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Keating et al.

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[54] **DIAGNOSIS OF WILLIAMS SYNDROME AND WILLIAMS SYNDROME COGNITIVE PROFILE BY ANALYSIS OF THE PRESENCE OR ABSENCE OF A LIM-KINASE GENE**

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[21] Appl. No.: **678,039**

[22] Filed: **Jul. 10, 1996**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 474,020, Jun. 7, 1995, which is a continuation of Ser. No. 41,576, Apr. 5, 1993, abandoned.

[51] **Int. Cl.**⁶ **C12Q 1/68**; C12P 19/34; C12N 15/00

[52] **U.S. Cl.** **435/6**; 435/91.1; 435/91.2; 536/23.1; 536/23.5; 536/24.31; 536/24.33; 935/76; 935/77

[58] **Field of Search** 435/6, 91.1, 91.2, 435/320.1, 183; 536/23.1, 23.5, 24.31, 24.33; 935/1, 8, 26, 76, 77, 78

[56] **References Cited**
PUBLICATIONS

Lowery et al., "Strong Corelation of Elastin Deletions, Detected by Fish, with Williams Syndrome: Evaluation of 235 Patients," *American Journal of Genetics*, vol. 57, pp. 49-53, 1995.

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[57] **ABSTRACT**

Williams syndrome (WS) is a developmental disorder that includes poor visuospatial constructive cognition. This syndrome has been studied to identify genes important for human cognitive development. Two families are described which have a partial WS phenotype; affected members have the specific WS cognitive profile and vascular disease, but lack other WS features. Submicroscopic chromosome 7q11.23 deletions cosegregate with this phenotype in both families. DNA sequence analyses of the region affected by the smallest (83.6 kb) deletion revealed two genes, elastin (ELN) and LIM-kinase1 (LIMK1). The latter encodes a novel protein kinase with LIM domains and is strongly expressed in the brain. Because ELN mutations cause vascular disease but not cognitive abnormalities, these data implicate LIMK1 hemizygoty in impaired visuospatial constructive cognition.

15 Claims, 8 Drawing Sheets

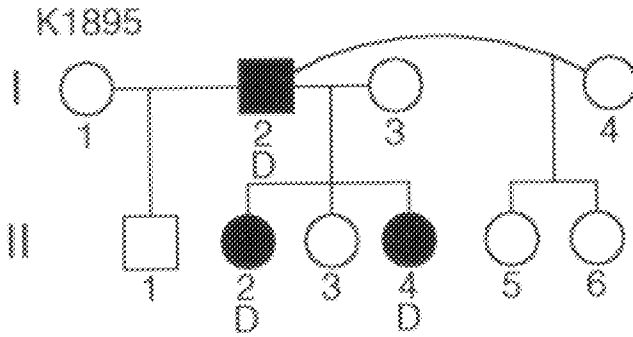


FIG. 1A

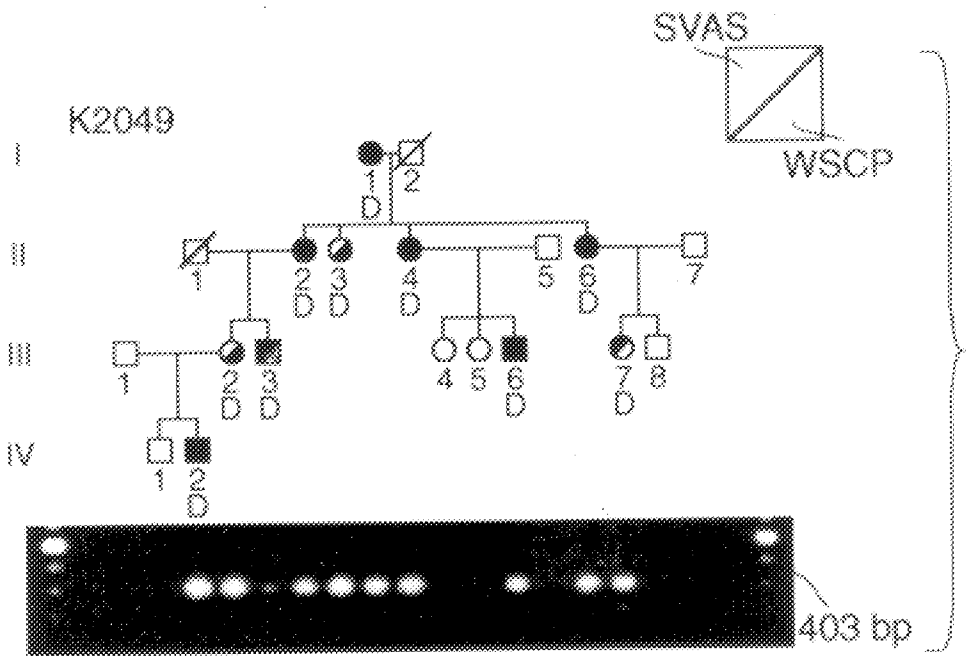
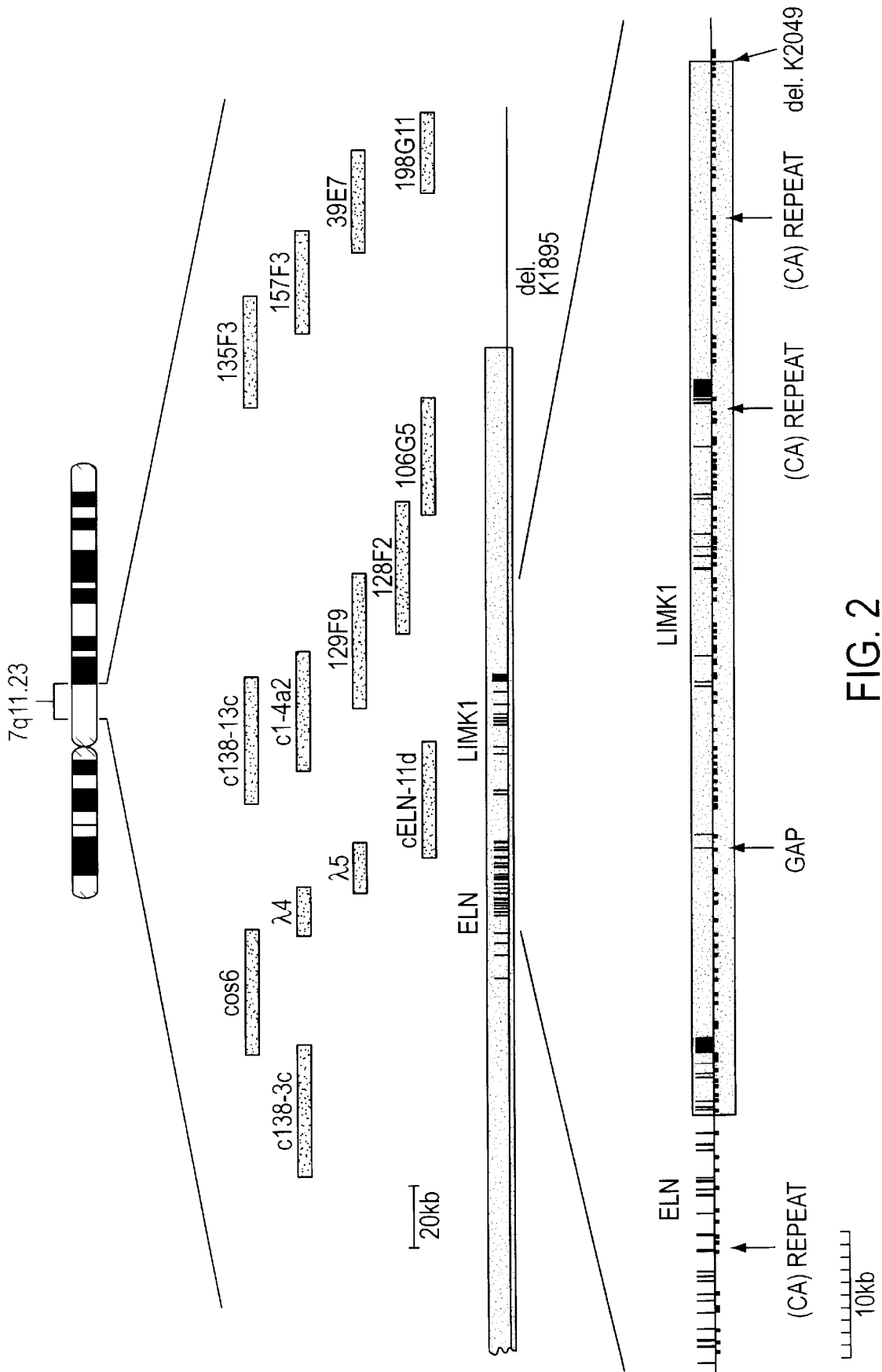


