but are not limited to, improvements in memory, attention, cognition, anxiety, and stabilization or reversal of mood disorder, autism spectrum disorder, psychosis and hyperactivity. Treating an ADHD or 22q deletion and/or duplication subject may comprise alleviating symptoms of inattentiveness, hyperactivity, and/or impulsiveness associated with ADHD, as well as improving associated phenotypes such as mood disorders and sleep disorders, anger control, and disruptive behaviors.

[0108] The mGluR proteins are typically placed into three sub-groups, group I receptors including mGluR1 and mGluR5 are classed as slow excitatory receptors. Group II includes mGluR2 and mGluR3. Group III includes mGluR4, mGluR6, mGluR7, and mGluR8. Groups II and III are classed as slow inhibitory receptors. The mGluRs are distinguished from the ionotropic GluRs or iGluRs, which are ion channel-associated glutamate receptors and are classed as fast excitatory receptors.

[0109] A "nonselective activator of mGluRs" refers to a molecule that activates mGluRs from more than one of the group I, II, and III categories. Thus, a nonselective activator of mGluRs may provide for a general stimulation of the mGluR networks. This is in contrast to specific mGluR activators that may only significantly activate a single mGluR, such as mGluR5, for example. Nonselective mGluR activators include, for example, nonselective mGluR agonists.

[0110] In some embodiments the nonselective mGluR activator is "fasoracetam." Fasoracetam is a nootropic (i.e., cognitive-enhancing) drug that can stimulate both group I and group II/III mGluRs in in vitro studies. (See Hirouchi M, et al. (2000) European Journal of Pharmacology 387:9-17.) Fasoracetam may stimulate adenylate cyclase activity through activation of group I mGluRs, while it may also inhibit adenylate cyclase activity by stimulating group II and III mGluRs. (Oka M, et al (1997) Brain Research 754:121-130.) Fasoracetam has been observed to be highly bioavailable (79%-97%) with a half-life of 5-6.5 hours in prior human studies (see Malykh A G, et al. (2010) Drugs 70(3): 287-312). Fasoracetam is a member of the racetam family of chemicals that share a five-carbon oxopyrrolidone ring.

[0111] The structure of fasoracetam is:



[0112] The term "fasoracetam" as used herein encompasses pharmaceutically acceptable hydrates and any solid state, amorphous, or crystalline forms of the fasoracetam molecule. For example, the term fasoracetam herein includes forms such as NFC-1: fasoracetam monohydrate. In addition to NFC-1, fasoracetam is also known as C-NS-105, NS105, NS-105, and LAM-105.

[0113] NFC-1 has been previously studied in Phase I-III clinical trials in dementia-related cognitive impairment but did not show sufficient efficacy in dementia in Phase III trials. These trials demonstrated that NFC-1 was generally safe and well tolerated for those indications. Phase III data indicated that NFC-1 showed beneficial effects on psychiatric symptoms in cerebral infarct patients and adult dementia patients with cerebrovascular diseases. Fasoracetam is a member of the racetam family of compounds. Another racetam compound, piracetam, has been tested in pediatric ADHD subjects and found to actually increase ADHD symptoms in those subjects compared to a placebo control. (See Akhundian, J., Iranian J. Pediatrics 2001, 11(2): 32-36.)

[0114] In each of the method of treatment embodiments, a metabotropic glutamate receptor positive allosteric modulator, a metabotropic glutamate receptor negative allosteric modulator, or a tachykinin-3/neurokinin-3 receptor (TACR-3/NK3R) antagonist may be administered alone or in combination with a nonselective activator of mGluRs, for example, to subjects having an alteration in a mGluR network gene. In some embodiments, the treatment agent comprises ADX63365, ADX50938, ADX71149, AMN082, a 1-(hetero)aryl-3-amino-pyrrolidine derivative, LY341495, ADX48621, GSK1144814, or SB223412.

VII. Methods of Administration and Dosage

[0115] In some embodiments, fasoracetam may be administered as fasoracetam monohydrate (NFC-1). In some embodiments, fasoracetam may be administered by mouth (i.e., per os). In some embodiments, fasoracetam may be administered as capsules, tablets, caplets, oral solutions, and oral suspensions. In some embodiments, fasoracetam capsules or tablets or the like may contain 50 mg, 100 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 600 mg, or 800 mg of fasoracetam, or any range bounded by two of the above numbers.

[0116] In some embodiments, fasoracetam at any of the 50 mg, 100 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, or 400 mg dosages above may be administered once daily, twice, or three times daily. In some embodiments, the total daily dose of fasoracetam may be 50 mg, 100 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, or 400 mg given once-daily or 50 mg, 100 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, or 400 mg given twice-daily. In some embodiments, fasoracetam dosing may be adjusted using a series of dose escalations. In some embodiments, pharmacokinetic data on drug level or clinical response are used to determine changes in dosing. In some embodiments, dose escalation of fasoracetam is not used. In some embodiments, subjects are treated at a dose of fasoracetam expected to be clinically efficacious without a dose-escalation protocol.

VIII. Therapeutic Combinations

[0117] In some embodiments, the nonselective activator of mGluR network proteins, such as fasoracetam, is used in combination with other agents for the treatment of ADHD and 22q deletion and/or duplication syndromes. In some embodiments, it is used in combination with current ADHD medications such as stimulant and/or nonstimulant drugs. "Stimulant" drugs used for treatment of ADHD are drugs that increase the levels of dopamine or other neurotransmitters in the brain. They are available in a variety of release forms from short to extended-release. Stimulants tend to improve attention span and focus and to regulate impulsive behaviors. Currently used stimulants include methylpheni-

dates (e.g. Concerta®; Ritalin®; Daytrana® patch; Methylin®; Metadate®), dexmethylphenidates (e.g., Focalin®), and amphetamines such as Adderall XR® (amphetamine mixed salts), Dexedrine® (dextroamphetamine), and Vyvanse® (lisdexamphetamine dimesylate).

[0118] "Nonstimulant" (also referred to herein as "non-stimulant") drugs for ADHD are drugs that may affect neurotransmitters but do not raise dopamine levels in the brain. Nonstimulants encompass a variety of drug classes. Currently used nonstimulant drugs include atomoxetine (Strattera®), which may prolong the action of norepinephrine in the brain, as well as the blood-pressure medications clonidine (Kapvay®) and guanfacine (Intuniv®), which may also improve mental functioning in ADHD patients.

[0119] In some embodiments, the activator may be used in combination with an anxiolytic (such as barbiturates, pregabalin, or benzodiazepines, including chlordiazepoxide, clorazepate, diazepam, flurazepam, halazepam, prazepam, lorazepam, lormetazepam, oxazepam, temazepam, clonazepam, flunitrazepam, nimetazepam, nitrazepam, adinazolam, alprazolam, estazolam, triazolam, climazolam, loprazolam, or midazolam). It may also be used in combination with antidepressants such as serotonin selective uptake inhibitors, e.g. fluoxetine, sertraline, and citalopram. Antidepressants include, for example, fluoxetine, escitalopram, bupropion, mirtazapine, amitriptyline, imipramine, venlafaxine, sertraline, paroxetine, or other compounds in the classes of tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, norepinephrine and dopamine reuptake inhibitors, monoamine oxidase inhibitors, or other drugs approved for the use of depression). In some embodiments, the other agent may be a beta-blocker (such as acebutolol, atenolol, betaxolol, bisoprolol, esmolol, nebivolol, metoprolol, cartelol, penbutolol, pindolol, carvedilol, labetalol, levobunolol, metipranolol, nadolol, propranolol, sotalol, timolol, or other selective or nonselective blockers of beta-adrenergic receptors). In some embodiments, the other agent may be an anti-psychotic drug such as aripiprazole or risperidone.

[0120] In some embodiments, fasoracetam may be used in combination with a non-pharmacologic treatment, such as psychotherapy or brain stimulation therapies. For example, in some embodiments the patient is further treated with brain stimulation, which may be vagus nerve stimulation, repetitive transcranial magnetic stimulation, magnetic seizure therapy, deep brain stimulation, or any other therapies involving modulation of brain function by electricity, magnets, or implants.