FIG. 1B



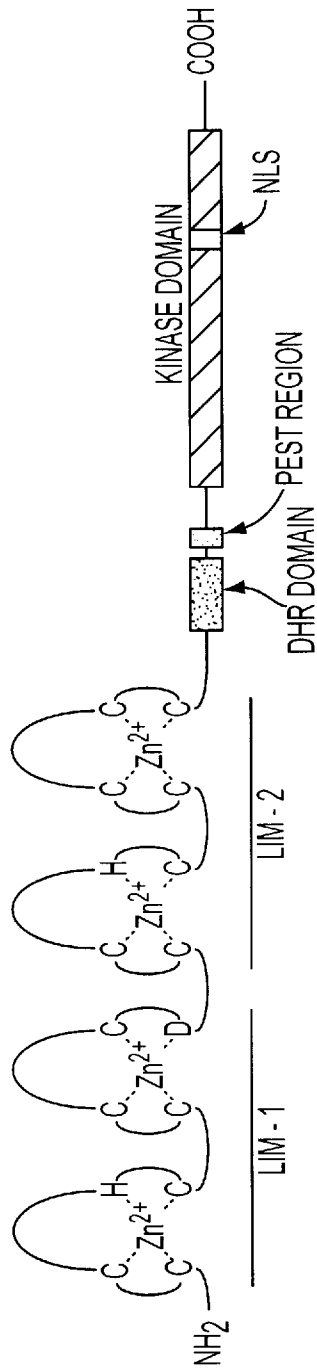


FIG. 3B

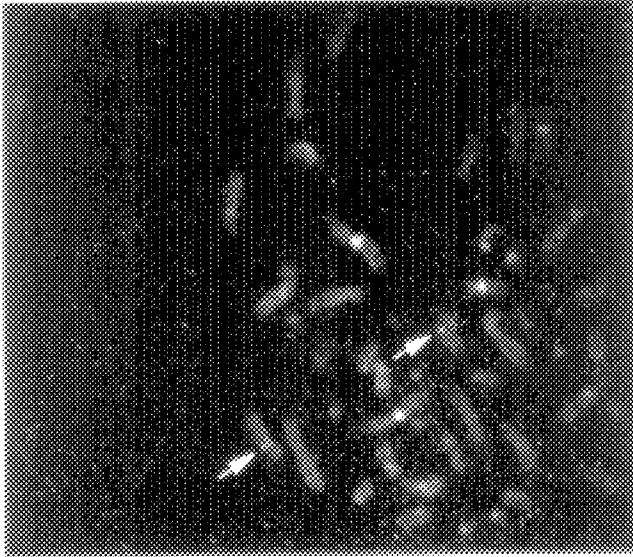


FIG. 4A

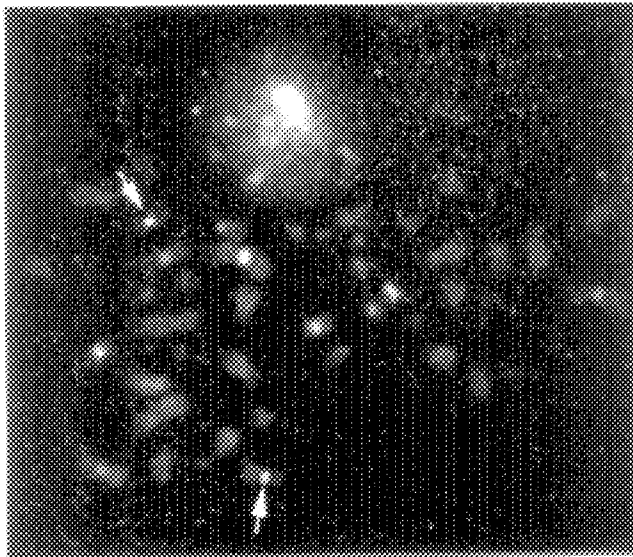


FIG. 4B

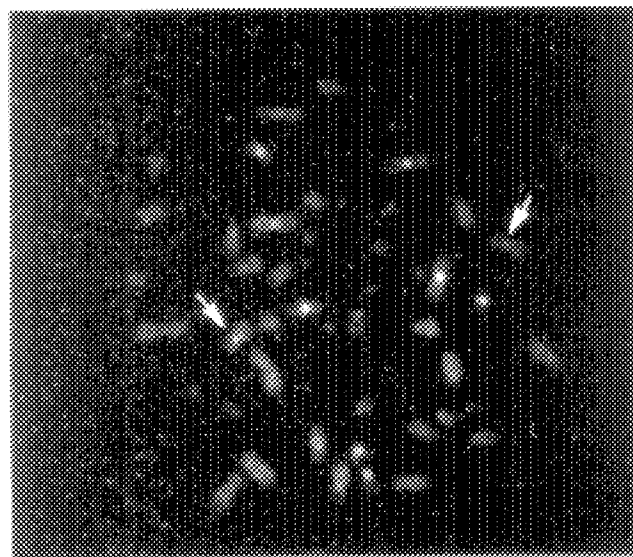


FIG. 4C



FIG. 4D

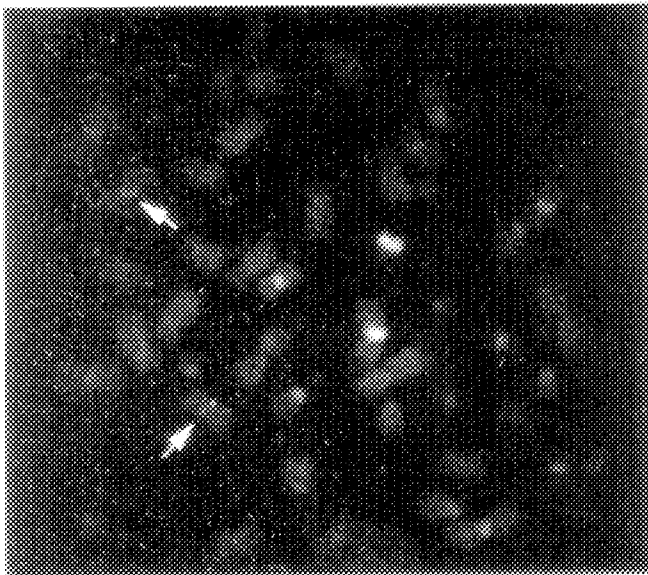


FIG. 4E

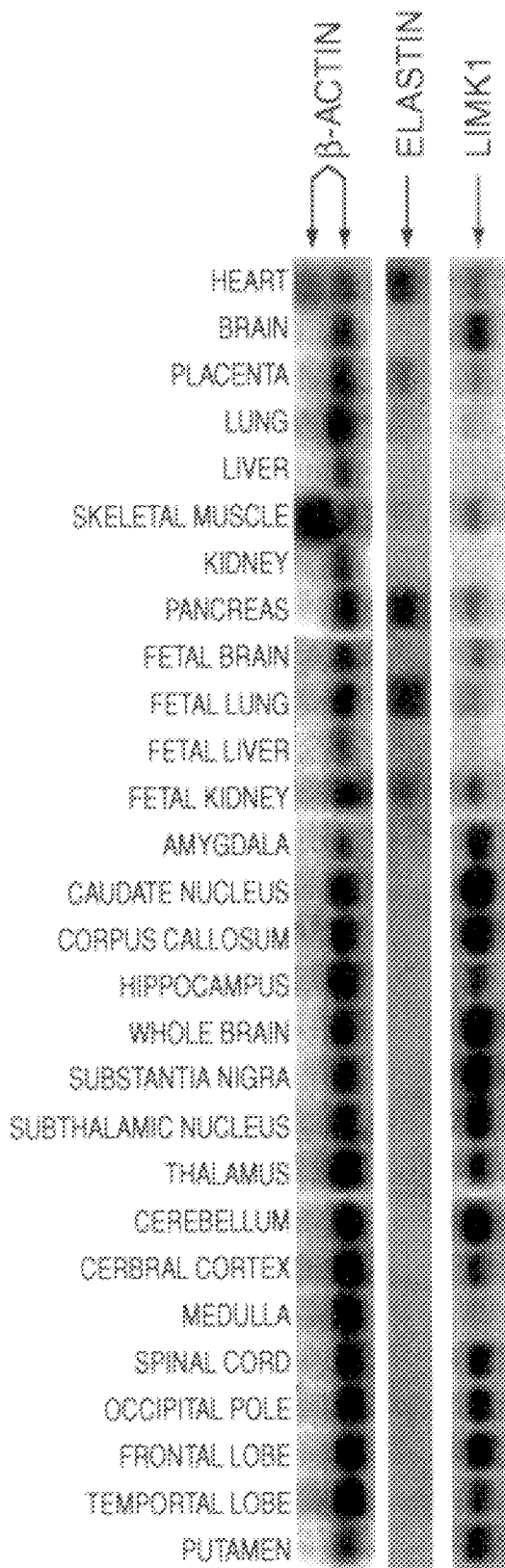


FIG. 5A

NORMALIZED LIMK1
EXPRESSION

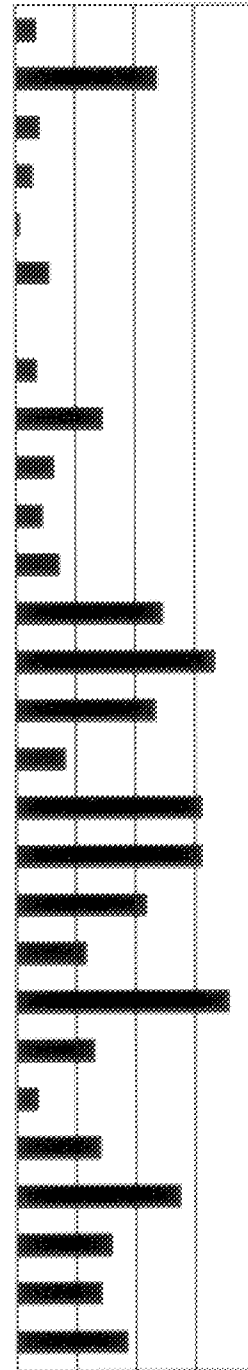


FIG. 5B

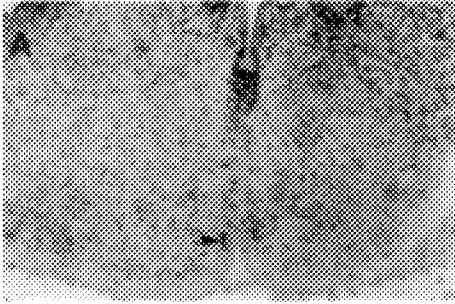


FIG. 6A

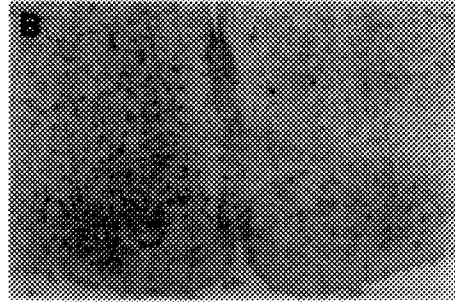


FIG. 6B

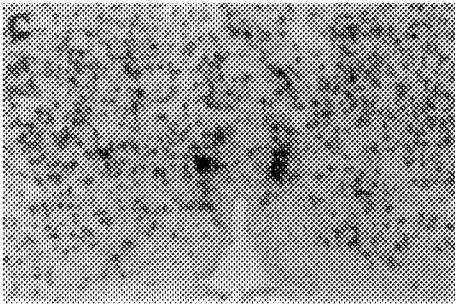


FIG. 6C

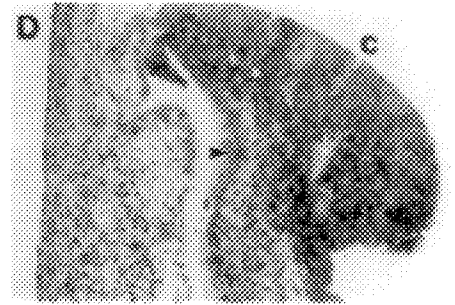


FIG. 6D

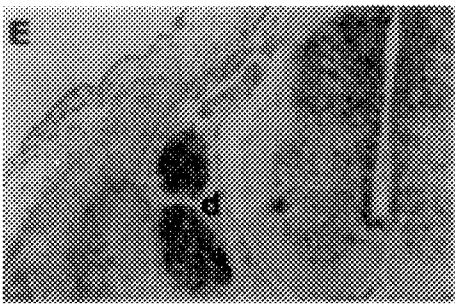


FIG. 6E

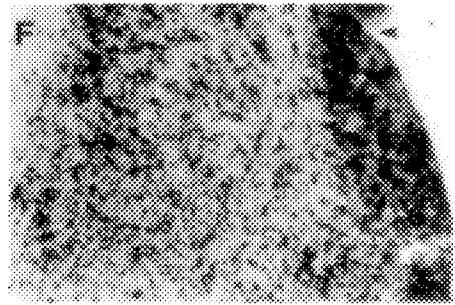


FIG. 6F

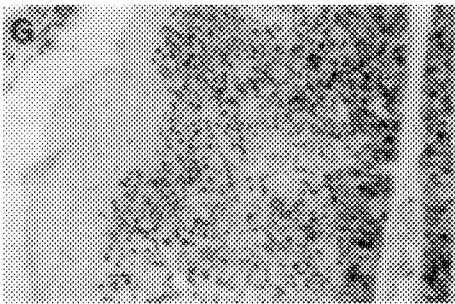


FIG. 6G

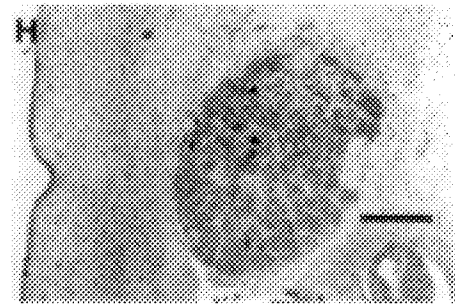


FIG. 6H

**DIAGNOSIS OF WILLIAMS SYNDROME
AND WILLIAMS SYNDROME COGNITIVE
PROFILE BY ANALYSIS OF THE PRESENCE
OR ABSENCE OF A LIM-KINASE GENE**

**CROSS REFERENCE TO RELATED
APPLICATIONS**

The present invention is a continuation-in-part of application Ser. No. 08/474,020, filed 7 Jun. 1995, which is a continuation of application Ser. No. 08/041,576, filed 5 Apr. 1993, which are both incorporated herein by reference.

This application was made with Government support under Grant No. R01HL4807 from the NHLBI, Grant No. R01HD29957 from the NICHD, and Grant No. M01-RR00064 from the Public Health Service. The United States Government has certain rights in the invention.

BACKGROUND OF THE INVENTION

The publications and other materials used herein to illuminate the background of the invention, and in particular, cases to provide additional details respecting the practice, are incorporated by reference, and for convenience are referenced in the following text by author and are listed alphabetically by author in the appended bibliography.

The ability to visualize an object (or picture) as a set of parts and construct a replica of the object from those parts is known as visuospatial constructive cognition. Neuroanatomical studies in humans and animals suggest that neurons in the posterior parietal cortex are critical for this process (Capruso et al., 1995). This cognitive function is likely mediated by a network of neurons capable of parallel processing. The molecular mechanisms underlying development of these networks, however, are not understood.

Williams syndrome (WS) is a complex developmental disorder that includes a specific cognitive profile (WSCP) characterized by relative strength in language and auditory rote memory and pronounced weakness in visuospatial constructive cognition (Udwin et al., 1987; Morris et al., 1988; Dilts et al., 1990; Bellugi et al., 1994; Mervis and Bertrand, in press; Mervis et al., in press). Additional features of WS include congenital heart and vascular disease, dysmorphic facial features, infantile hypercalcemia, mental retardation, and a characteristic personality. Most individuals with WS have mild or moderate mental retardation (mean IQ ranging from 55-60), but some have borderline normal intelligence or severe mental retardation. The characteristic personality includes excessive friendliness, loquaciousness, oversensitivity to the feelings of others, and extreme anxiety to please. This combination of features results in a remarkable phenotype that is readily distinguished from other disorders involving mental retardation. The incidence of WS is estimated to be 1 in 20,000 live births.

The visuospatial constructive cognitive deficit observed in WS is best demonstrated by tasks involving pattern construction. Performance of these tasks depends on an individual's ability to see an object in terms of a set of parts specified by the researcher and then use those parts to construct a replica of the pictured object. Specifically, individuals are shown a picture of a block design and must construct the corresponding pattern using cubes of varying colors and designs. Individuals with WS typically have difficulty constructing even simple patterns, such as a checkerboard consisting of four cubes. As a result, individuals with WS have marked difficulty in tasks involving the use of a pattern to assemble an object (e.g. building a model or assembling a simple piece of furniture).

Approximately 77% of individuals with WS have clinically apparent supravalvular aortic stenosis (SVAS), an obstructive vascular disease (Lowery et al., 1995). SVAS can be inherited as part of WS or as an isolated, autosomal dominant trait (Curran et al., 1993; Ewart et al., 1993b; Morris et al., 1993; Ewart et al., 1994). SVAS may be associated with some connective tissue abnormalities seen in WS, but other WS features are not observed. In particular, autosomal dominant SVAS is not associated with impaired visuospatial constructive cognition. Recently, genetic linkage and mutational analyses were used to show that mutations in elastin (ELN) cause autosomal dominant SVAS (Ewart et al., 1993a; Curran et al., 1993; Morris et al., 1993; Ewart et al., 1994). Known SVAS-associated mutations in ELN include a translocation, an intragenic deletion, and missense and nonsense mutations (Curran et al., 1993; Olson et al., 1995; unpublished data).

Because there is a phenotypic link between SVAS and WS, it was hypothesized that mutations involving ELN might also contribute to WS. It was discovered that WS results from submicroscopic deletions of chromosome 7q11.23 (Ewart et al., 1993a). Inherited or de novo deletion of one ELN allele was identified in 239 of 240 WS individuals (Ewart et al., 1993a; Lowery et al., 1995; and our unpublished data). These data indicated that ELN mutations cause isolated, autosomal dominant SVAS and that hemizyosity at the ELN locus is responsible for vascular pathology in WS. ELN hemizyosity may also account for some connective tissue abnormalities observed in individuals with autosomal dominant SVAS or WS, including premature aging of skin, some WS facial features, diverticulosis of the bladder and colon, hoarse voice, hernias and joint abnormalities. ELN mutations, however, do not account for all features of WS and are not the cause of impaired visuospatial constructive cognition. Because genomic deletions responsible for WS extend well beyond the ELN locus (unpublished data), it was hypothesized that WS is a contiguous gene deletion syndrome (Ewart et al., 1993a).

Here is reported the identification and characterization of two families with a partial WS phenotype, consisting of SVAS, some WS facial features, and impaired visuospatial constructive cognition, but lacking other features of this disorder. Affected members of these families harbor smaller chromosomal deletions (83.6 and ~300 kb) than those identified in individuals with classic WS (>500 kb), an observation that supports the hypothesis that WS is a contiguous gene deletion syndrome (Ewart et al., 1993a; Gilbert-Dussardier et al., 1995). DNA sequence analyses of the 83.6 kb deletion region have revealed, in addition to ELN, LIM-kinase 1 (LIMK1), a gene which encodes a protein kinase with LIM domains (Mizuno et al., 1994; Bernard et al., 1994). No other genes were identified in the region. Northern and in situ hybridization analyses indicate that LIMK1 is strongly expressed in discrete regions of the brain. Because ELN mutations cause vascular disease but not cognitive abnormalities, these data indicate that LIMK1 hemizyosity contributes to impaired visuospatial constructive cognition in WS.

SUMMARY OF THE INVENTION

To identify genes important for human cognitive development, Williams syndrome (WS), a developmental disorder that includes poor visuospatial constructive cognition, has been studied. Two families are here described with a partial WS phenotype; affected members have the specific WS cognitive profile and vascular disease, but lack other WS features. Submicroscopic chromosome 7q11.23

deletions cosegregate with this phenotype in both families. DNA sequence analyses of the region affected by the smallest (83.6 kb) deletion revealed two genes, elastin (ELN) and LIM-kinase1 (LIMK1). The latter encodes a novel protein kinase with LIM domains and is strongly expressed in the brain. Because ELN mutations cause vascular disease but not cognitive abnormalities, these data implicate LIMK1 hemizyosity in impaired visuospatial constructive cognition.

BRIEF DESCRIPTION OF THE FIGURES

FIGS. 1A and 1B. Co-inheritance of a partial WS phenotype and deletions involving ELN and LIMK1 in kindreds 1895 and 2049. A) Pedigree structure and phenotypic assignments for K1895 are shown. Individuals with SVAS are indicated by filled, upper half-circles (females) or squares (males). Individuals with the WSCP are indicated by filled, lower half-circles or squares. Phenotypically unaffected individuals are indicated by empty circles or squares. Individuals I-2, II-2, and II-4 were phenotypically affected with both SVAS and the WSCP. No features of WS were identified in other members of this kindred. Individuals harboring an ~300 kb deletion of chromosome 7q11.23, including the entire ELN and LIMK1 genes, are indicated by a D. Note that this deletion cosegregates with the SVAS/WSCP phenotype in this family. B) Phenotypic designations for members of K2049 are as described for FIG. 1A, except that an uncertain phenotype is indicated by stippling. Oligonucleotide primers 403f (5'-CCTACCTTTCCTGCTGCAAT-3' SEQ ID NO:37) and 403r (5'-AAAAGAGGCCGGGTATGGT-3' SEQ ID NO:38) were used to define a novel 403-bp PCR product that spans the 83.6-kb deletion in affected members of this family. The results of PCR analyses are shown below in the lane corresponding to each symbol. Note that this 83.6-kb deletion cosegregates with SVAS/WSCP in this family but that penetrance is incomplete.

FIG. 2. Physical map of the deletions identified in K1895 and K2049. Idiogram of chromosome 7 and a contiguous set of cosmids and phage λ from chromosome 7q11.23 are shown. The relative locations and the structures of ELN and LIMK1 are indicated; exons are indicated by vertical bars extending above the horizontal lines; repetitive elements (e.g., Alu repeats) are denoted by vertical bars extending below the lower horizontal line; the locations of three d(CA)-repeats are indicated (the ELN d(CA)-repeat has been previously defined; Foster et al., 1993). The small 250 bp gap in the sequence contig is immediately 5' of LIMK1. LIMK1 is located 15.4 kb 3' of ELN and is in the same orientation. The locations of the 300 kb deletion identified in K1895 and the 83.6 kb deletion identified in K2049 are indicated by shaded boxes. Note that both deletions disrupt ELN and delete LIMK1.

FIGS. 3A and 3B. Predicted structure of LIMK1. A) DNA sequence analyses were used to predict the amino acid sequence of LIMK1. Two possible start sites are indicated by asterisks. The second start site shows slightly better conformity to the Kozak consensus sequence (Kozak, 1989). Individual amino acids involved in zinc-finger formation as part of two LIM domains are indicated by lightly shaded boxes. A DHR domain between residues 165 and 258 is denoted by a darkly shaded box. A possible PEST domain identified in residues 264–289 is indicated by a lightly shaded box. A basic domain located in residues 499–506 (empty box) may mediate nuclear localization. The kinase domain, indicated by horizontal black bars, is divided into eleven subdomains (I–XI). Conserved amino acids in the

kinase domain are indicated by empty boxes (Hanks et al., 1988). B) Schematic representation of LIMK1 indicating major domains.

FIGS. 4A–4E. FISH analyses demonstrate hemizyosity of LIMK1 in individuals with a partial WS phenotype. Labeled LIMK1 cosmids c138-13c and c1-4a2 were hybridized with metaphase chromosomes from an affected member of K1895 (A) and of K2049 (B), an individual with classic WS (C), an individual with SVAS with a translocation disrupting ELN in exon 28 (D), and an individual with SVAS and no chromosomal anomaly (E). Centromere-specific markers are indicated by arrows (chromosome 7 for all individuals and chromosomes 6 and 7 for the translocation). Affected members of K1895, K2049, and classic WS individuals showed LIMK1 hemizyosity. The individual with SVAS and a t(6p21;7q11) translocation showed hybridization signals on the normal homologue, as well as on the 7q:6q translocation chromosome. An individual with SVAS, with no chromosomal abnormalities, showed LIMK1 hybridization signals on both chromosome 7 homologues. All individuals showed two hybridization signals for chromosome 7 centromere-specific marker.

FIGS. 5A–5B. LIMK1 is expressed strongly in the brain. FIG. 5A shows the results of Northern analyses. Human adult, fetal, and brain Northern blots (poly[A]⁺RNA, 2 μ g per lane) were hybridized with LIMK1, ELN, and β -actin probes. LIMK1 hybridized with an ~3.3 kb mRNA in most tissues examined, with highest expression in both fetal and adult brain. ELN also hybridized with an ~3.3 kb mRNA with highest expression in heart, pancreas, and fetal lung. FIG. 5B shows a graphic representation of LIMK1 expression levels after normalization to β -actin.

FIGS. 6A–6H. In situ hybridization analysis of LIMK1 expression in the nervous system of a Carnegie stage 20 (50 day postovulatory) human embryo. A 625-bp LIMK1 cRNA probe was labeled with DIG-UTP and visualized using anti-DIG alkaline phosphatase antibody. (A) Transverse section through rhombencephalon/medulla, fourth ventricle. LIMK1 expression is seen in the ependymal layer of the fourth ventricle and a lower level of expression extends into the mantle layer. The arrow indicates expression in the medial accessory olivary nucleus on either side of the midline; this area is shown in greater detail in C. (B) Similar section to (A) hybridized with the sense-strand cRNA probe as a negative control. (C) Medial accessory olivary nuclei shown in the center of (A). (D) Transverse section through the cerebellum (c) showing a high level of ependymal expression in the corpus cerebelli (fourth ventricle on the right and ectoderm on the left). Some expression is visible in the mesenchyme adjacent to the ectoderm, in particular in the presumptive dentate nucleus (arrow). (E) Transverse section through the cervical spinal cord showing generalized expression in the dorsal (top) part of the spinal cord and single-cell staining more ventrally (right). There is also expression in the dorsal root ganglia (d). (F) Section through the wall of the mesencephalon (the ventricle is on the far right); the ependymal layer is on the right and heavily stained, and the mantle layer in the center-left shows many cells expressing LIMK1. An arrow indicates the sulcus limitans. (G) Higher magnification of (E), showing the mid-area of the spinal cord, demonstrates a low level of confluent expression in the ependymal layer (right), widespread single-cell staining in the mantle layer (center), and lack of expression in the marginal layer (left). (H) Transverse section through the fifth nerve ganglion shows high expression in the center, in part of the inner ear (lower right, below the scale bar), and in the ectoderm (left). The scale bar represents either 100 μ m (C, F, and G) or 250 μ m (A, B, D, E, and H).

DETAILED DESCRIPTION OF THE INVENTION

Williams syndrome is a contiguous gene disorder resulting from mutations in or deletion of at least three distinct genes. These genes are located on chromosome 7 in the 7q11.23 region. Two of the genes involved in Williams syndrome are elastin (ELN) and LIM-Kinase (LIMK1). A minimum of at least one more gene located greater than 300 kb 3' of LIMK1 is also involved in Williams syndrome. The identity of this gene or genes has not yet been established. Williams syndrome results from loss of all of the involved genes. Loss of only one or two of the involved genes causes other disorders which involve only some of the aspects of Williams syndrome. A partial loss of functional elastin due to the presence of only one wild-type elastin gene results in the condition known as supravalvular aortic stenosis (SVAS) which is an obstructive vascular disease. Elastin is a structural protein important in large arteries, lungs and skin. A partial loss of both functional elastin and LIMK1 due to the presence of only one wild-type copy of each of the corresponding genes results in the condition known as Williams syndrome cognitive profile (WSCP). LIMK1 is a protein kinase which is highly expressed in the brain and is important in visuospatial constructive cognition. A functional loss of not only elastin and LIMK1 but also at least one more protein encoded by a gene 3' of LIMK1 results in development of classic Williams syndrome. Persons with SVAS and WSCP have only a subset of the characteristics seen in persons with classic Williams syndrome. Persons with Williams syndrome have been found to have a deletion of greater than 500 kb in the 7q11.23 region of one chromosome, this deletion including at least a portion of ELN, LIMK1 and at least 300 kb 3' of LIMK1. Although some families have been found which show deletions of ELN and LIMK1 but which deletions do not extend far enough 3' to delete a third gene (these families thus being characterized as having WSCP), in 99% of the cases studied a person who has a deletion in ELN is found to have a deletion of greater than 500 kb such that the deletion includes not only ELN but also LIMK1 and at least one other gene 3' of LIMK1 thus resulting in classic Williams syndrome. This is significant in that a hemizygous deletion of ELN indicates a 99% chance that the patient has classic Williams syndrome and not simply SVAS or WSCP.

It is here concluded that LIMK1 hemizyosity contributes to impaired visuospatial constructive cognition in WS. This conclusion is supported by the following observations: 1) SVAS and the WSCP are co-inherited in K1895 and K2049, as well as in classic WS, suggesting that the genes responsible for these two phenotypes are closely linked; 2) ELN and LIMK1 are contiguous genes that are both disrupted by an 83.6-kb deletion that cosegregates with SVAS and the WSCP in K2049; 3) DNA sequence analyses of the 83.6-kb deletion region and 24 kb of flanking sequence revealed only ELN and LIMK1; no other genes were identified in these sequences; 4) LIMK1 is highly expressed in the brain, consistent with its possible function in cognitive development; and 5) intragenic deletions and point mutations affecting only ELN cause SVAS but no cognitive impairment, indicating that ELN hemizyosity is not sufficient to cause impaired visuospatial constructive cognition in WS.

It is also very unlikely that ELN mutations are necessary for impaired visuospatial constructive cognition in WS. First, no correlation exists between the severity of the vascular disease and the severity of cognitive impairment in WS. Second, ELN is a structural protein that is important for

the development of elastic fibers in large arteries, lungs, and skin, but these elastic fibers are not found in the brain. Finally, ELN is not expressed in neurons and glial cells of the brain (R. Mecham, personal communication). Therefore, it is concluded that ELN mutations and secondary vascular disease are not sufficient, and almost certainly not necessary, for impaired visuospatial constructive cognition in WS.

The argument that LIMK1 hemizyosity contributes to impaired cognition would be confirmed by the identification of individuals with intragenic mutations of this gene. Preliminary experiments aimed at ascertainment of such individuals have not been successful. This is not surprising, because these individuals are probably rare and likely have a very subtle phenotype. To exclude the involvement of additional genes in development of the WSCP, the 83.6-kb deletion region and 24 kb of flanking sequence were sequenced. Programs designed to identify coding regions revealed only two genes, LIMK1 and ELN. While these analyses did not absolutely exclude the presence of a third gene, the sensitivity of the search algorithms was demonstrated by their identification of 15 of the 16 LIMK1 exons. It is highly likely, therefore, that all genes in this region were detected.

Previous studies of LIMK1 expression are consistent with a role for this gene in cognitive development. Northern analyses in rat showed LIMK1 expression in multiple tissues, with mRNA levels being highest in the brain (Mizuno et al., 1994). Bernard et al. (1994) identified ubiquitous murine embryonal expression, but found significant mRNA levels only in the adult brain. In situ hybridization and immunohistochemical studies performed in mice and humans localized LIMK1 mRNA and protein exclusively to neurons (basal ganglia, Purkinje cells, and pyramidal neurons; Bernard et al., 1994). Using Northern blot analysis, Proschel et al. (1995) demonstrated expression of LIMK1 in adult murine spinal cord, cortex, cerebellum, and placenta, with lower levels of mRNA in several other tissues. In situ hybridization of tissues collected during various stages of murine development indicated expression of LIMK1 in the developing brain, including the subpial layers of the frontal cortex, the midbrain roof, tectum, cerebellum, and neural epithelium of the olfactory bulb. In the adult mouse, LIMK1 expression persisted in the cerebral cortex. Our Northern data indicate expression of LIMK1 in multiple human fetal and adult tissues but mRNA levels were highest in brain. In situ hybridization data presented here also indicate that in developing human tissues, LIMK1 mRNA is predominantly found in brain, a localization consistent with the pattern of LIMK1 expression in the mouse and rat (Bernard et al., 1994; Cheng and Robertson, 1995; Nunoue et al., 1995; Proschel et al., 1995). The discrete organization of LIMK1 expression in the developing and adult nervous system, with consistent expression in the ependymal layer from which neurons are generated, is consistent with the hypothesis that this gene plays an important role in neural development.

The data suggest that impaired visuospatial constructive cognition in WS results from a quantitative reduction in LIMK1 mRNA and protein. This hypothesis is consistent with recent data examining the role of protein kinases in murine development. Impaired long-term potentiation, spatial learning, and hippocampal development were identified in mice deficient in the brain-specific protein kinases fyn (Grant et al., 1992) and the γ isoform of protein kinase C (Abeliovich et al., 1993a; Abeliovich et al., 1993b). Although the spatial learning deficits observed in these mice were not directly analogous to impaired visuospatial con-

structive cognition in humans with WS, the data do indicate a role for kinases in neuronal development.

The function of LIMK1 is not known, but the presence of specific functional domains suggests possibilities. LIM domains are zinc-binding motifs first identified in the developmentally important genes *lin-11*, *Isl-1*, and *mec-3* (Freyd et al., 1990; Karlsson et al., 1990; Way and Chalfie, 1988). LIM domains have been identified in isolation, or in combination with homeodomains, and are thought to modulate cell fate and differentiation (Schmeichel and Beckerle, 1994). LIMK1, by contrast, is unique because it contains a kinase domain in addition to two LIM domains. Predicted amino acid sequence analyses also indicate the presence of a possible PEST domain, a type of sequence that is often found in proteins with short half-lives. This observation suggests that levels of LIMK1 may be tightly regulated. Finally, the predicted amino acid sequence of LIMK1 indicates that cytoskeleton and nuclear localization signals may be present. Biochemical and developmental studies of LIMK1 function will be instrumental in defining the role of this protein in human cognitive development.

The phenotypic variability observed in this study results from variable expression and incomplete penetrance, consistent with results of previous studies of autosomal dominant SVAS and WS (Morris et al., 1988; Ewart et al., 1993a). Variable expression of dysmorphic facial features in individuals with isolated SVAS and classic WS have led to diagnostic confusion in the past (Grimm and Wesselhoeft, 1980), but in this and previous studies, it has been shown that individuals with autosomal dominant SVAS have 6 or fewer of the 16 facial features associated with classic WS. These data indicate that ELN mutations account for SVAS and some WS facial features, but that hemizygosity of another, contiguous gene accounts for other WS facial features. Continued deletional analyses should help define genes that contribute to the full WS phenotype, including those involved in the facial features, mental retardation, and the WS personality.

The DNA sequence analyses for the present studies revealed a high density of Alu repeats within the region deleted in K2049 (6-fold higher than the estimated mean density throughout the human genome; Hwu et al., 1986; Slightom et al., 1994), a density comparable to that found in the genomic region associated with DiGeorge syndrome (Budarf et al., 1995). Both WS and DiGeorge syndrome result from chromosomal rearrangements, which might be driven by the highly repetitive nature of the DNA. In this regard, it is interesting to note that we identified Alu sequences at both breakpoints in K2049, suggesting that a recombinational event between these elements may have been responsible for this deletion. Alu repeats have previously been implicated in an SVAS-associated translocation and in an intragenic deletion of ELN (Curran et al., 1993; Olson et al., 1995).

In summary, it has been here discovered that hemizygosity of LIM-kinase1, a protein kinase gene expressed in the brain, likely leads to impaired visuospatial constructive cognition in Williams syndrome. Further elucidation of the physiologic significance of this gene may result from gene targeting experiments in mice. Analyses of LIMK1 function should provide further insight into human cognitive development.

EXAMPLE 1

Identification of individuals with a partial WS phenotype

If WS is a contiguous gene deletion disorder, individuals with a partial WS phenotype should exist. To test this

hypothesis, individuals with SVAS were phenotypically characterized for the presence of additional WS features, including facial appearance, the WSCP, the WS personality, and mental retardation. Phenotypic studies included personal interview, physical examination, two-dimensional and Doppler echocardiography, IQ determination, WS personality assessment, and WSCP analyses.

Clinical characterization of participants

Medical records were reviewed and participants were examined by a clinical geneticist. Craniofacial features scored included dolichocephaly, broad brow, periorbital fullness, stellate iris, bitemporal narrowing, low nasal root, flat mala, full cheeks, long philtrum, small jaw, malocclusion, full nasal tip, wide mouth, full lips, prominent ear lobes, and facial asymmetry. Individuals with classic WS had 9 or more of the 16 features and met the diagnostic criteria of Preus (1984). Affected members of K1895 and K2049 had 0–6 of the 16 facial features and none of these individuals fit the diagnostic criteria for WS. The presence and extent of SVAS was determined by two-dimensional echocardiography and Doppler blood-flow analyses as described by Ensing et al. (1989). Individuals were scored as affected if there was narrowing of the ascending aorta demonstrated on echocardiography or if Doppler peak flow velocities were above normal (normal values for adults: aortic 1.0–1.7 m/s, pulmonary 0.6–0.9 m/s; children: aortic 1.2–1.8 m/s, pulmonary 0.7–1.1 m/s). Velocities within 0.2 m/s greater than the normal range were considered weakly positive. Individuals were also scored as positive if SVAS was documented by medical records of cardiac catheterization or surgery.

Determination of Williams Syndrome Cognitive Profile

The general pattern of cognitive strengths and weaknesses observed in WS (WSCP) has been described in several laboratories (Udwin et al., 1987; Bellugi et al., 1994; Mervis and Bertrand, in press; Mervis et al., in press), but until now, no formal method for assessment has been available. The profile assessment that was proposed is based on performance on the DAS (Elliot, 1990), a standardized measure of cognitive abilities. The DAS was specifically designed to identify relative strengths and weaknesses in cognitive abilities. The six core subtests assess language, spatial (visuospatial constructive cognition), and reasoning abilities. A diagnostic subtest measures auditory rote memory. Thus, the DAS covers all of the skills included in the cognitive profile associated with WS.

Individuals who met one or more of the following criteria were excluded from having the WSCP:

- i. pattern construction standard score \geq mean of the core subtest scores (visuospatial constructive ability too high relative to overall level of cognitive abilities)
- ii. pattern construction standard score \geq digit recall standard score (visuospatial constructive ability too high relative to auditory rote memory ability)
- iii. pattern construction standard score \geq 20th percentile (absolute level of visuospatial constructive ability too high)
- iv. none of the seven subtest standard scores $>$ 1st percentile (absolute level of ability too low).

Individuals who were not excluded were considered to have the WSCP and were evaluated further to determine the strength of their match to the WSCP. A maximum of 4 points could be earned (4 points=excellent fit, 3 points=very good fit, 2 points=good fit, and 0–1 point=poor fit to the WSCP).

- i. digit recall standard score $>$ mean of the core subtest standard scores (2 points).

- ii. verbal standard scores > pattern construction standard score
 - a. definition standard score (naming vocabulary was used for younger children) > pattern construction standard score (1 point).
 - b. similarities standard score > pattern construction standard score (1 point).

The DAS was used for individuals who were at least 2 ½ years old. For younger children, the WSCP was assessed using the mental scale of the Bayley Scales of Infant Development (Bayley, 1969; Bayley, 1993). The child was considered to have the WSCP if he or she passed a greater proportion of language items attempted than non-language items. Use of the Bayley to determine if a child's cognitive profile is consistent with the WSCP has been validated in a study comparing very young children with WS to very young children with Down syndrome (Mervis & Bertrand, in press). In the present study, the Bayley measure was used for one child (K1895 II-4), who was 15 months old at the time of assessment.

Individuals who did not complete the DAS were phenotypically characterized with the Wechsler Adult Intelligence Scale-Revised (WAIS-R) whenever possible. Exclusion criteria for the WAIS-R are listed below:

- i. block design standard score > digit span standard score
- ii. block design standard score > 20th percentile
- iii. none of the subtest standard scores > 1st percentile

Individuals who were not excluded on the basis of these criteria were considered to have a cognitive profile consistent with the WSCP if both their digit recall and similarities standard scores were greater than their block-design standard score. Those individuals who could not complete the entire WAIS-R were given the verbal portion of the WAIS-R and the Developmental Test of Visual-Motor Integration (VMI; Beery, 1989). Individuals were excluded from further consideration for the WSCP if their VMI age equivalent was greater than 10 years. Individuals who were not excluded were considered to have a cognitive profile consistent with the WSCP if their standard score on the verbal portion of the WAIS-R was greater than their standard score on the VMI.

Determination of the Williams Syndrome Personality
 Each member of K1895 and K2049 and 9 of the 11 individuals with isolated SVAS were independently assessed for the WS personality by two or three examiners (inter-rater agreement=100%). Of the 85 individuals with classic WS, 65 were assessed by two examiners (inter-rater agreement=98%) and the remainder by one examiner. Twenty-two of the 65 individuals in the control group were assessed by two examiners (inter-rater agreement=95%) and the remainder by one examiner. The following seven WS personality characteristics were evaluated: 1) the presence of an appealing personality; 2) excessive friendliness; 3) loquaciousness; 4) extreme sensitivity to others' feelings; 5) excessive anxiousness to please; 6) very high anxiety; and 7) an extreme interest in people. Phenotypic status was based on the number of characteristics that each individual possessed. Individuals with 4 to 7 of the characteristics were classified as having the WS personality; those with 3 were classified as uncertain; and those with 0 to 2 were classified as not having the WS personality.