IX. Efficacy Measures for Determining Responsiveness to Treatment

[0121] A number of different outcome measures or rating scales are validated for determining the efficacy of a treatment for ADHD, for example, in clinical trials. These can include measures of attention, tasks, and global measures of the severity or improvement of patients. Rating scales currently used in ADHD clinical trials in pediatric patients include the ADHD Rating Scale IV, Vanderbilt scale, actigraphy, Quotient ADHD test scale, and the PERMP-Math test scale. A Clinical global impressions severity/improvement (CGI-S and CGI-I) score is also frequently used as a secondary efficacy measurement as it may correspond well to the judgments of global well-being that clinicians make in their normal clinical practice of treating ADHD patients.

[0122] The ADHD Rating Scale IV is based on 18 inattentive and hyperactive/impulsive diagnostic criteria for ADHD provided in the Fourth Edition of the Diagnostic and Statistical Manual of Mental Disorders, 1994, (DSM-4) or the Fifth Edition, 2016, (DSM-V), published by the American Psychiatric Association. [Are the DSM-IV and DSM-V questions essentially the same]' Each of the 18 items is scored on a 4-point scale of 0, 1, 2, or 3, with 0 indicating no symptoms to 3 indicating severe symptoms. Accordingly, the Scale results in possible scores ranging from 0 to 54 with a higher score reflecting a more severe disease condition. There are a few versions of the ADHD Rating Scale IV depending upon who is recording the information, a parent/teacher or a clinician, and depending upon whether the patient is a pediatric or adult patient. But all versions are designed to assess the same set of 18 items.

[0123] The Vanderbilt Rating Scale is a measure that can be completed by parents or teachers (separate forms, see Vanderbilt Rating Scale Parents and Vanderbilt Rating Scale Teachers). The Vanderbilt scale rates the child's behavior on items such as attention, finishing tasks, hyperactivity, difficulty waiting, and measures of conduct or oppositional defiant disorders—as well as measures of overall school performance and interactions with others. The first 18 items on the Vanderbilt scale correspond to those of the ADHD Rating Scale IV above while the Vanderbilt scale also includes items 19-47 related to other mental disorders including ODD (items 19-26), conduct disorder (items 27-40), anxiety (items 41, 42, and 47), and depression (items 43-46). Each of the behavioral assessment items on the Vanderbilt Scale are rated 0, 1, 2, or 3, with 0=never occurring; 1=occasionally, 2=often, and 3=very often. Thus, the ADHD Rating Scale IV, ADHD Rating Scale V, and items 1-18 of the Vanderbilt Rating Scale are equivalent scales, while additional items on the Vanderbilt Scale assess co-morbid phenotypes and disorders.

[0124] The first 18 items of the Vanderbilt Rating Scale Parents are in the form of a questionnaire and include items such as: (3) does not seem to listen when spoken to directly; (4) does not follow through when given directions and fails to finish activities (not due to refusal or failure to understand); (9) is forgetful in daily activities; (10) fidgets with hands or feet or squirms in seat; (16) blurts out answers before questions have been completed; (17) has difficulty waiting his or her turn. Each of the items are rated on a scale of 0, 1, 2, or 3, with 0=never; 1=occasionally, 2=often, and 3=very often. A total score of 0 to 54 is computed based on the answers to the 18 questions.

[0125] As used herein an "ADHD rating scale score," "ADHD score" or "Vanderbilt ADHD score" are used interchangeably to refer to the computed score of the 18 items of the ADHD Rating Scale IV or V or the first 18 items of the Vanderbilt Rating Scale in any of their associated versions, e.g., for parent, teacher, or clinician to complete, and for a pediatric subject or adult subject. Clinical trials may assess the impact of drug or placebo on the ADHD score or Vanderbilt ADHD score (i.e. the score of 0 to 54 based on the first 18 items in the ADHD or Vanderbilt rating scale). In some cases, results of a clinical trial population may be analyzed by comparing the average score or a percentage change in score over time of administration of drug. Patients may be considered "improved," for example, if their Vanderbilt ADHD score is reduced by at least 25% compared to a placebo or pre-study baseline, and "robustly improved," for

example, if their score is reduced by at least 40% compared to a pre-study or placebo baseline.

[0126] Some embodiments of methods of treatment herein refer to administering to a subject an amount of a nonselective mGluR network activator effective to reduce an ADHD rating scale score or Vanderbilt ADHD score by at least 25%, such as at least 30% or at least 35% or at least 40%, after a certain period of treatment, such as 1, 2, 3, 4 or 5 weeks, in a majority of clinical trial subjects. In such embodiments, the amount for administration may, for example, be selected based on clinical results showing that the amount led to such a result in a majority of previously assessed clinical patients. For example, if a subject to be treated is a pediatric subject, the treatment amount may be selected on the basis of achieving such results in a majority of patients in a clinical trial of pediatric subjects.

[0127] The Clinical Global Impression Scale (CGI) is a widely-used assessment instrument in psychiatry and is a common secondary efficacy measure for ADHD clinical trials. The CGI scale generally asks the clinician to provide a global assessment of the patient's function, symptoms, and adverse events based on the clinician's experience with ADHD patients. The CGI scale has two component measurements, CGI-S (clinical global impression-severity; a measure of disease severity) and CGI-I (clinical global impression-improvement; a measure of improvement in symptoms). Both scales range from 1 to 7. The CGI-S scale ranges from 1 (normal) to 3 (mildly ill), 4 (moderately ill), 5 (markedly ill), 6 (severely ill) and 7 (among the most extremely impaired). The CGI-I scale ranges from 1 (very much improved), 2 (much improved), 3 (minimally improved), 4 (no change), 5 (minimally worse), 6 (much worse), to 7 (very much worse). In general, subjects with a CGI-I score of 1 or 2 compared to a base-line or placebo level are considered responders to a treatment regimen. For example, in some cases a responder to a drug regimen may show a reduction in ADHD score or Vanderbilt ADHD score of at least 25%, such as at least 30%, at least 35%, or at least 40%, as well as a CGI-I score of either 1 or 2 after a certain period of treatment, such as 1, 2, 3, 4, or 5 weeks. In some cases, a responder may show a change in CGI-I score after 1, 2, 3, 4, or 5 weeks, for example, of 1 to 2 points. In some cases, a responder may show a CGI-S score of 1 or 2 or 3 after 1, 2, 3, 4, or 5 weeks

[0128] In some embodiments of the methods herein, the amount of nonselective mGluR activator administered to a subject is chosen based on that amount's ability to give a CGI-I score of 1 or 2 in a majority of subjects in a clinical trial, for example a clinical trial of similar subjects. Thus, for example, if a pediatric clinical trial shows that a particular amount of activator gives a CGI-I score of 1 or 2 in a majority of patients in the trial after a particular period of time, that amount may be chosen to give to another pediatric subject as a treatment dose. Similarly, in some embodiments, the amount of nonselective mGluR activator administered to a subject is chosen based on an amount that gave a reduction of at least 25%, such as at least 35%, at least 35%, or at least 40% in Vanderbilt ADHD score in a clinical trial of similar subjects. In some embodiments, an amount is chosen for administration based on the amount that achieved a CGI-S score of 1-3, such as 1-2 in subjects after a period of treatment. In some cases, an amount is chosen for administration that gave a combination of these effects in a majority of clinical trial subjects.

[0129] The Permanent Product Measure of Performance (PERMP)-Math is an individualized mathematics test that can be performed by a patient periodically when on and off medication for ADHD. It is used, for example, to monitor classroom performance in an experimental laboratory setting.

[0130] In general, the PERMP test comprises 5 pages of 400 problems that subjects are directed to attempt over a 10-minute period. Subjects may be given a pre-test first to determine their mathematical skill level. Subjects are directed to answer as many questions as they can in the 10-minute period and the test is generally scored on a 0-800-point scale based on the number of questions attempted and the number of questions answered correctly within the time limit. Subjects receive a different version of the test at each setting.

[0131] Quotient ADHD scores use a medical device to measure hyperactivity, attention, and impulsivity in patients with ADHD. The Quotient ADHD tool uses motion tracking technology to track a patient's micro-movements while they complete a 15-20-minute computerized test. Following the patient's completion of the test, patterns of motions, the accuracy of responses, and fluctuations in attention state can be analyzed.