Determination of Mental Retardation/Developmental Delay
 Intelligence was assessed using the Bayley for children < 2 ½ years old, the DAS was used for individuals between the ages of 2 ½ and 18 years, and the WAIS-R was used for individuals who were 18 years or older. All measures were administered according to standard procedures. Individuals who were at least 6 years old were considered to have mental

retardation if their standard score was < 70 (> 2 standard deviations below the standardization sample mean). Individuals who were less than 6 years old were considered to have developmental delay if their standard score was < 70.

5 Results

Phenotypic assignment with respect to WSCP was based, whenever possible, on the pattern of performance on subscales of the Differential Ability Scale (DAS; Elliott, 1990), a standardized measure of cognitive abilities. When the DAS could not be administered, phenotypic assignment was based on performance on subscales of the Wechsler Adult Intelligence Scale-Revised (WAIS-R; Wechsler, 1981), the Developmental Test of Visual Motor Integration (VMI; Beery, 1989) or the Mental Scale of the Bayley Scales of Infant Development (Bayley, 1969; Bayley, 1993). Use of the Bayley to determine if a child's cognitive profile is consistent with the WSCP has been validated in a study comparing very young children with WS to very young children with Down syndrome (Mervis and Bertrand, in press). In the present study, the Bayley measure was used for only one child (K1895 II-4), who was 15 months old at the time of assessment. Quantitative data resulting from these tests were used to test for the presence of the WSCP, which involves weakness on the pattern construction subtest and strength on the digit recall subtest relative to performance on other subtests. The results of these studies are summarized in Tables 1-3.

To determine the sensitivity of the WSCP assessment, the DAS was also administered to 48 individuals with WS ranging in age from 4 to 47 years (IQ range 35-84). Of these individuals, 45 fit the WSCP; 40 had an excellent fit, 3 had a very good fit, and 2 had a good fit. To determine specificity, the performance of 25 control individuals with below-average IQ (IQ range 30-95) was also examined. Some of these controls had other syndromes (e.g., Down syndrome or Fragile X syndrome); the others had no specific diagnosis. Of these individuals, 23 of 25 definitely did not fit the WSCP. Thus, the WSCP measure has excellent sensitivity (0.94) and specificity (0.92).

The WS personality was assessed by examining individuals for seven personality characteristics commonly found in WS. Standardized assessments of personality could not be used because these methods do not address the unique characteristics included in the WS personality. Individuals who showed at least 4 of 7 of the characteristics were considered to have the WS personality. Individuals who showed 3 characteristics were classified as uncertain. Individuals who showed 2 or fewer characteristics were considered not to have the WS personality. To determine the sensitivity and specificity of our measure, we evaluated 85 individuals with WS and a control group of 65 individuals with mental retardation or borderline normal intelligence. Eighty-three of 85 WS individuals had the WS personality.

TABLE 1

Phenotypic evaluation of individuals with partial WS phenotype and control subjects						
Individual	SVAS	Facies	WSCP	WSP	MR/DD	DEL
K1895						
I-2	+	3	+	-	-	D(~300 kb)
I-3	-	0	-	-	-	N
II-1	-	0	-	-	-	N
65						
II-2	+	5	+	-	-	D(~300 kb)
II-3	-	0	-	-	-	N

TABLE 1-continued

Phenotypic evaluation of individuals with partial WS phenotype and control subjects						
Individual	SVAS	Facies	WSCP	WSP	MR/DD	DEL
II-4	+	2	+	-	-	D(>300 kb)
II-5	-	0	-	-	-	N
II-6	-	0	-	-	-	N
<u>K2049</u>						
I-1	+	4	+	-	-	D(83.6 kb)
II-2	+	2	+	-	-	D(83.6 kb)
II-3	-	2	+	-	-	D(83.6 kb)
II-4	+	0	+	-	-	D(83.6 kb)
II-5	-	0	-	-	-	N
II-6	+	4	+	-	-	D(83.6 kb)
II-7	-	0	-	-	-	N
III-1	-	0	-	-	-	N
III-2	-	0	+	-	-	D(83.6 kb)
III-3	+	0	U	-	-	D(83.6 kb)
III-4	-	0	-	-	-	N
III-5	-	0	-	-	-	N
III-6	+	0	+	-	+	D(83.6 kb)
III-7	+	0	-	-	-	D(83.6 kb)
III-8	-	0	-	-	-	N
IV-1	-	0	-	-	-	N
IV-2	+	6	+	-	-	D(83.6 kb)
<u>Classic WS</u>						
13759	+	13	+	6	+	D(>500 kb)
13946	+	16	+	+	+	D(>500 kb)
14033	+	15	+	+	+	D(>500 kb)
14101	+	13	+	+	+	D(>500 kb)
14576	-	14	+	+	+	D(>500 kb)
15083	+	13	+	+	+	D(>500 kb)
15266	+	13	+	+	+	D(>500 kb)
17402	+	13	+	+	+	D(>500 kb)
18031	-	14	+	+	+	D(>500 kb)
18296	+	14	+	+	+	D(>500 kb)
<u>Autosomal Dominant SVAS</u>						
12903	+	1	-	0	-	N
12905	+	3	-	0	-	N
12906	+	2	-	0	-	N
12907	+	0	-	0	-	N
13222	+	1	-	-	-	N
13835	+	0	-	-	-	N
14104	+	1	-	0	-	N
14107	+	0	-	0	-	N
17607	+	2	-	0	-	N
20583	+	2	-	-	-	N

Table 1. Phenotypic evaluation was completed in members of two families with a partial WS phenotype (K1895 and K2049), individuals with classic WS, and individuals with autosomal dominant SVAS resulting from ELN mutations. Phenotypic assignments included the presence (+) or absence (-) of SVAS, specific WS cognitive profile (WSCP), and mental retardation or developmental delay (MR/DD). Individuals were assigned 0-7 of 7 possible WS personality characteristics (WSP); individuals were considered affected if they had ≥ 4 characteristics and unaffected if they had ≤ 2 characteristics. The number of WS facial features present (Facies) is also indicated (0-16 of 16 possible WS facial features). The phenotypic assessments for WSCP were based on numerical scores obtained from one of the following standardized tests: 1) Differential Ability Scales; 2) Wechsler Adult Intelligence Scale-Revised; or 3) Mental Scale of the Bayley Scales of Infant Development. Individual III-3 of K2049 was characterized as phenotypically uncertain (U) with respect to WSCP because of a seizure disorder treated with anti-convulsant medication. Individual

III-6 had mild developmental delay, with an IQ=64; the 95% confidence interval was 58-71 (an IQ score of ≥ 70 would be in the normal range). The presence (D) or absence (N) of a chromosome 7q11.23 deletion is indicated at right. Note that SVAS, mild WS facial features, and the WSCP cosegregated with deletions in K1895 and K2049. Incomplete penetrance and variable expression were apparent in these kindreds.

TABLE 2

Assessment of WSCP for individuals completing the DAS						
Individual	Exclusion			Strength of Fit to WSCP		
	PC \geq T	PC \geq D	PC \geq 20%	D > T	V > PC	TOTAL
<u>K1895</u>						
I-2				2	2	4
I-3		x				
II-1	x	x				
II-2				2	2	4
II-3	x		x			
II-5	x		x			
II-6	x	x	x			
<u>K2049</u>						
III-1	x		x			
III-2				2	2	4
III-4	x					
III-5		x				
III-6				2	2	4
III-7		x				
III-8	x	x				
IV-1			x			
IV-2				2	2	4
<u>Classic WS</u>						
13759				2	2	4
13946				2	2	4
14033				2	2	4
14101				2	2	4
14576				2	2	4
15083				2	2	4
15266				2	2	4
17402				2	2	4
18031				2	2	4
18296				2	2	4
<u>Autosomal Dominant SVAS</u>						
12903	x	x	x			
12905	x	x	x			
12906			x			
12907	x		x			
13222	x	x	x			
13835	x	x	x			
14104	x	x	x			
14107	x	x	x			
17607	x	x	x			
20583	x	x	x			
<u>Normal</u>						
29998	x		x			
29999		x	x			

Table 2. WSCP evaluation using the DAS was completed in members of K1895, K2049, autosomal dominant SVAS, normal controls, and individuals with classic WS. DAS evaluation included assessment of pattern construction (PC), digit recall (D), verbal abilities (V), and mean standard score for the core subtests (T). The WSCP was excluded if PC \geq T, PC \geq D, or PC \geq 20th percentile. For individuals who were not excluded, level of fit to the WSCP was based on total score: 0-1 point=poor fit; 2=good fit; 3=very good fit; 4=excellent fit.

TABLE 3

Assessment of WSCP for individuals who did not complete the DAS					
INDIVIDUALS WHO COMPLETED THE WAIS-R					
Individual	Exclusion		Inclusion		WSCP
	PC \geq D	PC \geq 20%	D > PC	V > PC	
K2049					
I-1			◇	+	+
II-2			+	+	+
II-3			+	+	+
II-4			+	+	+
II-5	+				-
INDIVIDUALS WHO COMPLETED THE VERBAL WAIS-R AND THE VMI					
Individual	Exclusion		Inclusion		WSCP
	VMI AE > 10 years		Verbal WAIS-R > VMI		
K2049					
II-6			+		+
II-7	+				-
INDIVIDUAL WHO COMPLETED THE BAYLEY					
Individual	Bayley I		Bayley II		WSCP
	% LI > % NLI		% LI > % NLI		
K1895					
II-4		+	+		+

◇ Digit recall assessment was inappropriate, due to dementia

Table 3. Adults who could not complete the DAS were phenotypically characterized with the Wechsler Adult Intelligence Scale-Revised (WAIS-R) whenever possible. Phenotypic characterizations based on the WAIS-R included assessments of pattern construction (PC; block design subtest), digit recall (D), and verbal abilities (V). Inclusion criteria for Bayley I and Bayley II were based on passing a greater proportion of language items attempted (%LI) than non-language items attempted (%NLI). Individuals II-6 and II-7 of K2049 only completed the verbal portion of the WAIS-R, so additional characterization was completed using the Developmental Test of Visual Motor Integration (VMI). VMI AE=age equivalent for the VMI. Individual II-4 of K1895 was too young to complete the DAS, so phenotypic characterization was carried out using the Bayley test.

Sixty-four out of 65 control individuals did not have the WS personality. Thus, the WS personality measure had a sensitivity of 0.98 and a specificity of 0.98.

Phenotypic characterization of individuals with isolated, autosomal dominant SVAS indicated that these individuals did not manifest the other major features of WS (Table 1 and data not shown). Occasionally, an individual with autosomal dominant SVAS presented with a few WS facial features (\leq 6 of 16) and/or a hernia, but no other WS phenotypic characteristics were observed. In particular, no one with autosomal dominant SVAS showed evidence of the WSCP. Because these individuals each harbors a mutation (translocation or point mutation) that disrupts one ELN allele, the data indicate that ELN mutations cause vascular disease but not impaired visuospatial constructive cognition.

Continued ascertainment and phenotypic characterization revealed two families with a partial WS phenotype (FIGS. 1A and 1B). Most affected members of these families had SVAS, some WS facial features, and the WSCP. These

individuals showed levels of verbal ability and auditory short-term memory similar to those of unaffected family members, but their visuospatial constructive abilities were markedly impaired. Affected members lacked other features of WS, including the WS personality and mental retardation (Table 1). Serum calcium levels during infancy were available for only four individuals, but none showed evidence of hypercalcemia (data not shown). No WS phenotypic characteristics were present in unaffected family members.

Previous studies indicate marked intra- and inter-familial variability of expression and incomplete penetrance for autosomal dominant SVAS (Curran et al, 1993; Ewart et al., 1993b; Morris et al., 1993; Ewart et al., 1994). Similar variability was found in individuals with partial WS phenotypes. For example, SVAS was severe and required surgery in two members of K2049 (individuals III-3 and III-7) and had led to early death in three members of K1895 (individuals not shown on pedigree). Other affected members of these kindreds exhibited mild to moderate SVAS, and vascular disease was not clinically apparent in two members of K2049 (individuals II-3 and III-2). Some WS facial features (2-6 of the 16 possible facial characteristics associated with classic WS) were observed in all affected members of K1895 and in 5 of 10 affected members of K2049, but these features did not fulfill the diagnostic criteria for WS (\geq 9 of 16 facial features). WSCP was observed in all affected members of K1895 and in 8 of 10 affected members of K2049; one member of K2049 did not fulfill the diagnostic criteria for WSCP (individual III-7) and one individual (III-3) was classified as uncertain. These phenotypic studies indicate autosomal dominant co-inheritance of SVAS, some WS facial features, and WSCP in two families with variable phenotypic expression and incomplete penetrance. Identification of individuals with a partial WS phenotype supports the hypothesis that WS is a contiguous gene deletion syndrome.

EXAMPLE 2

Association of partial WS phenotypes with submicroscopic chromosome 7q11.23 deletions

If WS is a contiguous gene deletion syndrome, individuals with a partial WS phenotype should have smaller deletions in the chromosome 7q11.23 region than those seen with classic WS. To test this hypothesis, a partial physical map of the region deleted in WS was constructed. Because ELN is completely deleted in individuals with classic WS, these experiments were initiated by isolating and characterizing ELN genomic clones. These clones were used for genomic walking into regions flanking ELN. A set of contiguous cosmid clones generated by walking 3' of ELN is shown in FIG. 2. Attempts to extend the cloned coverage in a direction 5' of ELN using phage, cosmid, P1, P1 artificial chromosomes and yeast artificial chromosome (YAC) libraries were less successful; very few clones were isolated from this region and clones that were isolated were unstable. Clones were characterized by restriction enzyme analyses and placed on the physical map by somatic cell hybrid Southern analyses or sequence-tagged-site mapping by means of the polymerase chain reaction (PCR). These clones span ~350 kb of chromosome 7q11.23, including the entire ELN locus. No other genes were previously mapped to this region.

To determine if individuals with a partial WS phenotype carried deletions involving chromosome 7q11.23, fluorescence in situ hybridization (FISH) was performed using cosmids that span the ELN locus. All affected members of K1895 showed ELN hemizyosity, while unaffected members had two ELN alleles (FIG. 1A). Additional FISH analyses revealed hemizyosity with probes c138-13c,

c1-4a2, 106G5, and 135F3, but not with 157F3, 39E7, and 198G11 (data not shown). These results indicated that affected members of K1895 harbor a chromosome 7q11.23 deletion that includes ELN and extends through the locus corresponding to cosmid 135F3 (FIG. 2). Additional FISH analyses using YACs from this region are consistent with these data and indicate a deletion of approximately 300 kb (unpublished data). By contrast, FISH analyses of individuals with classic WS showed hemizyosity with all clones tested, suggesting that these deletions span more than 500 kb (unpublished data).

A deletion associated with SVAS in two members of K2049 (Ewart et al., 1994) was previously described. This deletion disrupted ELN, beginning in intron 27 and extending 3' of the gene. Oligonucleotides flanking the deletion breakpoints were used to define a novel PCR product of 403 bp in all phenotypically affected members of this kindred (FIG. 1B). This product was not seen in unaffected members. Physical mapping and restriction analyses indicated that the deletion had removed ~85 kb of genomic DNA (FIG. 2), a much smaller region than is missing in individuals with classic WS. These data indicate that a partial WS phenotype, including SVAS, some WS facial features, and WSCP, cosegregates with the ~85 kb deletion in this family. Because intragenic mutations of ELN cause isolated SVAS and some WS facial features (Curran et al., 1993; Morris et al., 1993; Olson et al., 1995), but not the WSCP (Table 1), a gene responsible for the impaired visuospatial constructive cognition must be located immediately 3' of ELN.

EXAMPLE 3

Identification of a Protein Kinase Immediately 3' of Elastin

To screen for a gene that contributes to impaired visuospatial constructive cognition, cosmids cELN-11d, c138-13c, and c1-4a2 were used in cDNA screening analyses, but no genes were identified. The specific hypothesis that hemizyosity of a gene encoding a protein kinase could cause the impaired visuospatial constructive cognition was also tested. This hypothesis was based on observations that targeted disruption of genes encoding protein kinases results in mice with impaired spatial learning (Grant et al., 1992; Abeliovich et al., 1993a, Abeliovich et al., 1993b). Oligonucleotides complementary to sequences conserved in tyrosine kinases were designed and PCR analyses were performed with genomic clones from the physical map. A specific product of 315 bp was identified from cosmid c138-13c. This PCR product was cloned; DNA sequence analyses revealed an open reading frame of 113 nucleotides with complete homology to LIM-kinase1 (LIMK1), a recently identified gene encoding a protein kinase with LIM domains (Mizuno et al., 1994; Bernard et al., 1994). Oligonucleotides based on published cDNA sequences were used in PCR experiments to clone LIMK1 cDNA from a human hippocampal cDNA library. PCR analyses of DNA from somatic cell hybrids, cosmids, P1s, and YACs localized LIMK1 to the deleted region on chromosome 7q11.23. These data place LIMK1 immediately 3' of ELN and within the ~85 kb deletion identified in K2049.