[0132] Actigraphy is non-invasive monitoring of human rest/activity cycles, using an actigraph worn by the patient to document body movements. Actigraphs can be worn during school, for example, to measure activity levels. Actigraphy analysis can measure changes in sleep and hyperactivity that may be seen with treatment for ADHD.

[0133] Additional questionnaires may also be used by clinicians to assess co-morbid symptoms such as anger control and disruptive behaviors as well as to assess co-morbid disease conditions.

X. Articles of Manufacture

[0134] In some embodiments, the invention comprises articles of manufacture that may be used in the methods and treatments described herein. In one embodiment, the manufacture is a solid support or microarray for use in detecting genetic alterations in some, or all, of the mGluR network genes listed in FIGS. **1-3** (i.e., Tiers 1-3). In some embodiments, genes contained in multiple Tiers are assessed within the same solid support or microarray. In some embodiments, certain mGluR network genes are excluded. In some embodiments, the GRM genes are excluded.

[0135] Thus, for example, in some embodiments in which mGluR network genes are assayed to determine if there is a genetic alteration in one or more of the genes, such as a CNV, a solid support or microarray, such as on a chip, is used that contains appropriate probes for determining the presence of genetic alterations in 10, 20, 30, 40, 50, 60, 70 or all of the Tier 1 genes. In some embodiments, the solid support or microarray may also include appropriate probes for determining the presence of genetic alterations in at least 10, 20, 30, 50, 100, 150, or all of the Tier 2 genes. In some embodiments, it may further include appropriate probes for determining the presence of genetic alterations in at least 10, 20, 50, 100, 200, 300, 400, 500 or all of the Tier 3 genes. For example, such a solid support, microarray, or chip may be used to determine the presence of genetic alterations such as CNVs or SNVs in the Tier 1, Tier 1+2, or Tier 1+2+3 mGluR gene networks as part of a method of treating an ADHD or 22q deletion and/or duplication patient.

[0136] In some embodiments, the manufacture is a set of probes for mGluR network genes of interest from Tiers 1, 2, and/or 3. In some embodiments the probes are labelled. In certain embodiments, the labels are non-naturally occurring. Similarly, sets of probes may be manufactured for determining the presence of genetic alterations in 10, 20, 30, 40, 50, 60, 70 or all of the Tier 1 genes. In some embodiments, probes may be manufactured for determining the presence of genetic alterations in at least 10, 20, 30, 50, 100, 150, or all of the Tier 2 genes. In some embodiments, probes may further include those for determining the presence of genetic alterations in at least 10, 20, 50, 100, 200, 300, 400, 500 or all of the Tier 3 genes. These various probe sets may be used in methods of determining the presence of genetic alterations, such as CNVs and SNVs in the Tier 1, Tier 1+2, or Tier 1+2+3 mGluR gene networks as part of a method of treating an ADHD or 22q deletion and/or duplication patient

EXAMPLES

Example 1: Treatment of ADHD Patients with CNVs in mGluR Network Genes with NFC-1 (Fasoracetam Monohydrate)

[0137] An open-label Phase Ib clinical trial was initiated to investigate the safety, pharmacokinetics and efficacy of NFC-1 (fasoracetam monohydrate) in adolescent subjects between the ages of 12 and 17 previously diagnosed with ADHD who also had at least one genetic alteration in an mGluR network gene.

[0138] The study included 30 subjects who were between ages 12 and 17, of any ancestry or race, and of weight within the 5th to 95th percentile for their age, and otherwise judged to be in good medical health. The subjects suffered from ADHD as defined by the Diagnostic and Statistical Manual of Mental Disorders, 5th Ed (DSM-5) and a Vanderbilt ADHD score of greater than or equal to 16 (as determined by parent or teacher) at baseline either with or without conventional ADHD therapy. Subjects were genotyped and included in the trial if they possess at least one genetic alteration in the form of at least one copy number variation (deletion or duplication) in an mGluR network gene that potentially disrupts the function of the gene. Seventeen of the 30 subjects have a CNV in a Tier 1 mGluR network gene, while 7 subjects have a CNV in a Tier 2 gene and 6 in a Tier 3 gene. Two of the 30 ADHD subjects of the trial also suffered from 22q syndrome, one with 22q deletion syndrome and one with 22q duplication syndrome. Several trial subjects showed evidence of co-morbid phenotypes such as anxiety, mood disorders, sleep disturbance such as insomnia, depression, ODD, or conduct disorder in addition to ADHD at enrollment, based on the results of items 19-47 of the Vanderbilt Scale.

[0139] Exclusion criteria comprised subjects suffering from a clinically significant illness, either mental or physical, that, in the investigator's opinion, might confound the results of the study or that might prevent them from completing the study, subjects that are pregnant or nursing, subjects that test positive for illicit drugs of that have a history of drug abuse, subjects that consume alcoholic beverages, or subjects for which the investigator is otherwise concerned regarding their compliance or suitability.

[0140] NFC-1 capsules of either 50 mg or 200 mg comprising fasoracetam monohydrate as active ingredient and placebo capsules comprising microcellulose were used for the study. The design of the trial was a phone screening (1 day), enrollment phase (1 to 2 days), a wash-out phase for subjects currently on ADHD medications (1-14 days), pharmacokinetic (PK) assessment (2 days), followed by a dose-escalation phase (35 days) and a follow-up phone visit approximately four weeks after the last dose, for a maximum of 127 days. All ADHD medications were discontinued during the wash-out phase prior to the study. The wash-out period for stimulants was 2-3 days and that for atomoxetine or noradrenergic agonists was 10-12 days. No new ADHD medications were started during the study.

[0141] All subjects participated in the PK assessment. For the PK portion of the trial, subjects received a one-time dose of 50 to 800 mg NFC-1 and blood samples were taken just prior to dosing and at 0.5. 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours after dosing. The 30 subjects were placed into 5 groups of 6 subjects for PK and initial safety assessment, each group receiving a different dose ranging of 50, 100, 200, 400, or 800 mg. The PK parameters Cmax, Tmax, and AUC0-24 h were calculated based on NFC-1 levels in serum.

[0142] Dose-escalation phase of the trial followed the PK and initial safety assessment and ran over a 5-week period. During week 1, all subjects were administered placebo capsules twice daily. After one week of placebo treatment, patients were started on 50 mg bid NFC-1 for 1 week. If safety and responsiveness data from prior dose level of fasoracetam indicated it was appropriate, subjects were then escalated to the next higher dose (100, 200, or 400 mg). Subjects who showed tolerance to the 50 mg bid dose as well as response to the drug were to be maintained at that level for the remaining 3 weeks of the trial. Subjects who showed tolerance but lack of response or partial response to the 50 mg bid dose were to be moved up to the next higher dose of 100 mg during the following week. Subjects who showed tolerance at 100 mg but lack of response or partial response were to be moved up to the 200 mg dose the following week while those who showed both tolerance and response at 100 mg were to be kept at 100 mg bid for the remainder of the trial. Similarly, subjects moved up to the 200 mg dose who showed both tolerance and response were to be kept at 200 mg for the final week of the trial while those showing tolerance but lack of response or partial response were moved to a 400 mg dose for the final week. Of the 30 trial subjects, 3 received a maximum dose of 100 mg, 9 received a maximum dose of 200 mg, and the remaining 18 received a maximum dose of 400 mg.

[0143] All efficacy assessments, except actigraphy, were made at study enrollment ("enrollment baseline") and again, including actigraphy, once-per-week for the placebo week ("week 1" or "placebo baseline") and at each of the 4 weeks of NFC-1 treatment. These efficacy measures include items 1-18 of the Vanderbilt scale assessing symptoms related to inattentiveness and hyperactivity-impulsiveness as well as additional questions 19-47 of the Vanderbilt scale assessing other behavioral symptoms (conducted by parent), actigraphy for quantitative measurement of activity, Quotient® ADHD test for objective measurement of micro-motion and shifts in attention state, PERMP-Math test, and CGI-I and

CGI-S for assessment of global functioning. Prior to receiving the PK assessment dose, subjects returned to the clinic to be administered the PERMP-Math tests, subjected to actigraphy (set to activate at the time of first placebo dose 2 days later), and to be given a general physical examination including vital signs and weight, blood and urine sampling, and a pregnancy test for female subjects. During the 5-week placebo and dose-escalation phases of the study, subjects visited the clinic again at the end of each week to be administered the Quotient® and PERMP-Math tests, subjected to actigraphy, Vanderbilt and BRIEF measurements (conducted by parent), and to be given a general physical examination including vital signs and weight, blood and urine sampling, and a pregnancy test for female subjects.