Oligonucleotides based on published cDNA sequences were used in PCR experiments to clone a LIMK1 cDNA from a human hippocampal library (LIMK1 nucleotides 96-2039). A human hippocampal cDNA library (catalog #936205, Stratagene), was plated at a density of 5×10^4 pfu/15 cm plate to obtain 1×10^9 total pfu. Duplicate filters were probed with cELN-11d, c138-13c, and c1-4a2, which had been radiolabeled to a high specific activity ($>1.0 \times 10^9$ cpm/ μ g DNA) using random hexamer priming as described by Feinberg and Vogelstein (1984). LIMK1 cDNA frag-

ments were obtained from the same hippocampal cDNA library using PCR with rTth DNA polymerase and various primers designed from the published LIMK1 cDNA sequence (Mizuno et al., 1994). The open reading frame (LIMK1 nucleotides 93-1936) was amplified and cloned using the following primers: 5'-ATGAGGTTGACGCTACTTTGTTGC-3' (SEQ ID NO:1) and 5'-TCAGTCGGGGACCTCAGGGTGGG C-3' (SEQ ID NO:2).

PCR primers were designed to amplify the region of homology in the kinase domains of PDGF receptor, HER2, HER3, FGF-FLG, FGF-BEK, insulin receptor, and IRR (sequences obtained from Genbank). The primers used were 5'-GACTTTGGGCTGGCTCGAGACATG C-3' (SEQ ID NO:3) and 5'-CTCCGGAGCCATCCACTTGACTGGC-3' (SEQ ID NO:4). PCR conditions were one cycle of 94° C. for 10 min, followed by 30 cycles of 94° C. for 1 min, 49° C. for 1 min, and 72° C. for 1 min, ending with one cycle of 72° C. for 10 min. Clones c138-3c, cELN-11d, and c138-13c were used as templates. Products were cloned into pBlue-script II SK (Stratagene) using standard T/A cloning technology (Marchuk et al., 1991) and sequenced.

Genomic clones were obtained from the following sources: c138-3c, λ 4, λ 5, cELN-11d, and c138-13c were derived from primary cosmid and phage libraries constructed earlier in our laboratory (Curran et al., 1993; Ewart et al., 1994). Cosmids cos6 and c1-4a2 were obtained from an amplified placental library (Stratagene). Cosmids 129F9, 128F2, 106G5, 135F3, 157F3, 39E7, and 198G11 were isolated from the chromosome 7-specific flow-sorted cosmid library constructed at the Lawrence Livermore National Laboratories.

DNA Sequence Analyses and Testing of Putative Coding Regions

Cycle sequencing with oligonucleotides generated from the LIMK1 cDNA sequence and from our DNA sequence analyses was used to define the structure of LIMK1 using cosmids cELN-11d, c138-13c, and c1-4a2. Cycle sequencing of cosmids was performed using 1.5 pmol of primer, 15 fmol of template, and the dsDNA Cycle Sequencing System (GibcoBRL). Reaction conditions were 94° C. for 3 min, 20 cycles of 94° C. for 30 s, 55° C. for 30 s, 72° C. for 1 min, 10 cycles of 94° C. for 30 s and 72° C. for 1 min. Cycle sequencing products were electrophoresed on 6% denaturing polyacrylamide gels (National Diagnostics) the same day the reactions were performed. Also, the addition of formamide to a final concentration of 4% allowed cycle sequencing of regions that could not be sequenced by standard conditions.

Sanger sequencing was performed using the Sequenase v2.0 DNA Sequencing Kit (United States Biochemical) under standard conditions. Sequence analysis relied on the IG software package and the BLAST network service from the National Center for Biotechnology Information.

The intron-exon structure and predicted amino acid sequences are shown in Table 4 and FIG. 3. LIMK1 is composed of 16 exons, spans 37 kb, and is located 15.4 kb 3' of ELN (FIG. 2). Predicted amino acid sequence analyses revealed two putative LIM domains (amino acids 25-75 for LIM-1, 84-137 LIM-2; Way and Chalfie, 1988; Freyd et al., 1990; Karlsson et al., 1990), a Dlg homology region (DHR; amino acids 165-258; Ponting, 1995), a possible PEST domain (PESTFIND score=6.3; amino acids 264-289; Rogers et al., 1986), a kinase domain (amino acids 345-594), and a putative nuclear localization signal (NLS; amino acids 499-506; Forbes, 1992). Comprehensive DNA sequence analyses confirmed the location and structure of LIMK1.

Together, these data place LIMK1 immediately 3' of ELN and within the ~85 kb deletion identified in K2049.

were performed as described above. Four cosmids and two phage (cos6, λ4, λ5, cELN-11d, c1-4a2, and 129F9) that

TABLE 4

LIMK1 genomic structure			
Exon #	Intron	Exon Size	Intron
	... ATGAGGTTGA (SEQ ID NO: 5)	(55) ^a	GGAGAGGAAAGgtgctgcccggccgcccggcgc (SEQ ID NO: 6)
2	actccctccaccctcagGAAGCGAGTT (SEQ ID NO: 7)	(97)	ACTGCTTCAGgtagggtgggggtcccagg (SEQ ID NO: 8)
3	gcccggcccctctctcagGTGTTGTGAC (SEQ ID NO: 9)	(139)	ACTGGTTATGtgtagcgcgccctgcttgc (SEQ ID NO: 10)
4	ctctctacccccaccagGTGGCTGGGG (SEQ ID NO: 11)	(110)	AGCTGTACTGtgtagtgcttggcccctcc (SEQ ID NO: 12)
5	cacccggcggctcttgcagCGGGCACTGC (SEQ ID NO: 13)	(207)	GCGTCCAGGGgtgagtgcccggcctgcga (SEQ ID NO: 14)
6	gacccctgcttaccacagAGTGGATCCG (SEQ ID NO: 15)	(106)	CCTGGACGAGgtacgctctgagctctgtg (SEQ ID NO: 16)
7	caatgctctgttccccagATTGACCTGC (SEQ ID NO: 17)	(167)	AACCTGTCTTgtaagtcagcctgctctcg (SEQ ID NO: 18)
8	gcacatgtgtgccccagGAGGAGCTGC (SEQ ID NO: 19)	(184)	GGCTATCAAGgtacagagcatgccggctc (SEQ ID NO: 20)
9	ctctgtgtccacacagcagGTGACACACC (SEQ ID NO: 21)	(87)	CCTCAAGGAGgtcagtgagcggaaatccct (SEQ ID NO: 22)
10	gctctttgtgccccgcagGTGAAGGTCA (SEQ ID NO: 23)	(132)	CAAGAGCATGgtgagctctggcagagcca (SEQ ID NO: 24)
11	ccattcttctcatccagGACAGCCAGT (SEQ ID NO: 25)	(60)	ATCAGGGATGgtgagtgcccgggtgctct (SEQ ID NO: 26)
12	tcctgttccccctcctagGCCTACCTCC (SEQ ID NO: 27)	(66)	GGTCCCGcGAGgtgagtaaccaggcccaccg (SEQ ID NO: 28)
13	accggcttaccctccagAACAGAATG (SEQ ID NO: 29)	(157)	ATGATCAACGgtagtggttccagccctgcc (SEQ ID NO: 30)
14	cagtcggtctctttatcagGCCGCAGTA (SEQ ID NO: 31)	(56)	CCGTGCGAGgtaggtccagggtggtag (SEQ ID NO: 32)
15	ccggcctgtactggcagATCATCGGGC (SEQ ID NO: 33)	(158)	CCGAGAAGAGgtgagtgagggtggccctg (SEQ ID NO: 34)
16	ccccccacctgcccagGCCATCTTT (SEQ ID NO: 35)	(163) ^a	CCCCGACTGA... (SEQ ID NO: 36)

Cosegregation of LIMK1 Hemizyosity and Impaired Visuospatial Constructive Cognition

To test the hypothesis that LIMK1 hemizyosity contributes to the WSCP, FISH analyses were performed with metaphase chromosomes from individuals with both partial and classic WS phenotypes using cosmids cELN-11d, c138-13c, and c1-4a2. Cosmid probes c138-13c and c1-4a2 were labeled with biotin using a nick translation kit (GibcoBRL). Metaphase chromosome spreads were prepared from EBV transformed lymphoblastoid cell lines derived by standard procedures of colcemid arrest, hypotonic treatment and acetic acid-methanol fixation. Slides were prepared as described by Lichter et al. (1988) and hybridized with a probe mixture containing c138-13c, c1-4a2, human C₀t-1 DNA, and a chromosome 7-specific alpha satellite cocktail (Oncor, Inc.). For other hybridizations, cosmids 135F3, 157F3, 39E7, and 198G11 were used. Following overnight hybridization and subsequent washing, slides were incubated with streptavidin-Cy3 (cosmids) and anti-digoxigenin FITC (chromosome 7 marker). Slides were counterstained with DAPI/Antifade (Oncor, Inc.). Metaphases were scored using an epifluorescence Olympus PX50 microscope with a triple band pass filter, and then captured using a cooled CCD camera and imaging system designed specifically for FISH (Oncor, Inc.).

LIMK1 was completely deleted from one chromosome 7 homologue in affected members of K1895 and K2049 and in 62 of 62 individuals with classic WS (e.g., FIG. 4A-4C). LIMK1 was not deleted in 6 of 6 individuals with isolated and de novo SVAS who showed some WS facial features (e.g., FIG. 4D). LIMK1 hemizyosity was not observed among more than 100 control individuals (FIG. 4E and data not shown). These data indicate that LIMK1 is deleted in individuals with classic and partial WS but not in individuals with isolated SVAS, and suggest that LIMK1 hemizyosity contributes to the WSCP.

EXAMPLE 4

Direct DNA sequence analysis of the ~85 kb deletion region reveals only LIMK1 and ELN

To determine if LIMK1 is the only gene from this region likely to contribute to cognitive development, the ~85 kb segment deleted in K2049, along with flanking sequences, was sequenced. Cycle sequencing and Sanger sequencing

form an overlapping contig of the entire 83.6 kb deletion region in K2049 and the flanking sequences surrounding the breakpoints were sequenced. A modification of the sequencing procedure described by Mardis (1994) was used. Approximately 900 single-stranded M13 clones were sequenced for each cosmid using dye-primer chemistry (Applied Biosystems, Epicentre Technologies, and Amersham). Products from the sequencing reactions were run on either an ABI 373a Stretch DNA Sequencer or an ABI 377 Prism DNA Sequencer. The sequence data were processed using the XGAP algorithms (Dear and Staden, 1991; Dear and Staden, 1992). Gaps in the 83.6kb contig were filled in by one of the following methods: 1) direct sequencing of cosmids using specific primers; 2) sequencing of PCR products generated using primers that flank the gaps; or 3) subcloning restriction fragments containing the gaps into pBluescript II SK (Stratagene) and sequencing them using dye-primers.

The 83.6-kb sequence was analyzed for known genes using GENQUEST and BLAST servers. Potential coding exons, polyadenylation sites, and CpG islands were identified by versions 1.2 and 2 of the GRAIL neural network. All putative coding regions with either excellent or good scores were tested for mRNA expression by either Northern-blot analysis (human MTN blot 1 and human fetal MTN blot) or a combination of Northern-blot analysis and RT-PCR.

RT-PCR was performed according to manufacturer's instructions using 200 ng of total RNA and the ThermoStar rTth Reverse Transcriptase RNA PCR kit (Perkin Elmer). Controls included 100 ng of genomic DNA, 100 ng of genomic DNA that had been digested with 10 units of DNase I, and a water blank. RNA samples were prepared with and without DNase I treatment. Reverse transcription was performed for 15 minutes at 60° C. PCR was performed for either 35 or 50 cycles on a Perkin Elmer 9600 GeneAmp PCR System using the following cycling conditions: 1) initial denaturation at 94° C. for 3 minutes; 2) subsequent denaturation at 95° C. for 10 seconds; 3) annealing and extension at 60° C. for 15 seconds. Products were electrophoresed through a 5% 3:1 agarose gel (FMC) and visualized by staining with ethidium bromide.

DNA sequence analyses defined two ordered contigs of 41,566 and 65,607 base pairs. These contigs were separated by a gap of approximately 250 base pairs (FIG. 2). Due to

its high GC content, this gap could not be sequenced using primer walking, amplified PCR products, or subcloning. The restriction maps predicted from DNA sequence analyses were identical to maps generated using BamHI, EcoRI, and HindIII. The size of the deletion was 83.6 kb. The sequences were analyzed for the presence of known genes using the GRAIL, GENQUEST, and BLAST servers (Shah et al., 1994; Altschul et al., 1990). Only ELN and LIMK1 were detected.

Comparison between the cDNA and genomic sequence revealed 16 LIMK1 exons that span 37 kb of genomic DNA. Sequence analyses also indicated that LIMK1 is located 15.4 kb 3' of ELN (FIG. 2). Predicted amino acid sequence analyses identified all previously described domains including LIM-1, LIM-2, a Dlg homology region, a putative nuclear localization signal, and a kinase domain (Mizuno et al., 1994; Ponting, 1995). In addition, sequence analyses revealed a possible PEST domain (PESTFIND score=6.3; amino acids 264–289; Rogers et al., 1986).

Sequences were also scanned for potential coding regions using versions 1.2 and 2 of the GRAIL neural network (Table 5). Except for ELN (GRAIL identified 16 of 30 exons) and LIMK1 (15 of 16 exons), no other putative exons categorized as excellent were identified by GRAIL. Additionally, GRAIL identified seven possible coding sequences categorized as good (six within the 83.6 kb deletion region) and eleven categorized as marginal. All possible coding sequences classified as good were tested using either multiple-tissue Northern analyses or a combination of Northern analyses and reverse transcription-PCR of total RNA extracted from fetal and adult human brain (Table 5 and data not shown). No evidence for expression of these additional possible coding sequences was found.

A remarkable finding of DNA sequence analyses was the high density of Alu repetitive elements in the 83.6 kb deletion region. A total of 120 full or partial Alu sequences was identified, for an average density of ~1.4/kb. This is 6-fold more than the estimated average density of 0.25/kb (Hwu et al., 1986; Slightom et al., 1994). One partial LINE sequence and one MER14-like element were also identified, as well as three large d(CA)-repeats (FIG. 2). One of the d(CA)-repeats had been previously identified (Foster et al., 1993). Sequence analyses also defined the breakpoints for the K2049 deletion; both breakpoints consisted of Alu repeats, suggesting that a recombination event between these Alu sequences may have been responsible for the deletion.

TABLE 5

GRAIL Analyses of DNA Sequences within the 83.6 kb Deleted Region					
Putative Coding Region	Size (bp)	Graill Version	Graill Quality	Strand (F/R)	Exclusion
ELN-29	60	1.2	E	F	—
ELN-30	75	1.2,2	E	F	—
208pr3	114	1.2	G	R	N,RP
124pr3	85	1.2	G	R	N,RP
90pr1	123	1.2	G	R	N,RP
LIMK-2	97	1.2,2	E	F	—
441pr1	141	1.2,2	G	F	N,RP
LIMK-3	139	1.2,2	E	F	—
LIMK-4	110	1.2,2	E	F	—
LIMK-5	207	1.2,2	E	F	—
LIMK-6	106	1.2,2	E	F	—
LIMK-7	167	1.2,2	E	F	—
LIMK-8a	36	2	E	F	—
LIMK-8b	123	1.2,2	E	F	—
LIMK-9	87	1.2,2	E	F	—

TABLE 5-continued

GRAIL Analyses of DNA Sequences within the 83.6 kb Deleted Region					
Putative Coding Region	Size (bp)	Graill Version	Graill Quality	Strand (F/R)	Exclusion
LIMK-10	132	1.2,2	E	F	—
LIMK-11	60	2	G	F	—
LIMK-12	66	1.2,2	E	F	—
604pr2	39	2	G	F	N,*
LIMK-13	157	1.2,2	E	F	—
LIMK-14	56	1.2,2	G	F	—
LIMK-15	158	1.2,2	E	F	—
LIMK-16	163	1.2,2	E	F	—
604pr3	31	2	G	R	N,*

Table 5. Only the putative coding regions with either excellent or good scores are listed in this table. The putative coding regions are either named after the gene and exon number (e.g., ELN-29 is exon 29 of the elastin gene) or given an assigned name (e.g., 208pr3). Putative exons are given either excellent (E) or good (G) scores. F=forward strand in relation to ELN and LIMK; R=reverse strand. N=no evidence for expression by Northern blot analysis; RP=no evidence for expression by RT-PCR; *=putative coding region not tested by RT-PCR because the coding region was too short; -=not tested because the putative coding region is an exon of a known gene.