[0144] For data analysis, subjects were considered as a whole as well as by genetic tier (1, 2, or 3) or by genetic tier group (1 and 2 vs. 3). The subject number, maximum dose administered, age, genetic tier, and the placebo baseline (i.e. week 1) and final (i.e. week 5) CGI-I, Vanderbilt, and PERMP results for all of the 30 subjects are shown in Table 1 below. Subjects 110 and 127 suffer from both ADHD and 22q deletion and/or duplication syndromes. Thirteen subjects had a diagnosis of ODD, and one of these subjects did not complete the trial. Thus, twelve subjects, numbers 102, 103, 108, 111, 112, 114, 117, 122, 125, 126, 128, and 130 suffer from both ADHD and ODD and completed the trial.

[0145] See, Table 1 on next page (remainder of page intentionally left blank).

[0146] Based on Table 1, the mean starting and ending CGI-I scores for the 30 subjects are 3.67 at week 1 (placebo baseline) and 2.27 at week 5, for a mean improvement of 1.4. This indicates, in general, that the subjects were "much improved" or "very much improved" on average (CGI-I of 1 or 2) by the end of the dose escalation phase of treatment. The change in CGI-I scores from enrollment baseline to week 5 for the 30 trial subjects are summarized in Tables 2(a)-(c) below. As shown below, the mean improvement in CGI-I score for all subjects is 1.57, which corresponds to a "much improved" to "very much improved" state. Subjects in genetic Tiers 1 and 2 were more improved than those in Tier 3, with P=0.0402.

[0147] Tables 2(a), (b), (c): CGI-I at week 5 compared to that at the pre-study enrollment baseline for all subjects, by genetic tier, and by tier group

TABLE 2a

a) All Subjects

N	Mean	Std Dev	Median	N missing	25^{th} percentile	75^{th} percentile
30	1.57	1.01	2	1	1	2

TABLE 1

Overall Study Placebo Baseline to Final Results

Subject Number	Max Dose	Age	Genetic Tier	Genetic Tier Group	Baseline CGI = I	Baseline Vanderbilt	Baseline PERMP	Final CGI = I	Final Vanderbilt	Final PERMP	Change in CGI = I	Change in Vanderbilt	Change in PERMP
101	200	14	2	1/2	4	47	73	2	12	71	−2	−35	−2
102	200	12	1	1/2	5	41	104	3	39	80	−2	−2	−24
103	200	17	1	1/2	3	38	85	2	30	74	−1	−8	−11
104	200	14	2	1/2	5	37	121	2	23	103	−3	−14	−18
105	200	15	3	3	4	6	92	2	3	111	−2	−3	19
106	100	17	3	3	3	8	78	2	0	101	−1	−8	23
107	200	12	1	1/2	4	9	72	2	0	76	−2	−9	4
108	200	17	1	1/2	4	50	129	2	18	160	−2	−32	31
109	400	16	1	1/2	3	10	130	1	6	87	−2	−4	−43
110	400	13	1	1/2	4	22	45	2	17	71	−2	−5	26
111	400	13	1	1/2	3	30	97	2	34	88	−1	4	−9
112	400	14	2	1/2	3	49	70	2	36	93	−1	−13	23
113	100	12	1	1/2	3	32	125	3	22	125	0	−10	0
114	100	14	1	1/2	5	49	133	4	17	135	−1	−32	2
115	400	13	2	1/2	3	25	59	3	46	48	0	21	−11
117	400	16	1	1/2	0	28	56	2	12	68	2	−16	12
118	400	14	1	1/2	4	13	78	2	0	92	−2	−13	14
119	400	12	2	1/2	3	16	76	2	17	64	−1	1	−12
120	400	12	1	1/2	4	15	99	2	15	99	−2	0	0
121	200	17	1	1/2	5	36	125	2	31	55	−3	−5	−70
122	400	16	1	1/2	3	33	96	3	24	80	0	−9	−16
123	400	14	2	1/2	4	24	75	2	14	71	−2	−10	−4
124	400	14	3	3	4	33	71	2	12	34	−2	−21	−37
125	400	17	2	1/2	3	39	95	2	23	104	−1	−16	9
126	400	17	3	3	4	35	92	3	29	64	−1	−6	−28
127	400	12	1	1/2	6	44	78	2	33	64	−4	−11	−14
128	400	13	1	1/2	3	36	48	1	16	46	−2	−20	−2
129	400	17	3	3	4		60	3		75	−1		15
130	400	16	3	3	3	36	191	3	35	168	0	−1	−23
216	200	17	1	1/2	4	2	109	3	1	152	−1	−1	43

TABLE 2b

b) By Genetic Tier

Genetic Tier	N	Mean	Std Dev	Median	N missing	25th percentile	75th percentile
1	16	1.81	0.91	2	1	1	2
2	7	1.57	1.13	1	0	1	3
3	6	0.86	0.90	1	0	0	2

TABLE 2c

c) By Tier Group

Genetic Tier	N	Mean	Std Dev	Median	N missing	25th percentile	75th percentile
1 or 2	23	1.74	0.96	2	1	1	2
3	7	0.86	0.90	1	0	0	2

[0148] CGI-S scores declined from an average of about 4 to an average of about 3 from enrollment to week 5. The change in CGI-S score from enrollment baseline to week 5 is shown in Tables 2(d)-(f) below and the mean change was approximately 1 over all subjects.

[0149] Table 2(d)-(f): Changes in CGI-S scores from pre-study enrollment baseline to week 5 in all subjects, by genetic tier, and by tier group.

TABLE 2d

d) All subjects

N	Mean	Std Dev	Median	N missing	25th percentile	75th percentile
30	0.93	0.74	1	1	0	2

TABLE 2e

e) By genetic tier

Genetic Tier	N	Mean	Std Dev	Median	N missing	25th percentile	75th percentile
1	16	1.125	0.87	1	1	1	2
2	7	1.0	0.58	1	0	1	1
3	6	0.5	0.55	0.5	0	0	1

TABLE 2f

f) By tier group

Genetic Tier	N	Mean	Std Dev	Median	N missing	25th percentile	75th percentile
1 or 2	23	1.09	0.73	1	1	1	1
3	7	0.43	0.53	0	0	0	1

[0150] Table 3 provides an analysis of the percentages of subjects in the total study population and genetic tiers considered responders, i.e. having a CGI-I score of 1 or 2 in each week of the dose escalation phase of the trial. These data are also depicted graphically in FIG. **4**. As shown in both Table 3 and FIG. **4**, at week 4, about 55% of the subjects were considered responders based on CGI-I score, including 56% in Tier 1 and 50% in Tier 2, while none of the 6 Tier 3 subjects were significant responders. By week 5 of the dose escalation, 83% of the trial subjects were considered responders based on CGI-I score, including 81% and 86% in genetic Tiers 1 and 2 and 40% in genetic Tier 3. In the table below, "N" represents the number of subjects for which a CGI-I score was measured and "%" indicates the percentage of subjects showing a CGI-I score of 1 or 2 compared to the genetic tier group or compared to the total study population (in the "overall" row of the table).

TABLE 3

CGI-I Scores: Proportions of Subjects Responding at Each Study Visit

	Week 1		Week 2		Week 3		Week 4		Week 5	
Tier	N	%	N	%	N	%	N	%	N	%
1	16	0	17	24	15	53	16	56	16	81
2	7	0	7	43	7	29	6	50	7	86
3	6	0	6	0	6	0	6	0	5	40
Overall	29	0	30	29	28	45	28	55	28	83

[0151] Mean Vanderbilt ADHD scores (with standard error) at each week of the study are shown in Table 4 below. These values are calculated using Repeated Measures Analysis of Variance (RMANOVA). This analysis adjusts for within-subject changes in the repeated efficacy measures in order to more readily detect changes attributable to experimental effects. Note that the standard error is identical for each weekly value in Table 4 below because it was estimated from the RMANOVA statistical model. As Table 4 shows, the mean Vanderbilt ADHD score decreased each week from the placebo baseline (week 1) to week 5. The change in within-patient means is also statistically significant ($p<0.001$), which supports the conclusion that Vanderbilt scores in this population decreased with the time-course of participation in this study.