EXAMPLE 5

LIMK1 and ELN Expression in the Developing Brain

To determine the expression pattern of LIMK1, Northern analyses were performed with mRNA extracted from fetal and adult tissues. Northern blots containing ~2 µg/lane of poly(A)⁺ mRNA were purchased from Clontech (human MTN blot 1, human brain blots 2 and 3, human fetal MTN blot, and a mouse MTN blot). The blots were hybridized in ExpressHyb solution (Clontech) according to the manufacturer's instruction, with either ³²P-end-labeled LIMK1 oligonucleotide probe (704–742 bp) or LIMK1 (104–2038 bp), ELN (1–1123 bp), and β-actin cDNA clones that had been radiolabeled using random hexamer priming (Feinberg and Vogelstein, 1984). Each LIMK1 Northern blot was analyzed by phosphorimage analyses (Molecular Dynamics) to determine the amounts of LIMK1 RNA relative to β-actin mRNA.

A LIMK1 oligonucleotide probe hybridized to a single mRNA of 3.3 kb in all fetal and adult tissues examined (FIG. 5). Phosphorimage analyses indicated that mRNA levels varied considerably but were highest in both fetal and adult brain. Northern analyses of tissue from different regions of the adult human brain demonstrated that LIMK1 is ubiquitously expressed, with mRNA levels highest in the cerebellum, caudate nucleus, substantia nigra, and the occipital pole (FIG. 5). Analyses of adult murine tissues indicated that LIMK1 is most strongly expressed in testes and brain (data not shown). These data establish that LIMK1 is widely expressed during fetal and adult life, but that LIMK1 mRNA levels are highest in the brain.

In situ hybridization analyses of LIMK1 expression in the embryonic human nervous system demonstrated that LIMK1 is expressed in several discrete regions of the brain and spinal cord (FIG. 6). In situ hybridization was performed on 6 mm-thick, paraffin embedded sections of freshly prepared human embryos, which were obtained from the MRC-funded Human Embryonic Tissue Bank, Institute of Child Health, London. A digoxigenin-labeled 625-bp cRNA probe specific to the 3'-untranslated portion of

LIMK1 cDNA was used to avoid areas of homology with other genes encoding proteins containing LIM and kinase domains; similar results were obtained, however, in some sections hybridized with a cDNA probe covering the kinase region and some of the 3'-untranslated sequence. The in situ protocol was based on the detection of digoxigenin-labeled RNA by alkaline phosphatase-conjugated anti-DIG FAB fragments (Boehringer Mannheim), as previously described (Wilkinson, 1992; Birren et al., 1993). Brightfield microphotography was carried out with an Olympus BH-2 and Fujichrome 64T film.

Analyses of LIMK1 expression in a Carnegie stage 20 (postovulatory day 50) human embryo revealed expression in the ependymal layer of the fourth ventricle, with a lower level of expression extending into the mantle layer. LIMK1 was expressed in specific regions of the brain, with notably high levels in the medial olivary nucleus. In the cerebellum, expression was seen again in ependymal layer. Staining also occurred in ependymal layer of the mesencephalon, which additionally contained many LIMK1-expressing cells in the mantle layer. In the spinal cord, LIMK1 was expressed in a diffuse pattern dorsally, with single-cell staining ventrally. In the mid-area of the spinal cord, expression was again seen in ependymal and mantle layers. Within the peripheral nervous system, extensive expression of LIMK1 was seen in spinal ganglia, in the fifth nerve ganglion, and in part of the inner ear.

To determine if ELN is expressed in the brain, Northern analyses were performed with mRNA extracted from fetal and adult tissues. ELN was strongly expressed in adult heart and pancreas and in fetal lung, but exhibited negligible expression in adult and fetal brain.

EXAMPLE 6

Distinguishing between SVAS, WSCP and WS

Supravalvular aortic stenosis (SVAS), Williams syndrome cognitive profile (WSCP) and Williams syndrome are inherited diseases which are related in that they involve a set of contiguous genes. Persons with mutations in the elastin gene but who are wild-type for LIMK1 and do not have deletions 3' of LIMK1 have SVAS. Persons who have mutations affecting both elastin and LIMK1 (hemizygoty) but do not have deletions greater than about 300 kb 3' of the ELN gene are diagnosed as having WSCP. Persons who are mutated in both the ELN and LIMK1 genes (and have one wild-type copy of each of these genes) and have a deletion of greater than 300 kb from the 3' end of the LIMK1 gene in the 3' direction are diagnosed as having WS. One may conclude that SVAS is due to a mutation in or loss of a single gene (ELN), WSCP is a result of mutations in or loss of two genes (ELN and LIMK1), and WS results from mutations in or a loss of at least 3 genes (ELN, LIMK1 and an unidentified gene or genes located on chromosome 7 greater than 300 kb 3' of LIMK1). It is possible to diagnose which disease a patient may have by use of chromosomal analysis. The complete sequence of the elastin and LIMK1 cDNAs have been published (Indik et al., 1987; Fazio et al., 1988; Mizuno et al., 1994; Cheng and Robertson, 1995). SEQ ID NO:39 shows a cDNA sequence of elastin (from Fazio et al., 1998 and Indik et al., 1987) and SEQ ID NO:40 shows the amino acid sequence encoded by this cDNA sequence. SEQ ID NO:41 Shows a cDNA sequence for LIMK1 (from Mizuno et al., 1994). SEQ ID NO:42 shows the amino acid sequence encoded by SEQ ID NO:41. Using the known nucleic acid sequences for these two genes it is possible to assay for mutations in these genes. This can be done by any desired technique such as by sequencing to determine the presence of mutations, especially the presence of deletions or trans-

locations affecting the genes, or by in situ hybridization to determine whether these genes are hemizygous or homo- or heterozygous. Using the knowledge of these two genes one can assay to determine if the patient has at least SVAS (i.e., loss of or mutation in at least ELN), or at least WSCP (loss of or mutation in both ELN and LIMK1). To determine whether an individual has WS it is helpful to examine the chromosome beyond the 3' ends of ELN and LIMK1. To date, all Williams syndrome patients analyzed have been found to have a major deletion in chromosome 7 which includes deletion of both the ELN (at least partially) and LIMK1 genes as well as greater than another 300 kb 3' of the LIMK1 gene. Patients who have deletions of 100 kb or smaller 3' of the LIMK1 gene have been diagnosed as having WSCP but not WS. The use of probes to analyze for the extent of deletion of chromosome 7 in individuals can distinguish between WSCP and WS.

FIG. 2 shows a map of chromosome 7 in the region of ELN and LIMK1 with a series of overlapping cosmids covering this region. The range of coverage from c138-3c through 198G11 is approximately 350 kb. In situ hybridization with 135F3, for example, can be used to determine if there is a deletion of 100 kb or less 3' of LIMK1. If 135F3 hybridizes to both sets of chromosomes then the individual probably will not have WS since the deletion will be too small to delete the third, as yet unknown, gene which lies 3' of ELN and LIMK1 and which must be mutated or deleted to cause WS. To date, all WS individuals have been found to have a deletion greater than 500 kb covering ELN and LIMK1 and greater than 300 kb 3' of LIMK1. Furthermore, it has been seen that when a person does have a deletion in ELN there is a 99% chance that this is a major deletion of greater than 500 kb including LIMK1 and the other gene or genes involved in WS. This means that the presence of a deletion in ELN in one chromosome is 99% indicative of the presence of WS.

While the invention has been disclosed in this patent application by reference to the details of preferred embodiments of the invention, it is to be understood that the disclosure is intended in an illustrative rather than in a limiting sense, as it is contemplated that modifications will readily occur to those skilled in the art, within the spirit of the invention and the scope of the appended claims.

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SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i i i) NUMBER OF SEQUENCES: 42

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 24 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(i i) MOLECULE TYPE: other nucleic acid

- (A) DESCRIPTION: /desc = "Primer sequence"

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:1:

ATGAGGTTGA CGCTACTTTG TTGC

2 4

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 24 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

-continued

(i i) MOLECULE TYPE: other nucleic acid
 (A) DESCRIPTION: /desc = "Primer sequence"

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:2:
 T C A G T C G G G G A C C T C A G G G T G G G C 2 4

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 25 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(i i) MOLECULE TYPE: other nucleic acid
 (A) DESCRIPTION: /desc = "Primer sequence"

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:3:
 G A C T T T G G G C T G G C T C G A G A C A T G C 2 5

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 25 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(i i) MOLECULE TYPE: other nucleic acid
 (A) DESCRIPTION: /desc = "Primer sequence"

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:4:
 C T C C G G A G C C A T C C A C T T G A C T G G C 2 5

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 10 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: double
 (D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
 (A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:5:
 A T G A G G T T G A 1 0

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 30 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: double
 (D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
 (A) ORGANISM: Homo sapiens

-continued

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:6:

GGAGAGGAAAG GTGCGCGGGC CGCGGGGCGC

3 0

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:

- (A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:7:

ACTCCCTTCC CACCCTGCAG GAAGCGAGTT

3 0

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:

- (A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:8:

ACTGCTTCAG GTAGGGTGGG GTGCCCAGGG

3 0

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:

- (A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:9:

GCCCCGCCCC TCTCCTGCAG GTGTTGTGAC

3 0

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

-continued

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:10:

ACTGGTTATG GTGAGCGCCC CCTGCCTTGC

3 0

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 30 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: double

(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:11:

CCTCCTCACC CCCGCACCAG GTGGCTGGGG

3 0

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 30 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: double

(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:12:

AGCTGTA CTG GTGAGTG CCT TGGCCCCCTCC

3 0

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 30 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: double

(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:13:

CACCCCGGCG GCTCTTG CAG CGGGCACTGC

3 0

(2) INFORMATION FOR SEQ ID NO:14:

-continued

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 30 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: double
 (D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
 (A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:14:

GCGTCCAGGG GTGAGTGGCC GGCCTGCCGA 3 0

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 30 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: double
 (D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
 (A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:15:

GACCCCTGCC TTACCCACAG AGTGGATCCG 3 0

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 30 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: double
 (D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
 (A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:16:

CCTGGACGAG GTACGGTCCT GAGTCTGTGG 3 0

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 30 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: double
 (D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:

-continued

(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:17:

CACATGCCTG CTGTCCCCAG ATTGACCTGC

3 0

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:18:

AACCTGTCTT GTAAGTCAGC CTGCTCCTCG

3 0

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:19:

GCACCATGTG TGCCCCCAG GAGGAGCTGC

3 0

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:20:

GGCTATCAAG GTACAGAGCA TGCCAGGGTC

3 0

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

-continued

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
 (A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:21:

CCTCTGTGTC CCACACGCAG GTGACACACC 3 0

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 30 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: double
 (D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
 (A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:22:

CCTCAAGGAG GTCAGTGAGC GGAATGCCCT 3 0

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 30 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: double
 (D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
 (A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:23:

GCCTGTTTGT GCCCCGCCAG GTGAAGGTCA 3 0

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 30 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: double
 (D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
 (A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:24:

CAAGAGCATG GTGAGTCCTG GGCAGAGCCA 3 0

-continued

(2) INFORMATION FOR SEQ ID NO:25:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 30 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: double
 - (D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

- (v i) ORIGINAL SOURCE:
 - (A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:25:

CCATTCTTTC TCCATCCCAG GACAGCCAGT

3 0

(2) INFORMATION FOR SEQ ID NO:26:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 30 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: double
 - (D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

- (v i) ORIGINAL SOURCE:
 - (A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:26:

ATCAGGGATG GTGAGTGAGC CGGGTGCTCT

3 0

(2) INFORMATION FOR SEQ ID NO:27:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 30 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: double
 - (D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

- (v i) ORIGINAL SOURCE:
 - (A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:27:

TCCC GTGTCC CCGTCCCTAG GCCTACCTCC

3 0

(2) INFORMATION FOR SEQ ID NO:28:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 30 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: double
 - (D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

-continued

(v i) ORIGINAL SOURCE:
 (A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:28:

GGTCCGCGAG GTGAGTACCA GGGCCCCACG

3 0

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 30 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: double
 (D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
 (A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:29:

ACCCGGCTTC ACCTTCCCAG AACAAAGAATG

3 0

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 30 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: double
 (D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
 (A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:30:

ATGATCAACG GTAGTGTTT AGCCCTGCC

3 0

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 30 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: double
 (D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
 (A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:31:

CAGTCGGTCT CTTTATCCAG GCCGCAGCTA

3 0

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 30 base pairs
 (B) TYPE: nucleic acid

-continued

(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:32:

CCTGTGCGAG GTAGGTCCAG GGTGGGTAG

3 0

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:33:

CCGGGCCTTG TACTGGACAG ATCATCGGGC

3 0

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:34:

CCGAGAAGAG GTGAGTGGGG TGGGGCCCTG

3 0

(2) INFORMATION FOR SEQ ID NO:35:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:35:

-continued

 CCCACCCACC TGTCACCAG GCCATCCTT

3 0

(2) INFORMATION FOR SEQ ID NO:36:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 10 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: double
 - (D) TOPOLOGY: linear

- (i i) MOLECULE TYPE: DNA (genomic)

- (i i i) HYPOTHETICAL: NO

- (i v) ANTI-SENSE: NO

- (v i) ORIGINAL SOURCE:
 - (A) ORGANISM: Homo sapiens

- (x i) SEQUENCE DESCRIPTION: SEQ ID NO:36:

CCCCGACTGA

1 0

(2) INFORMATION FOR SEQ ID NO:37:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 20 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

- (i i) MOLECULE TYPE: other nucleic acid
 - (A) DESCRIPTION: /desc = "Primer sequence"

- (i i i) HYPOTHETICAL: NO

- (i v) ANTI-SENSE: NO

- (v i) ORIGINAL SOURCE:
 - (A) ORGANISM: Homo sapiens

- (x i) SEQUENCE DESCRIPTION: SEQ ID NO:37:

CCTACCTTTC CTGCTGCAAT

2 0

(2) INFORMATION FOR SEQ ID NO:38:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 20 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

- (i i) MOLECULE TYPE: other nucleic acid
 - (A) DESCRIPTION: /desc = "Primer sequence"

- (i i i) HYPOTHETICAL: NO

- (i v) ANTI-SENSE: YES

- (v i) ORIGINAL SOURCE:
 - (A) ORGANISM: Homo sapiens

- (x i) SEQUENCE DESCRIPTION: SEQ ID NO:38:

AAAAAGAGGC CGGGTATGGT

2 0

(2) INFORMATION FOR SEQ ID NO:39:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 2427 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: double
 - (D) TOPOLOGY: linear