TABLE 4

Mean Vanderbilt ADHD Scores at each week of the study based on Repeated Measures Analysis for the overall study population

	Week 1	Week 2	Week 3	Week 4	Week 5
Mean (SEM)	29.1 (8.1)	26.4 (8.1)	24.0 (8.1)	23.3 (8.1)	22.5 (8.1)

[0152] Table 5 below presents the number and percent of subjects showing improvement in Vanderbilt ADHD scores each week compared to either pre-study baseline or placebo baseline (week 1) both by genetic tier and by the overall study population. These results are also shown graphically in FIGS. **5***a* and **5***b*. An at least 25% decrease in Vanderbilt ADHD score is considered responsive and improved, while an at least 40% decrease in score is considered a robust improvement.

TABLE 5

Number and Percent of Subjects with Improvement in Vanderbilt ADHD Score

	Week 1		Week 2		Week 3		Week 4		Week 5	
Tier	N	%	N	%	N	%	N	%	N	%
Relative to Pre-Study (Enrollment) Baseline										
1	17	47	17	47	16	75	16	88	16	75
2	7	29	7	29	7	14	7	43	7	86
3	5	40	4	50	5	40	5	40	4	75
Overall	29	41	28	43	28	54	28	68	27	78
Relative to Placebo (Week 1) Baseline										
1	—	—	17	29	16	50	16	56	16	56
2	—	—	7	29	7	43	7	43	7	71
3	—	—	4	0	5	20	5	0	4	0
Overall	—	—	28	25	28	43	28	43	27	52

[0153] As shown in Table 5 and FIG. **5**, 78% of subjects were responsive to treatment based on the Vanderbilt ADHD score at week 5 compared to baseline while 52% were responsive at week 5 compared to placebo baseline. A higher percentage of subjects in genetic Tiers 1 and 2 were responsive compared to subjects in Tier 3. The proportions of patients who were robustly improved at week 5 compared to study baseline and placebo baseline are shown graphically in FIGS. **7***a* and **7***b* and are further shown in Table 6. As can be seen from the figures and table, 52% of subjects were robustly improved compared to baseline while 37% were robustly improved compared to placebo baseline and all of those were in the genetic Tiers 1 and 2.

TABLE 6

Number of Subjects Demonstrating Robust Improvement at Each Week

	Week 1		Week 2		Week 3		Week 4		Week 5	
Tier	N	%	N	%	N	%	N	%	N	%
Relative to Pre-Study (Enrollment) Baseline										
1	17	29	3	35	16	50	16	56	16	63
2	7	14	7	14	7	0	7	14	7	29
3	5	40	4	50	5	40	5	40	4	50
Overall	29	28	28	32	28	36	28	43	27	52
Relative to Placebo (Week 1) Baseline										
1	—	—	17	12	16	44	16	50	16	44
2	—	—	7	0	7	0	7	14	7	43
3	—	—	4	0	5	0	5	0	4	0
Overall	—	—	28	7	28	25	28	32	27	37

[0154] As shown in Table 1, 18 of the 30 subjects in the study completed the dose escalation to 400 mg bid at week 5. The proportion of those 18 subjects who show improvement (i.e. response) and robust improvement in Vanderbilt ADHD scores at week 5 compared to the pre-study baseline or to the week 1 placebo baseline is shown in Tables 7 and 8 and FIGS. **7** and **8**, respectively.

TABLE 7

Number and Percent of Subjects Completing the Dose Escalation to 400 mg bid that Show Improvement in Vanderbilt ADHD Scores Compared to Pre-Study Baseline and Week 1 Placebo Baseline

	Week 1		Week 2		Week 3		Week 4		Week 5	
Tier	N	%	N	%	N	%	N	%	N	%
Relative to Pre-Study (Enrollment) Baseline										
1	9	56	9	56	9	89	9	89	9	89
2	5	40	5	20	5	20	5	20	5	80
3	3	0	3	33	3	0	3	0	3	67
Overall	17	41	17	41	17	53	17	53	17	82
Relative to Placebo (Week 1) Baseline										
1	—	—	9	22	9	44	9	44	9	56
2	—	—	5	0	5	20	5	20	5	60
3	—	—	3	33	3	33	3	0	3	0
Overall	—	—	17	14	17	36	17	36	17	57

TABLE 8

Number and Percent of Subjects Completing the Dose Escalation to 400 mg bid that Show Robust Improvement in Vanderbilt ADHD Scores Compared to Pre-Study Baseline and Week 1 Placebo Baseline

	Week 1		Week 2		Week 3		Week 4		Week 5	
Tier	N	%	N	%	N	%	N	%	N	%
Relative to Pre-Study (Enrollment) Baseline										
1	9	22	9	44	9	44	9	56	9	67
2	5	20	5	20	5	0	5	20	5	20
3	3	0	3	33	3	0	3	0	3	33
Overall	17	18	17	35	17	24	17	35	17	47
Relative to Placebo (Week 1) Baseline										
1	—	—	9	11	9	44	9	33	9	33
2	—	—	5	0	5	0	5	0	5	40
3	—	—	3	33	3	0	3	0	3	0
Overall	—	—	17	7	17	29	17	21	17	36

[0155] Based on the data in Table 1, the mean change in PERMP score from pre-study baseline to week 5 was negative 3.43. When analyzed based on genetic tier, there were no significant differences from the overall mean change. Those in Tiers 1 and 2 had a mean change in PERMP of negative 3.0 (mean of negative 3.35 for Tier 1 and negative 2.14 for Tier 2) while those in Tier 3 had a mean change of negative 5.17. While the PERMP scores showed little change, this may be due at least in part to uncontrolled environmental factors due to the way in which the PERMP test was conducted. The test was conducted at the time of clinic visits and thus, for each subject, was not necessarily given at the same time post dose or same time of day from one week to the next. The test was also conducted during a clinic visit and not in a classroom setting. Thus, clinic waiting room distractions, for example, could have varied from one visit to the next and were not controlled.

[0156] Overall, the parent-assessed Vanderbilt ADHD scores show that about 75-80% of the subjects had at least a 25% reduction in score at the end of the dose escalation phase of the study (i.e., the end of week 5) compared to

pre-study baseline. About 63% of subjects showed a robust improvement, i.e., a change in Vanderbilt ADHD score of at least 40%. In addition, about 80-85% of subjects showed a CGI-I score of 1 or 2 at week 5, indicating that they were much improved or very much improved by week 5 of the study compared to pre-study baseline. PERMP results did not show significant change over the course of the study.

[0157] The results from actigraphy demonstrated significant reduction in bursts of medium/high intensity movements at the highest dose of NFC-1 (400 mg bid) in comparison with placebo ($P<0.001$). As shown in FIGS. **9***a*-**9***c*, the observed reduction in moderate to vigorous physical activity (MVPA) from week 1 (placebo) to week 5 for genetic Tier-1 (FIG. **9***a*); genetic Tier-2 (FIG. **9***b*); and genetic Tier-3 (FIG. **9***c*) was most prominent in 400 mg bid dose group.

[0158] The results from the QUOTIENT® ADHD test demonstrated a high level of noise. Nonetheless, as shown in FIG. **10**, clinical trial subjects in the Tier-1 genetic group had significant improvement in the test's measure of inattention between week 1 (placebo) and week 5 (400 mg twice daily) as can be seen by the reduction in inattention in the Tier-1 group ($P<0.05$) from a normalized inattention value of just over 100 to about 90 between weeks 4 and 5 of the dose escalation.

[0159] Subjects 110 and 127 of the study, both in genetic Tier 1, have either a deletion or a duplication at 22q that comprises the RANBP1 gene, an interactor of mGluR3, and thus have a 22q syndrome in addition to a diagnosis of ADHD. Both subjects completed the entire dose escalation to 400 mg bid by week 5 of the study. Subject 110 had a measured IQ of 91 prior to the study, showed a 1-point improvement in CGI-S by week 5 compared to week 1 indicating a change from moderately to mildly ill, and a CGI-I of 2 indicating much improvement. Subject 110 also showed a change in Vanderbilt ADHD score of 5 points from 22 to 17 by week 5 compared to week 1.

[0160] Subject 127 had a measured IQ of 65 prior to the study, had a CGI-S of 6 at week 1 indicating a severe disease and improved 2 points in CGI-S to 4, denoting moderate disease by week 3 and maintained that improvement through to week 5. Subject 127, like subject 110, also had a CGI-I of 2, indicating that the subject was much improved in the clinician's opinion by end of the dose escalation. Subject 127 also showed a robust decrease in Vanderbilt ADHD score at week 3 from 44 to 25, although no Vanderbilt ADHD score was provided at week 4, and the score at week 5 was 33. The overall CGI, Vanderbilt ADHD and PERMP results for subjects 110 and 127 are shown in the table below. Both of these 22Q subjects had improvement in 22Q symptoms while taking NFC-1, including improvements in abnormal social skills/interactions, lack of engagement, anxiety, mood swings, depression, inattention, hyperactivity and reduced performance at school (in life in general). Thus, NFC-1 is useful in 22q syndrome patients.

TABLE 9

Weekly Data for 22q Syndrome Subjects 110 and 127

Test	Enrollment	Week 1	Week 2	Week 3	Week 4	Week 5
Subject 110						
CGI-S	4	4	4	4	4	3
CGI-I	—	4	3	2	2	2
Vanderbilt	33	22	20	17	16	17
PERMP	36.5	45	55	51	75	71
Subject 127						
CGI-S	5	6	6	4	4	4
CGI-I	—	6	3	2	2	2
Vanderbilt	41	44	45	25	nd	33
PERMP	60.5	78	167	68	72	64

"nd" indicates no data submitted and "—" indicates measurement not taken.

[0161] Thirteen out of the thirty subjects enrolled in the trial demonstrated symptoms of ODD as well as ADHD. Subjects were identified as ODD from the K-SADS-P V6 performed at screening and Vanderbilt scores for ODD at screening and at week 1 (scores of 2 or 3 on at least 4 of the 8 Vanderbilt items that assess ODD, i.e., items 19 to 26). By the end of the dose escalation phase of the trial at week 5, four of the twelve subjects (nos. 108, 117, 125, and 128) no longer met the screening criteria for ODD. Of the remaining eight, four showed improvements of 2 or more points from week 1 to week 5.

[0162] Subject 108, whose enrollment and week 1 placebo baseline scores on items 19-26 ("Vanderbilt ODD scores") were 23 and 19, respectively, out of a maximum score of 24, by the end of week 5 had a score of 7 out of 24 with no individual scores above 2. Subject 117 had a placebo baseline Vanderbilt ODD score of 19 and a week 5 score of 8 with only one question with a score of 2. Subject 128 had enrollment and placebo Vanderbilt ODD baseline scores of 23 and 24, respectively that fell to 8/24 by week 5 with no individual score above 1. In addition, by the end of week 5, the Vanderbilt ODD scores for all 13 of the subjects were improved from week 1 to week 5. Eleven out of the 13 subjects showed improvement of at least 3 points while 6 out of the 13 showed improvement of at least 8 points from week 1 to week 5.

[0163] In addition, 3 out of the 13 subjects screening positive for ODD at enrollment were on anti-psychotic medications both at enrollment and throughout the study. Subjects 111 and 126 were on Abilify® (aripiprazole) while subject 122 was on Risperdal® (risperidone). The Vanderbilt ODD scores for each of those 3 subjects nonetheless improved between weeks 1 and 5.

[0164] One subject screening positive for ODD (no. 130) also screened positive for conduct disorder (CD), based on scores of 2 or 3 for 3 out of the 15 behaviors assessed by items 27-40 of the Vanderbilt Scale at enrollment and again at week 1. By week 5, that individual's Vanderbilt ODD score improved by 3 points from 24/24 at week 1 to 21/24 and Vanderbilt CD score improved by 4 points from 16/16 at week 1 to 12/16 at week 5.

[0165] Certain subjects in the study also displayed other co-morbid phenotypes such as anxiety, depression, mood disorders, and sleep disturbances such as insomnia, according to the information recorded in the enrollment and week 1. Two subjects had maximum scores of 3 on 2 of the 3 Vanderbilt items 41, 42, and 47 that are related to anxiety at enrollment. At week 5, these subjects scored 3 on all 3 items. One of those subjects also scored 3 on 3 of the 4 Vanderbilt items related to depression (items 43-46) at enrollment and

scored 3 on all 4 items at week 1. By week 5, this subject scored either 1 or 2 on all 4 items, indicating improvement in depression symptoms.

[0166] Results of the BRIEF scale were also analyzed for changes in anxiety/mood scores in all 30 subjects. The BRIEF scale, performed by parents, includes a set of items that relate to anxiety and mood, specifically the following:

[0167] 1. Over-reacts to small problems;

[0168] 6. Upset with new situations;

[0169] 7. Explosive-angry outbursts;

[0170] 12. Upset by changes in plans;

[0171] 13. Disturbed by change of teacher/class;

[0172] 20. Easily tearful;

[0173] 23. Resists change of routine, foods, plans;

[0174] 25. Outbursts for little reason;

[0175] 26. Mood changes frequently;

[0176] 30. Trouble getting used to new situations;

[0177] 45. Reacts more strongly to situations than other children;

[0178] 50. Mood easily influenced by situation;

[0179] 62. Angry or tearful outbursts are intense but end suddenly;

[0180] 64. Small events trigger big reactions; and

[0181] 70. Becomes upset too easily.

[0182] The answers to these questions are scored as "never," "sometimes," or "often." The BRIEF test was administered at enrollment and again after each week of the dose escalation treatment from placebo week to week 5. All scores for all 30 subjects for each question above were added up for enrollment and week 5, giving 1 point for each "never" or "often" score. It was found that the total "never" score for all questions for all subjects at enrollment was 125 and at week 5 was 191, showing a trend toward improvement. Similarly, the total "often" score at enrollment was 154 while the total "often" score at week 5 was 77, again showing a trend toward improvement in anxiety and mood symptoms.

Example 2: Phase 2 Study of Treatment of ADHD Patients with CNVs in mGluR Network Genes with NFC-1 (Fasoracetam Monohydrate)

[0183] A randomized, double-blind, placebo-controlled, parallel-group phase 2 study of ADHD subjects 12-17 years old is conducted to compare the safety and efficacy of NFC-1 with that of placebo. Approximately 90 male and female subjects will receive randomized treatment with NFC-1 or placebo to obtain 80 subjects that complete the study as planned. Subjects have ADHD as defined by the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) and Version 5 of the Attention Deficit Hyperactivity Disorder Rating Scale (ADHD RS-5)>28 at Baseline with or without conventional ADHD therapy. About 45 subjects will be in each treatment group.

[0184] Subjects will be randomly assigned to receive either NFC-1 or placebo on Day −1 and will start taking the product at a dose of 100 mg twice daily on Day 1. Dosing will be optimized to 100 mg, 200 mg, or 400 mg twice daily, as appropriate, over the 4 weeks of treatment (dose optimization phase), based on clinical response and tolerability. If the subject tolerates a dose well, the dose will be maintained for an additional 2 weeks (dose maintenance phase) when the primary assessments of efficacy and tolerability will be performed. Efficacy will be assessed by the ADHD rating scale score, CGI-I, CGI-S, the Adolescent Sleep Hygiene Scale (ASHS), and the Screen for Childhood Anxiety-related Emotional Disorders (SCARED). The ASHS is a self-report questionnaire assessing sleep practices theoretically important for optimal sleep in adolescents aged 12 years of age. It assesses physiological (e.g., evening caffeine consumption), cognitive (e.g., thinking about things that need to be done at bedtime), emotional (e.g., going to bed feeling upset), sleep environment (e.g., falling asleep with the lights on), sleep stability (e.g., different bedtime/wake time pattern on weekdays and at weekends), substance use (e.g., evening alcohol use), daytime sleep (e.g., napping), and having a bedtime routine. The SCARED is a child self-report instrument for ages 8-18 years used to screen for childhood anxiety disorders including general anxiety disorder, separation anxiety disorder, panic disorder, and social phobia. In addition, it assesses symptoms related to school phobias. The SCARED consists of 41 items and 5 factors that parallel the DSM-IV classification of anxiety disorders. The scale has good internal consistency, test-retest reliability, and discriminant validity, and it is sensitive to treatment response. Safety and adverse events will also be assessed during the study.

Example 3: A 12-Week, Double-Blind, Placebo-Controlled, Randomized Withdrawal Study of NFC-1 (Fasoracetam Monohydrate) in Subjects with 22q11.2 Deletion Syndrome

[0185] A 12-week Phase I trial will be conducted to assess safety and tolerability of twice-daily oral doses of NFC-1 in subjects 12-17 years with 22q11.2 deletion syndrome (22q11DS) with concomitant neuropsychiatric disease: ADHD and/or autism spectrum disorder (ASD). Five weeks of open-label dose optimization will be followed by 7 weeks of double-blind, placebo-controlled, randomized withdrawal assessment in subjects 12-17 years old. About 40 subjects will be initiated, dose optimized, and maintained on NFC-1 over a period of 5 weeks.

[0186] Doses will be administered orally twice daily and will be optimized to 50. 100, 200 or 400 mg twice daily as appropriate over the initial 5 weeks. Response to treatment is defined as achieving significant improvement in symptoms as indicated by a CGI-I score of <3 and a CGI-S score of <4 after 5 weeks of dose optimization.

[0187] At the end of Week 5, subjects will be randomized to NFC-1 or placebo if they have a CGI-I score of <3 and a CGI-S score of <4 (responders) in order to conduct the 7-week withdrawal phase of the trial. Subjects in the withdrawal phase will then be assessed for maintenance of efficacy or treatment failure (defined as a 2 or more-point increase in CGI-S compared to scores at the end of Week 5) over the subsequent 7 weeks. Subjects experiencing a relapse (defined as an increase of at least 2 points on the CGI-S score at the end of Week 5) will discontinue treatment.

[0188] Efficacy and the effect of NFC-1 on individual symptoms will be assessed using CGI-I, CGI-S, ADHD rating scale score, the Pediatric Anxiety Rating Scale (PARS), Aberrant Behavior Checklist (ABC), and the Childhood Autism Rating Scale 2 (CARSTM-2). The ABC test is a symptom checklist for assessing problem behaviors in individuals with mental retardation. It involves clinical assessment of the person's degree of mental retardation, medical status, and current medical condition and involves assessment of 58 specific symptoms to be conducted by

parents, educators, psychologists, nurses or physicians with knowledge of the subject. Among the behaviors assessed are irritability/agitation, lethargy/social withdrawal, stereotypic behavior, hyperactivity/noncompliance, and inappropriate speech. PARS is a clinician-rated scale of anxiety symptoms in pediatric subjects consisting of a list of 50 anxiety related symptoms. Each of the 50 items is scored on a scale of 0 to 5 with 0 indicating no symptoms and 5 indicating severe symptoms. The CARSTM-2 rating scale is a question-based scale that helps to assess symptoms of childhood autism. The scale is given in points of 1 for normal, 2 for mildly abnormal, 3 for moderately abnormal, and 4 for severely abnormal. The questionnaire assesses 15 items such as relating to people, imitation, emotional response, adaptation to change, visual response, listening response, fear/nervousness, verbal and non-verbal communication, and activity level. Scores range from 15 to 60, depending on the score for each item (1-4).

Example 4: Blind Screen of Biorepository Samples for mGluR Network CNVs and Link to ADHD Diagnosis

[0189] A total of 3445 biorepository samples from the biorepository at the Center for Applied Genomics at Children's Hospital of Philadelphia having records of psychiatric evaluation were studied to determine how many of the samples have one or more CNVs in a Tier 1 or 2 mGluR network gene. The genotype tester/analyzer was not aware of the subject's psychiatric diagnosis while performing the CNV analysis. A goal of the study was to estimate the predictive value of CNVs in mGluR network genes by analyzing how many of the CNV positive samples had been previously confirmed from the accompanying psychiatric evaluation data to have ADHD. Of the 3445 samples, 155 were confirmed to have at least one CNV in a Tier 1 or Tier 2 mGluR network gene, or about 4.5%. Of the 155 having a CNV in a Tier 1 or 2 mGluR network gene, 138 were previously confirmed to have ADHD, whereas there were no such records for the remaining 17 subjects. In addition, about 60% of the 138 ADHD subjects also had co-morbid anxiety symptoms.

[0190] Of the 17 subjects for whom there were no records, 14 families were successfully contacted and questioned as to whether the subject had been diagnosed with ADHD. 13 of the 14 families confirmed that the subject indeed had been diagnosed with ADHD. Note that one of the 13 had Down Syndrome, and was considered negative for ADHD for purposes of this study. Thus, overall, of the 155 subjects with at least on CNV in an mGluR network gene, 138+12 subjects (150), or about 97%, also had been diagnosed with ADHD, while there was no data for 3 of the remaining 5 subjects. These data indicate that presence of a CNV in a Tier 1 or 2 mGluR network gene may be a powerful indicator of ADHD in pediatric subjects.

Example 5: Study of Phenotypes Associated with mGluR Network CNVs

[0191] A total of 1,000 ADHD patients aged 6-17 years were enrolled in a trial to consider phenotypes that may be associated with CNVs in Tier 1 or 2 mGluR network genes. Study sites collected saliva for a DNA sample. Each DNA sample was then subjected to DNA extraction, genetic sequencing, and biobanking of DNA.

[0192] Genetic sequencing results together with medical history were used to evaluate genotype (based on genetic sequencing) and phenotype (based on interviews conducted by a clinician with the subject's parent(s)/guardian(s)). Subjects had ADHD as defined by the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-V).

[0193] A single clinician, blinded to the genotype data, provided a series of questions related to potential behavioral or health phenotypes to the parent(s) or legal guardian(s) of the subjects. For each individual phenotype, the parent/guardian was asked: "Is this a current concern" and a Yes or No answer was collected. The clinician determined the frequency of Yes and No responses to generate phenotype data.

[0194] The study found that prevalence of anger control as a current concern was 58.9% in ADHD subjects with a Tier 1 or 2 mGluR network gene CNV but only 47.4% in ADHD subjects without such an mGluR network gene CNV. This difference was statistically significant (odds ratio of 1.59, P=0.003). This odds ratio of greater than 1 implies a higher prevalence of current anger control concerns in ADHD subjects who had a Tier 1 or 2 mGluR network gene CNV versus those without such a CNV.

[0195] The prevalence of disruptive behavior as a current concern for parents was 57.1% in ADHD subjects with a Tier 1 or 2 mGluR network gene CNV and 43.9% in ADHD subjects without such an mGluR network gene CNV. This difference was also statistically significant (odds ratio of 1.70, P<0.001), indicating a higher prevalence of current disruptive behavior concerns in ADHD subjects who also had an mGluR network gene mutation versus those without a mutation.

Example 6: Copy Number Variation in mGluR Network Genes in ADHD Subjects with Co-Morbid Disorders

[0196] Samples from 2707 known ADHD pediatric subjects (mean age of about 10-10.5 years) were genotyped on 550/610 Illumina chips to determine if they have one or more CNVs in Tier 1 or Tier 2 genes. The 2707 subjects included 759 females and 1778 males of African American or white ethnicity (1063 and 1483, respectively). 430 of the 2707 subjects (16.9%) had at least one CNV in an mGluR Tier 1 or Tier 2 gene.

[0197] The 2707 subjects' records were also checked to determine if they had co-morbid diagnoses according to the World Health Organization International Classification of Diseases 9th Edition (ICD-9). Of the 2707 subjects, 1902 (about 70%) had comorbidities while 805 did not. Of those 1902 subjects with comorbidities, about 30% had more than one comorbidity, and about 20% had two or more, while smaller percentages had larger numbers of comorbidities.

[0198] The most prevalent comorbidities, each occurring in more than 100 of the subjects, are listed in Table 10. The table lists the comorbidities by ICD-9 code and provides the number of cases among the 2707 subjects (column titled "N") and name for each co-morbid condition or disorder.

TABLE 10

The most prevalent comorbidities

ICD-9 Code	N	Name
N_299.00	342	Autistic disorder, current or active state
N_299.80	267	Other specified pervasive developmental disorders, current or active state

TABLE 10-continued

The most prevalent comorbidities

ICD-9 Code	N	Name
N_299.90	179	Unspecified pervasive developmental disorder, current or active state
N_300.00	407	Anxiety state unspecified
N_311	244	Depressive disorder not elsewhere classified
N_312.9	568	Unspecified disturbance of conduct
N_313.81	313	Oppositional defiant disorder (ODD)
N_314.9	120	Unspecified hyperkinetic syndrome of childhood
N_315.2	320	Other specific developmental learning difficulties
N_315.31	189	Expressive language disorder
N_315.32	157	Mixed receptive-expressive language disorder
N_315.39	327	Other developmental speech disorder
N_315.4	116	Developmental coordination disorder
N_315.5	160	Mixed development disorder
N_315.8	398	Other specified delays in development
N_315.9	479	Unspecified delay in development
N_319	110	Unspecified intellectual disabilities

[0199] The comorbidies in Table 10 tend to cluster into a few different groups: disorders related to anxiety, depression, or mood; prevalent developmental disorders; less prevalent developmental disorders; and autism and related disorders.

[0200] The genotype data and the comorbidity data were then combined to determine how many of the subjects with CNVs in Tier 1 or 2 mGluR network genes also had comorbidities. It was found that 316 of the subjects with such a CNV also had at least one comorbidity (about 18% of the CNV-positive subjects or about 12% of the total subjects) while 114 of the subjects without a Tier 1 or 2 mGluR network gene CNV had at least one comorbidity (about 15% of the CNV-negative subjects or about 4% of the total subjects). This difference showed a P value of 0.118. Thus, comorbidities tended to be more common in CNV-positive than in CNV-negative subjects overall. When only subjects identifying as white ethnicity are considered, there was a highly significant correlation between mGluR CNVs and ADHD comorbidities. Specifically, 218 of 1483 subjects had at least one CNV in a Tier 1 or 2 mGluR network gene, and, of those 218 subjects, 169 also had a comorbidity whereas 49 did not. That difference showed a P value of 0.004.

[0201] The foregoing written specification is considered to be sufficient to enable one skilled in the art to practice the embodiments. The foregoing description and Examples detail certain embodiments and describes the best mode contemplated by the inventors. It will be appreciated, however, that no matter how detailed the foregoing may appear in text, the embodiment may be practiced in many ways and should be construed in accordance with the appended claims and any equivalents thereof.

[0202] As used herein, the term about refers to a numeric value, including, for example, whole numbers, fractions, and percentages, whether or not explicitly indicated. The term about generally refers to a range of numerical values (e.g., +/−5-10% of the recited range) that one of ordinary skill in the art would consider equivalent to the recited value (e.g., having the same function or result). When terms such as at least and about precede a list of numerical values or ranges, the terms modify all of the values or ranges provided in the list. In some instances, the term about may include numerical values that are rounded to the nearest significant figure.

1. (canceled)
2. (canceled)
3. (canceled)
4. (canceled)
5. (canceled)
6. (canceled)
7. (canceled)
8. (canceled)
9. (canceled)
10. (canceled)
11. (canceled)
12. (canceled)
13. (canceled)
14. (canceled)
15. (canceled)
16. (canceled)
17. (canceled)
18. (canceled)
19. (canceled)
20. (canceled)
21. (canceled)
22. (canceled)
23. (canceled)
24. (canceled)

25. A method of treating attention deficit hyperactivity disorder (ADHD) in a subject comprising administering fasoracetam to a subject who has a copy number variation (CNV) in at least one metabotropic glutamate receptor (mGluR) gene at a dose of 100-400 mg twice daily, thereby treating ADHD.

26. The method of claim **25**, wherein the fasoracetam is administered at a dose of 100-200 mg twice daily.

27. (canceled)
28. (canceled)

29. The method of claim **25**, wherein the subject has CNVs in at least two mGluR network genes.

30. The method of claim **25**, wherein the subject is a pediatric or adolescent subject.

31. (canceled)
32. (canceled)
33. (canceled)
34. (canceled)
35. (canceled)
36. (canceled)
37. (canceled)
38. (canceled)
39. (canceled)

40. The method of claim **25**, wherein the subject has a CNV in at least one Tier 1 mGluR network gene.

41. The method of claim **25**, wherein the subject has a CNV in at least one Tier 2 mGluR network gene.

42. (canceled)

43. The method of **25**, wherein the subject does not have a CNV in any of GRM1, GRM2, GRM3, GRM4, GRM5, GRM6, GRM7 or GRM8.

44. The method of claim **25**, wherein the subject has at least one CNV in a Tier 1 or Tier 2 mGluR network gene but does not have a CNV in a Tier 3 mGluR network gene.

45. The method of claim **25**, wherein treating ADHD in the subject comprises reducing at least one of inattentiveness, hyperactivity, or impulsiveness.

46. The method of claim **25**, wherein the subject has one or more of the following changes in symptoms after at least four weeks of treatment with the fasoracetam:

a. the subject has symptoms of difficulty controlling anger and the anger control symptoms are reduced;
b. the subject has symptoms of disruptive behavior and the disruptive behavior symptoms are reduced;
c. the subject's CGI-I is reduced by at least 1;
d. the subject's CGI-I score after is 1 or 2;
e. the subject's CGI-S score is 1;
f. the subject's ADHD Rating Scale score is reduced by at least 25%
g. the subject has symptoms of inattentiveness and the inattentiveness symptoms are reduced;
h. the subject has symptoms of hyperactivity and the hyperactivity symptoms are reduced;
i. the subject has symptoms of impulsiveness and the impulsiveness symptoms are reduced;
j. the subject has symptoms of anger and irritability, argumentation and defiance, and/or vindictiveness-and the symptoms are reduced; and
k. the subject has symptoms of movement disorder and the movement disorder symptoms are reduced.

47. A method of treating 22q deletion and/or duplication syndrome in a subject comprising administering an effective amount of fasoracetam a subject with 22q deletion and/or duplication syndrome, thereby treating 22q deletion and/or duplication syndrome.

48. The method of claim **47**, wherein the subject has a CNV in RANBP1.

49. The method of claim **47**, wherein the subject has a deletion or a duplication at 22q11.2.

50. The method of claim **47**, wherein the subject has a CNV in a Tier 1, Tier 2, or Tier 3 mGluR network gene.

51. The method of claim **47**, wherein the subject has attention deficit hyperactivity disorder (ADHD).

52. The method of claim **47**, wherein the subject is a pediatric or adolescent subject.

53. (canceled)

54. (canceled)

55. The method of claim **47**, wherein the fasoracetam is administered at a dose of 100-400 mg twice daily.

56. The method of claim **55**, wherein the fasoracetam is administered at a dose of 100-200 mg twice daily.

57. (canceled)

58. (canceled)

59. (canceled)

60. (canceled)

61. (canceled)

62. (canceled)

63. (canceled)

64. (canceled)

65. (canceled)

66. The method of claim **47**, wherein the fasoracetam is administered in an amount effective to result in a clinical general impression-improvement (CGI-I) score of 1 or 2 and/or an improvement of at least 25% in an ADHD rating scale score after four weeks of treatment in a majority of subjects of at least one clinical trial.

67. The method of claim **47**, wherein 22q deletion and/or duplication syndrome is deemed treated if at least one of impulsiveness, hyperactivity, or inattentiveness is improved in the subject.

68. The method of claim **47**, wherein the subject does not have a CNV in any of GRM1, GRM2, GRM3, GRM4, GRM5, GRM6, GRM7 or GRM8.

69. (canceled)

70. (canceled)

71. (canceled)

72. (canceled)

73. (canceled)

74. (canceled)

75. (canceled)

76. (canceled)

77. (canceled)

78. (canceled)

79. (canceled)

80. The method of claim **25**, wherein the fasoracetam is administered in an amount effective to result in an improvement of at least 40% in an ADHD rating scale score after four weeks of treatment in a majority of subjects of at least one clinical trial.

81. The method of claim **47**, wherein the fasoracetam is administered in an amount effective to result in an improvement of at least 40% in an ADHD rating scale score after four weeks of treatment in a majority of subjects of at least one clinical trial.

82. The method of claim **25**, wherein the fasoracetam is administered at a dose of 200-400 mg twice daily.

83. The method of claim **47**, wherein the fasoracetam is administered at a dose of 200-400 mg twice daily.

* * * * *