- (i i) MOLECULE TYPE: cDNA

-continued

245				250				255								
GCT Ala 260	AAA Lys	GCA Ala	GCA Ala	GCA Ala	AAG Lys 265	TTC Phe	GGT Gly	GCT Ala	GGA Gly	GCA Ala 270	GCC Ala	GGA Gly	GTC Val	CTC Leu	CCT Pro 275	873
GGT Gly	GTT Val	GGA Gly	GGG Gly	GCT Ala 280	GGT Gly	GTT Val	CCT Pro	GGC Gly	GTG Val 285	CCT Pro	GGG Gly	GCA Ala	ATT Ile	CCT Pro 290	GGA Gly	921
ATT Ile	GGA Gly	GGC Gly	ATC Ile 295	GCA Ala	GGC Gly	GTT Val	GGG Gly	ACT Thr 300	CCA Pro	GCT Ala	GCA Ala	GCT Ala	GCA Ala 305	GCT Ala	GCA Ala	969
GCA Ala	GCA Ala	GCC Ala 310	GCT Ala	AAG Lys	GCA Ala	GCC Ala	AAG Lys 315	TAT Tyr	GGA Gly	GCT Ala	GCT Ala	GCA Ala 320	GGC Gly	TTA Leu	GTG Val	1017
CCT Pro 325	GGT Gly	GGG Gly	CCA Pro	GGC Gly	TTT Phe	GGC Gly 330	CCG Pro	GGA Gly	GTA Val	GTT Val	GGT Gly 335	GTC Val	CCA Pro	GGA Gly	GCT Ala	1065
GGC Gly 340	GTT Val	CCA Pro	GGT Gly	GTT Val	GGT Gly 345	GTC Val	CCA Pro	GGA Gly	GCT Ala	GGG Gly 350	ATT Ile	CCA Pro	GTT Val	GTC Val	CCA Pro 355	1113
GGT Gly	GCT Ala	GGG Gly	ATC Ile 360	CCA Pro 360	GGT Gly	GCT Ala	GCG Ala	GTT Val	CCA Pro 365	GGG Gly	GTT Val	GTG Val	TCA Ser	CCA Pro 370	GAA Glu	1161
GCA Ala	GCT Ala	GCT Ala	AAG Lys 375	GCA Ala	GCT Ala	GCA Ala	AAG Lys	GCA Ala 380	GCC Ala	AAA Lys	TAC Tyr	GGG Gly	GCC Ala 385	AGG Arg	CCC Pro	1209
GGA Gly	GTC Val	GGA Gly 390	GTT Val	GGA Gly	GGC Gly	ATT Ile 395	CCT Pro 395	ACT Thr	TAC Tyr	GGG Gly	GTT Val	GGA Gly 400	GCT Ala	GGG Gly	GGC Gly	1257
TTT Phe 405	CCC Pro	GGC Gly	TTT Phe	GGT Gly	GTC Val	GGA Gly 410	GTC Val	GGA Gly	GGT Gly	ATC Ile 415	CCT Pro	GGA Gly	GTC Val	GCA Ala	GGT Gly	1305
GTC Val 420	CCT Pro	AGT Ser	GTC Val	GGA Gly 425	GGT Gly	GTT Val	CCC Pro	GGA Gly	GTC Val	GGA Gly 430	GGT Gly	GTC Val	CCG Pro	GGA Gly	GTT Val 435	1353
GGC Gly	ATT Ile	TCC Ser	CCC Pro	GAA Glu 440	GCT Ala	CAG Gln	GCA Ala	GCA Ala	GCT Ala 445	GCC Ala	GCC Ala	AAG Lys	GCT Ala	GCC Ala 450	AAG Lys	1401
TAC Tyr	GGT Gly	GCT Ala	GCA Ala 455	GGA Gly	GCA Ala	GGA Gly	GTG Val	CTG Leu 460	GGT Gly	GGG Gly	CTA Leu	GTG Val	CCA Pro 465	GGT Gly	CCC Pro	1449
CAG Gln 470	GCG Ala	GCA Ala	GTC Val	CCA Pro	GGT Gly	GTG Val	CCG Pro 475	GGC Gly	ACG Thr	GGA Gly	GGA Gly	GTG Val 480	CCA Pro	GGA Gly	GTG Val	1497
GGG Gly 485	ACC Thr	CCA Pro	GCA Ala	GCT Ala	GCA Ala	GCT Ala 490	GCT Ala	AAA Lys	GCA Ala	GCC Ala	GCC Ala 495	AAA Lys	GCC Ala	GCC Ala	CAG Gln	1545
TTT Phe 500	GCT Ala	CTT Leu	CTC Leu	AAT Asn 505	CTT Leu	GCA Ala	GGG Gly	TTA Leu	GTT Val	CCT Pro 510	GGT Gly	GTC Val	GGC Gly	GTG Val	GCT Ala 515	1593
CCT Pro	GGA Gly	GTT Val	GGC Gly	GTG Val 520	GCT Ala	CCT Pro	GGT Gly	GTC Val	GGT Gly 525	GTG Val	GCT Ala	CCT Pro	GGA Gly	GTT Val 530	GGC Gly	1641
TTG Leu	GCT Ala	CCT Pro	GGA Gly 535	GTT Val	GGC Gly	GTG Val	GCT Ala	CCT Pro 540	GGA Gly	GTT Val	GGT Gly	GTG Val	GCT Ala 545	CCT Pro	GGC Gly	1689
GTT Val	GGC Gly	GTG Val 550	GCT Ala	CCC Pro	GGC Gly	ATT Ile 555	GGC Gly	CCT Pro	GGT Gly	GGA Gly	GTT Val	GCA Ala 560	GCT Ala	GCA Ala	GCA Ala	1737
AAA Lys	TCC Ser	GCT Ala	GCC Ala	AAG Lys	GTG Val	GCT Ala	GCC Ala	AAA Lys	GCC Ala	CAG Gln	CTC Leu	CGA Arg	GCT Ala	GCA Ala	GCT Ala	1785

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565				570				575								
GGG Gly 580	CTT Leu	GGT Gly	GCT Ala	GGC Gly	ATC Ile 585	CCT Pro	GGA Gly	CTT Leu	GGA Gly	GTT Val 590	GGT Gly	GTC Val	GGC Gly	GTC Val	CCT Pro 595	1833
GGA Gly	CTT Leu	GGA Gly	GTT Val	GGT Gly 600	GCT Ala	GGT Gly	GTT Val	CCT Pro	GGA Gly 605	CTT Leu	GGA Gly	GTT Val	GGT Gly	GCT Ala 610	GGT Gly	1881
GTT Val	CCT Pro	GGC Gly	TTC Phe 615	GGG Gly	GCA Ala	GGT Gly	GCA Ala	GAT Asp 620	GAG Glu	GGA Gly	GTT Val	AGG Arg	CGG Arg 625	AGC Ser	CTG Leu	1929
TCC Ser	CCT Pro	GAG Glu 630	CTC Leu	AGG Arg	GAA Glu	GGA Gly	GAT Asp 635	CCC Pro	TCC Ser	TCC Ser	TCT Ser	CAG Gln 640	CAC His	CTC Leu	CCC Pro	1977
AGC Ser	ACC Thr 645	CCC Pro	TCA Ser	TCA Ser	CCC Pro	AGG Arg 650	GTA Val	CCT Pro	GGA Gly	GCC Ala	CTG Leu 655	GCT Ala	GCC Ala	GCT Ala	AAA Lys	2025
GCA Ala 660	GCC Ala	AAA Lys	TAT Tyr	GGA Gly	GCA Ala 665	GCA Ala	GTG Val	CCT Pro	GGG Gly	GTC Val 670	CTT Leu	GGA Gly	GGG Gly	CTC Leu	GGG Gly 675	2073
GCT Ala	CTC Leu	GGT Gly	GGA Gly	GTA Val 680	GGC Gly	ATC Ile	CCA Pro	GGC Gly	GGT Gly 685	GTG Val	GTG Val	GGA Gly	GCC Ala	GGA Gly 690	CCC Pro	2121
GCC Ala	GCC Ala	GCC Ala	GCT Ala 695	GCC Ala	GCA Ala	GCC Ala	AAA Lys 700	GCT Ala 705	GCT Ala	GCC Ala	AAA Lys	GCC Ala 705	GCC Ala	CAG Gln 705	TTT Phe	2169
GGC Gly	CTA Leu	GTG Val 710	GGA Gly	GCC Ala	GCT Ala	GGG Gly	CTC Leu 715	GGA Gly	GGA Gly	CTC Leu	GGA Gly 720	GTC Val 720	GGA Gly	GGG Gly	CTT Leu	2217
GGA Gly	GTT Val 725	CCA Pro	GGT Gly	GTT Val	GGG Gly	GGC Gly 730	CTT Leu	GGA Gly	GGT Gly	ATA Ile 735	CCT Pro 735	CCA Pro	GCT Ala	GCA Ala	GCC Ala	2265
GCT Ala 740	AAA Lys	GCA Ala	GCT Ala	AAA Lys	TAC Tyr 745	GGT Gly	GCT Ala	GCT Ala	GGC Gly 750	CTT Leu 750	GGA Gly	GGT Gly	GTC Val	CTA Leu 755	GGG Gly 755	2313
GGT Gly	GCC Ala	GGG Gly	CAG Gln 760	TTC Phe 760	CCA Pro	CTT Leu	GGA Gly	GGA Gly	GTG Val 765	GCA Ala	GCA Ala	AGA Arg	CCT Pro	GGC Gly 770	TTC Phe	2361
GGA Gly	TTG Leu	TCT Ser	CCC Pro 775	ATT Ile	TTC Phe	CCA Pro	GGT Gly	GGG Gly 780	GCC Ala	TGC Cys	CTG Leu	GGG Gly	AAA Lys 785	GCT Ala	TGT Cys	2409
GGC Gly	CGG Arg	AAG Lys 790	AGA Arg	AAA Lys	TGA											2427

(2) INFORMATION FOR SEQ ID NO:40:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 792 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: protein

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:40:

Met Ala Gly Leu Thr Ala Ala Ala Pro Arg Pro Gly Val Leu Leu Leu
1 5 10 15

Leu Leu Ser Ile Leu His Pro Ser Arg Pro Gly Gly Val Pro Gly Ala
20 25 30

Ile Pro Gly Gly Val Pro Gly Gly Val Phe Tyr Pro Gly Ala Gly Leu
35 40 45

Gly Ala Leu Gly Gly Gly Ala Leu Gly Pro Gly Gly Lys Pro Leu Lys

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50			55			60									
Pro 65	Val	Pro	Gly	Gly	Leu 70	Ala	Gly	Ala	Gly	Leu 75	Gly	Ala	Gly	Leu	Gly 80
Ala	Phe	Pro	Ala	Val 85	Thr	Phe	Pro	Gly	Ala 90	Leu	Val	Pro	Gly	Gly 95	Val
Ala	Asp	Ala	Ala 100	Ala	Ala	Tyr	Lys	Ala 105	Ala	Lys	Ala	Gly	Ala 110	Gly	Leu
Gly	Gly	Val 115	Pro	Gly	Val	Gly	Gly 120	Leu	Gly	Val	Ser	Ala 125	Gly	Ala	Val
Val	Pro 130	Gln	Pro	Gly	Ala	Gly 135	Val	Lys	Pro	Gly	Lys 140	Val	Pro	Gly	Val
Gly 145	Leu	Pro	Gly	Val	Tyr 150	Pro	Gly	Gly	Val	Leu 155	Pro	Gly	Ala	Arg	Phe 160
Pro	Gly	Val	Gly	Val 165	Leu	Pro	Gly	Val	Pro 170	Thr	Gly	Ala	Gly	Val 175	Lys
Pro	Lys	Ala	Pro 180	Gly	Val	Gly	Gly	Ala 185	Phe	Ala	Gly	Ile	Pro 190	Gly	Val
Gly	Pro	Phe 195	Gly	Gly	Pro	Gln	Pro	Gly 200	Val	Pro	Leu	Gly 205	Tyr	Pro	Ile
Lys	Ala 210	Pro	Lys	Leu	Pro	Gly 215	Gly	Tyr	Gly	Leu	Pro 220	Tyr	Thr	Thr	Gly
Lys 225	Leu	Pro	Tyr	Gly	Tyr 230	Gly	Pro	Gly	Gly	Val 235	Ala	Gly	Ala	Ala	Gly 240
Lys	Ala	Gly	Tyr	Pro 245	Thr	Gly	Thr	Gly	Val 250	Gly	Pro	Gln	Ala	Ala 255	Ala
Ala	Ala	Ala	Ala 260	Lys	Ala	Ala	Ala	Lys 265	Phe	Gly	Ala	Gly	Ala 270	Ala	Gly
Val	Leu	Pro 275	Gly	Val	Gly	Gly	Ala 280	Gly	Val	Pro	Gly	Val 285	Pro	Gly	Ala
Ile	Pro 290	Gly	Ile	Gly	Gly	Ile 295	Ala	Gly	Val	Gly	Thr 300	Pro	Ala	Ala	Ala
Ala 305	Ala	Ala	Ala	Ala	Ala 310	Ala	Lys	Ala	Ala	Lys 315	Tyr	Gly	Ala	Ala	Ala 320
Gly	Leu	Val	Pro	Gly 325	Gly	Pro	Gly	Phe	Gly 330	Pro	Gly	Val	Val	Gly 335	Val
Pro	Gly	Ala	Gly 340	Val	Pro	Gly	Val	Gly 345	Val	Pro	Gly	Ala	Gly 350	Ile	Pro
Val	Val	Pro 355	Gly	Ala	Gly	Ile	Pro 360	Gly	Ala	Ala	Val	Pro 365	Gly	Val	Val
Ser	Pro 370	Glu	Ala	Ala	Ala	Lys 375	Ala	Ala	Ala	Lys 380	Ala	Ala	Lys	Tyr	Gly
Ala 385	Arg	Pro	Gly	Val	Gly 390	Val	Gly	Gly	Ile	Pro 395	Thr	Tyr	Gly	Val	Gly 400
Ala	Gly	Gly	Phe	Pro 405	Gly	Phe	Gly	Val	Gly 410	Val	Gly	Gly	Ile	Pro 415	Gly
Val	Ala	Gly	Val 420	Pro	Ser	Val	Gly	Gly 425	Val	Pro	Gly	Val	Gly 430	Gly	Val
Pro	Gly	Val 435	Gly	Ile	Ser	Pro	Glu 440	Ala	Gln	Ala	Ala	Ala 445	Ala	Ala	Lys
Ala 450	Ala	Lys	Tyr	Gly	Ala	Ala 455	Gly	Ala	Gly	Val	Leu 460	Gly	Gly	Leu	Val
Pro 465	Gly	Pro	Gln	Ala	Ala 470	Val	Pro	Gly	Val	Pro 475	Gly	Thr	Gly	Gly	Val 480

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Pro	Gly	Val	Gly	Thr	Pro	Ala	Ala	Ala	Ala	Ala	Lys	Ala	Ala	Ala	Lys
				485					490					495	
Ala	Ala	Gln	Phe	Ala	Leu	Leu	Asn	Leu	Ala	Gly	Leu	Val	Pro	Gly	Val
			500					505					510		
Gly	Val	Ala	Pro	Gly	Val	Gly	Val	Ala	Pro	Gly	Val	Gly	Val	Ala	Pro
		515					520					525			
Gly	Val	Gly	Leu	Ala	Pro	Gly	Val	Gly	Val	Ala	Pro	Gly	Val	Gly	Val
	530					535					540				
Ala	Pro	Gly	Val	Gly	Val	Ala	Pro	Gly	Ile	Gly	Pro	Gly	Gly	Val	Ala
545					550					555					560
Ala	Ala	Ala	Lys	Ser	Ala	Ala	Lys	Val	Ala	Ala	Lys	Ala	Gln	Leu	Arg
				565					570					575	
Ala	Ala	Ala	Gly	Leu	Gly	Ala	Gly	Ile	Pro	Gly	Leu	Gly	Val	Gly	Val
			580					585					590		
Gly	Val	Pro	Gly	Leu	Gly	Val	Gly	Ala	Gly	Val	Pro	Gly	Leu	Gly	Val
		595					600					605			
Gly	Ala	Gly	Val	Pro	Gly	Phe	Gly	Ala	Gly	Ala	Asp	Glu	Gly	Val	Arg
	610					615					620				
Arg	Ser	Leu	Ser	Pro	Glu	Leu	Arg	Glu	Gly	Asp	Pro	Ser	Ser	Ser	Gln
625					630					635					640
His	Leu	Pro	Ser	Thr	Pro	Ser	Ser	Pro	Arg	Val	Pro	Gly	Ala	Leu	Ala
				645					650					655	
Ala	Ala	Lys	Ala	Ala	Lys	Tyr	Gly	Ala	Ala	Val	Pro	Gly	Val	Leu	Gly
			660					665					670		
Gly	Leu	Gly	Ala	Leu	Gly	Gly	Val	Gly	Ile	Pro	Gly	Gly	Val	Val	Gly
		675					680					685			
Ala	Gly	Pro	Ala	Ala	Ala	Ala	Ala	Ala	Ala	Lys	Ala	Ala	Ala	Lys	Ala
	690					695					700				
Ala	Gln	Phe	Gly	Leu	Val	Gly	Ala	Ala	Gly	Leu	Gly	Gly	Leu	Gly	Val
705					710					715					720
Gly	Gly	Leu	Gly	Val	Pro	Gly	Val	Gly	Gly	Leu	Gly	Gly	Ile	Pro	Pro
				725				730						735	
Ala	Ala	Ala	Ala	Lys	Ala	Ala	Lys	Tyr	Gly	Ala	Ala	Gly	Leu	Gly	Gly
			740					745					750		
Val	Leu	Gly	Gly	Ala	Gly	Gln	Phe	Pro	Leu	Gly	Gly	Val	Ala	Ala	Arg
		755					760					765			
Pro	Gly	Phe	Gly	Leu	Ser	Pro	Ile	Phe	Pro	Gly	Gly	Ala	Cys	Leu	Gly
	770					775						780			
Lys	Ala	Cys	Gly	Arg	Lys	Arg	Lys								
785					790										

(2) INFORMATION FOR SEQ ID NO:41:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 3262 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(i i) MOLECULE TYPE: cDNA

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:

- (A) ORGANISM: Homo sapiens

(i x) FEATURE:

- (A) NAME/KEY: CDS

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280				285				290								
AGG Arg 295	AGC Ser	TGC Cys	AGC Ser	ATC Ile	GAC Asp 300	AGG Arg	TCT Ser	CCG Pro	GGC Gly	GCT Ala 305	GGC Gly	TCA Ser	CTG Leu	GGC Gly	TCC Ser 310	1025
CCG Pro	GCC Ala	TCC Ser	CAG Gln	CGC Arg 315	AAG Lys	GAC Asp	CTG Leu	GGT Gly	CGC Arg 320	TCT Ser	GAG Glu	TCC Ser	CTC Leu	CGC Arg 325	GTA Val	1073
GTC Val	TGC Cys	CGG Arg	CCA Pro 330	CAC His	CGC Arg	ATC Ile	TTC Phe	CGG Arg 335	CCG Pro	TCG Ser	GAC Asp	CTC Leu	ATC Ile 340	CAC His	GGG Gly	1121
GAG Glu	GTG Val	CTG Leu 345	GGC Gly	AAG Lys	GGC Gly	TGC Cys	TTC Phe 350	GGC Gly	CAG Gln	GCT Ala	ATC Ile	AAG Lys 355	GTG Val	ACA Thr	CAC His	1169
CGT Arg	GAG Glu 360	ACA Thr	GGT Gly	GAG Glu	GTG Val 365	ATG Met	GTG Val	ATG Met	AAG Lys	GAG Glu	CTG Leu 370	ATC Ile	CGG Arg	TTC Phe	GAC Asp	1217
GAG Glu 375	GAG Glu	ACC Thr	CAG Gln	AGG Arg	ACG Thr 380	TTC Phe	CTC Leu	AAG Lys	GAG Glu	GTG Val 385	AAG Lys	GTC Val	ATG Met	CGA Arg	TGC Cys 390	1265
CTG Leu	GAA Glu	CAC His	CCC Pro	AAC Asn 395	GTG Val	CTC Leu	AAG Lys	TTC Phe	ATC Ile 400	GGG Gly	GTG Val	CTC Leu	TAC Tyr	AAG Lys 405	GAC Asp	1313
AAG Lys	AGG Arg	CTC Leu	AAC Asn 410	TTC Phe	ATC Ile	ACT Thr	GAG Glu	TAC Tyr 415	ATC Ile	AAG Lys	GGC Gly	GGC Gly	ACG Thr 420	CTC Leu	CGG Arg	1361
GGC Gly	ATC Ile	ATC Ile 425	AAG Lys	AGC Ser	ATG Met	GAC Asp	AGC Ser 430	CAG Gln	TAC Tyr	CCA Pro	TGG Trp	AGC Gln 435	CAG Gln	AGA Arg	GTG Val	1409
AGC Ser	TTT Phe 440	GCC Ala	AAG Lys	GAC Asp	ATC Ile	GCA Ala 445	TCA Ser	GGG Gly	ATG Met	GCC Ala	TAC Tyr 450	CTC Leu	CAC His	TCC Ser	ATG Met	1457
AAC Asn 455	ATC Ile	ATC Ile	CAC His	CGA Arg	GAC Asp 460	CTC Leu	AAC Asn	TCC Ser	CAC His	AAC Asn 465	TGC Cys	CTG Leu	GTC Val	CGC Arg	GAG Glu 470	1505
AAC Asn	AAG Lys	AAT Asn	GTG Val 475	GTG Val	GTG Ala	GCT Ala	GAC Asp	TTC Phe	GGG Gly 480	CTG Leu	GCG Ala	CGT Arg	CTC Leu	ATG Met 485	GTG Val	1553
GAC Asp	GAG Glu	AAG Lys	ACT Thr 490	CAG Gln	CCT Pro	GAG Glu	GGC Gly	CTG Leu 495	CGG Arg	AGC Ser	CTC Leu	AAG Lys 500	AAG Lys	CCA Pro	GAC Asp	1601
CGC Arg	AAG Lys 505	AAG Lys	CGC Arg	TAC Tyr	ACC Thr	GTG Val 510	GTG Val	GGC Gly	AAC Asn	CCC Pro	TAC Tyr 515	TGG Trp	ATG Met	GCA Ala	CCT Pro	1649
GAG Glu 520	ATG Met	ATC Ile	AAC Asn	GGC Gly	CGC Arg	AGC Ser 525	TAT Tyr	GAT Asp	GAG Glu	AAG Lys	GTG Val 530	GAT Asp	GTG Val	TTC Phe	TCC Ser	1697
TTT Phe 535	GGG Gly	ATC Ile	GTC Val	CTG Leu	TGC Cys 540	GAG Glu	ATC Ile	ATC Ile	GGG Gly	CGG Arg 545	GTG Val	AAC Asn	GCA Ala	GAC Asp	CCT Pro 550	1745
GAC Asp	TAC Tyr	CTG Leu	CCC Pro	CGC Arg 555	ACC Thr	ATG Met	GAC Asp	TTT Phe	GGC Gly 560	CTC Leu	AAC Asn	GTG Val	CGA Arg	GGA Gly 565	TTC Phe	1793
CTG Leu	GAC Asp	CGC Arg	TAC Tyr 570	TGC Cys	CCC Pro	CCA Pro	AAC Asn	TGC Cys 575	CCC Pro	CCG Pro	AGC Ser	TTC Phe	TTC Phe 580	CCC Pro	ATC Ile	1841
ACC Thr	GTG Val	CGC Arg 585	TGT Cys	TGC Cys	GAT Asp	CTG Leu	GAC Asp 590	CCC Pro	GAG Glu	AAG Lys	AGG Arg	CCA Pro 595	TCC Ser	TTT Phe	GTG Val	1889
AAG Lys	CTG Leu	GAA Glu	CAC His	TGG Trp	CTG Leu	GAG Glu	ACC Thr	CTC Leu	CGC Arg	ATG Met	CAC His	CTG Leu	GCC Ala	GGC Gly	CAC His	1937

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600					605					610						
CTG	CCA	CTG	GGC	CCA	CAG	CTG	GAG	CAG	CTG	GAC	AGA	GGT	TTC	TGG	GAG	1985
Leu	Pro	Leu	Gly	Pro	Gln	Leu	Glu	Gln	Leu	Asp	Arg	Gly	Phe	Trp	Glu	
615					620					625					630	
ACC	TAC	CGG	CGC	GGC	GAG	AGC	GGA	CTG	CCT	GCC	CAC	CCT	GAG	GTC	CCC	2033
Thr	Tyr	Arg	Arg	Gly	Glu	Ser	Gly	Leu	Pro	Ala	His	Pro	Glu	Val	Pro	
				635					640					645		
GAC	TGAGCCAGGG	CCACTCAGCT	GCCCCTGTCC	CCACCTCTGG	AGAATCCACC											2086
Asp																
CCCACCAGAT	TCCTCCGCGG	GAGGTGGCCC	TCAGCTGGGA	CAGTGGGGAC	CCAGGCTTCT											2146
CCTCAGAGCC	AGGCCCTGAC	TTGCCTTCTC	CCACCCCGTG	GACCGCTTCC	CCTGCCTTCT											2206
CTCTGCCGTG	GCCCAGAGCC	GGCCCAGCTG	CACACACACA	CCATGCTCTC	GCCCTGCTGT											2266
AACCTCTGTC	TTGGCAGGGC	TGTCCCCTCT	TGCTTCTCCT	TGCATGAGCT	GGAGGGCCTG											2326
TGTGAGTTAC	GCCCCTTTCC	ACACGCCGCT	GCCCCAGCAA	CCCTGTTTAC	GCTCCACCTG											2386
TCTGGTCCAT	AGCTCCCTGG	AGGCTGGGCC	AGGAGGCAGC	CTCCGAACCA	TGCCCCATAT											2446
AACGCTTGGG	TGCGTGGGAG	GGCGCACATC	AGGGCAGAGG	CCAAGTTCCA	GGTGTCTGTG											2506
TTCCAGGAA	CCAAATGGGG	AGTCTGGGGC	CCGTTTTCCC	CCCAGGGGGT	GTCTAGGTAG											2566
CAACAGGTAT	CGAGGACTCT	CCAAACCCCC	AAAGCAGAGA	GAGGGCTGAT	CCCATGGGGC											2626
GGAGGTCCCC	AGTGGCTGAG	CAAACAGCCC	CTTCTCTCGC	TTTGGGTCTT	TTTTTTGTTT											2686
CTTTCTTAAA	GCCACTTTAG	TGAGAAGCAG	GTACCAAGCC	TCAGGGTGAA	GGGGGTCCCT											2746
TGAGGGAGCG	TGGAGCTGCG	GTGCCCTGGC	CGGCGATGGG	GAGGAGCCGG	CTCCGGCAGT											2806
GAGAGGATAG	GCACAGTGGA	CCGGGCAGGT	GTCCACCAGC	AGCTCAGCCC	CTGCAGTCAT											2866
CTCAGAGCCC	CTTCCCGGGC	CTCTCCCCCA	AGGCTCCCTG	CCCCTCCTCA	TGCCCTCTG											2926
TCCTCTGCGT	TTTTTCTGTG	TAATCTATTT	TTAAGAAGA	GTTTGTATTA	TTTTTTCATA											2986
CGGCTGCAGC	AGCAGCTGCC	AGGGGCTTGG	GATTTTATTT	TTGTGGCGGG	CGGGGGTGGG											3046
AGGGCCATTT	TGTCACCTTG	CCTCAGTTGA	GCATCTAGGA	AGTATTAATA	CTGTGAAGCT											3106
TTCTCAGTGC	ACTTTGAACC	TGGAAAACAA	TCCCAACAGG	CCCGTGGGAC	CATGACTTAG											3166
GGAGGTGGGA	CCCACCCACC	CCCATCCAGG	AACCGTGACG	TCCAAGGAAC	CAAACCCAGA											3226
CGCAGAACAA	TAAAATAAAT	TCCGTACTCC	CCACCC													3262

(2) INFORMATION FOR SEQ ID NO:42:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 647 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: protein

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:42:

Met	Arg	Leu	Thr	Leu	Leu	Cys	Cys	Thr	Trp	Arg	Glu	Glu	Arg	Met	Gly	
1				5					10					15		
Glu	Glu	Gly	Ser	Glu	Leu	Pro	Val	Cys	Ala	Ser	Cys	Gly	Gln	Arg	Ile	
			20					25					30			
Tyr	Asp	Gly	Gln	Tyr	Leu	Gln	Ala	Leu	Asn	Ala	Asp	Trp	His	Ala	Asp	
		35					40					45				
Cys	Phe	Arg	Cys	Cys	Asp	Cys	Ser	Ala	Ser	Leu	Ser	His	Gln	Tyr	Tyr	
	50					55					60					
Glu	Lys	Asp	Gly	Gln	Leu	Phe	Cys	Lys	Lys	Asp	Tyr	Trp	Ala	Arg	Tyr	
65					70					75					80	

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Gly	Glu	Ser	Cys	His 85	Gly	Cys	Ser	Glu	Gln 90	Ile	Thr	Lys	Gly	Leu 95	Val
Met	Val	Ala	Gly 100	Glu	Leu	Lys	Tyr	His 105	Pro	Glu	Cys	Phe	Ile 110	Cys	Leu
Thr	Cys	Gly 115	Thr	Phe	Ile	Gly	Asp 120	Gly	Asp	Thr	Tyr	Thr 125	Leu	Val	Glu
His	Ser 130	Lys	Leu	Tyr	Cys	Gly 135	His	Cys	Tyr	Tyr	Gln 140	Thr	Val	Val	Thr
Pro 145	Val	Ile	Glu	Gln	Ile 150	Leu	Pro	Asp	Ser	Pro 155	Gly	Ser	His	Leu	Pro 160
His	Thr	Val	Thr	Leu 165	Val	Ser	Ile	Pro	Ala 170	Ser	Ser	His	Gly	Lys	Arg 175
Gly	Leu	Ser	Val 180	Ser	Ile	Asp	Pro	Pro 185	His	Gly	Pro	Pro	Gly	Cys	Gly
Thr	Glu	His 195	Ser	His	Thr	Val	Arg 200	Val	Gln	Gly	Val	Asp 205	Pro	Gly	Cys
Met	Ser 210	Pro	Asp	Val	Lys	Asn 215	Ser	Ile	His	Val	Gly	Asp	Arg	Ile	Leu
Glu 225	Ile	Asn	Gly	Thr	Pro 230	Ile	Arg	Asn	Val	Pro 235	Leu	Asp	Glu	Ile	Asp 240
Leu	Leu	Ile	Gln	Glu 245	Thr	Ser	Arg	Leu	Leu 250	Gln	Leu	Thr	Leu	Glu	His 255
Asp	Pro	His	Asp 260	Thr	Leu	Gly	His	Gly 265	Leu	Gly	Pro	Glu	Thr 270	Ser	Pro
Leu	Ser	Ser 275	Pro	Ala	Tyr	Thr	Pro 280	Ser	Gly	Glu	Ala	Gly	Ser	Ser	Ala
Arg	Gln 290	Lys	Pro	Val	Leu	Arg 295	Ser	Cys	Ser	Ile	Asp 300	Arg	Ser	Pro	Gly
Ala 305	Gly	Ser	Leu	Gly	Ser 310	Pro	Ala	Ser	Gln	Arg 315	Lys	Asp	Leu	Gly	Arg 320
Ser	Glu	Ser	Leu	Arg 325	Val	Val	Cys	Arg	Pro 330	His	Arg	Ile	Phe	Arg	Pro 335
Ser	Asp	Leu	Ile 340	His	Gly	Glu	Val	Leu 345	Gly	Lys	Gly	Cys	Phe 350	Gly	Gln
Ala	Ile	Lys 355	Val	Thr	His	Arg	Glu 360	Thr	Gly	Glu	Val	Met 365	Val	Met	Lys
Glu 370	Leu	Ile	Arg	Phe	Asp	Glu 375	Glu	Thr	Gln	Arg	Thr 380	Phe	Leu	Lys	Glu
Val 385	Lys	Val	Met	Arg	Cys 390	Leu	Glu	His	Pro	Asn 395	Val	Leu	Lys	Phe	Ile 400
Gly	Val	Leu	Tyr	Lys 405	Asp	Lys	Arg	Leu	Asn 410	Phe	Ile	Thr	Glu	Tyr	Ile 415
Lys	Gly	Gly	Thr 420	Leu	Arg	Gly	Ile	Ile 425	Lys	Ser	Met	Asp	Ser	Gln	Tyr
Pro	Trp	Ser 435	Gln	Arg	Val	Ser	Phe 440	Ala	Lys	Asp	Ile	Ala 445	Ser	Gly	Met
Ala 450	Tyr	Leu	His	Ser	Met	Asn 455	Ile	Ile	His	Arg	Asp 460	Leu	Asn	Ser	His
Asn 465	Cys	Leu	Val	Arg	Glu 470	Asn	Lys	Asn	Val	Val 475	Val	Ala	Asp	Phe	Gly 480
Leu	Ala	Arg	Leu	Met 485	Val	Asp	Glu	Lys	Thr 490	Gln	Pro	Glu	Gly	Leu	Arg 495
Ser	Leu	Lys	Lys 500	Pro	Asp	Arg	Lys	Lys 505	Arg	Tyr	Thr	Val	Val	Gly	Asn 510

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Pro	Tyr	Trp	Met	Ala	Pro	Glu	Met	Ile	Asn	Gly	Arg	Ser	Tyr	Asp	Glu
		515					520					525			
Lys	Val	Asp	Val	Phe	Ser	Phe	Gly	Ile	Val	Leu	Cys	Glu	Ile	Ile	Gly
	530					535					540				
Arg	Val	Asn	Ala	Asp	Pro	Asp	Tyr	Leu	Pro	Arg	Thr	Met	Asp	Phe	Gly
545					550					555					560
Leu	Asn	Val	Arg	Gly	Phe	Leu	Asp	Arg	Tyr	Cys	Pro	Pro	Asn	Cys	Pro
				565					570					575	
Pro	Ser	Phe	Phe	Pro	Ile	Thr	Val	Arg	Cys	Cys	Asp	Leu	Asp	Pro	Glu
			580					585					590		
Lys	Arg	Pro	Ser	Phe	Val	Lys	Leu	Glu	His	Trp	Leu	Glu	Thr	Leu	Arg
		595					600					605			
Met	His	Leu	Ala	Gly	His	Leu	Pro	Leu	Gly	Pro	Gln	Leu	Glu	Gln	Leu
	610					615					620				
Asp	Arg	Gly	Phe	Trp	Glu	Thr	Tyr	Arg	Arg	Gly	Glu	Ser	Gly	Leu	Pro
625					630					635					640
Ala	His	Pro	Glu	Val	Pro	Asp									
				645											

What is claimed is:

1. A method for determining the presence of impaired visuospatial constructive cognition, said method comprising determining zygosity in an individual of LIM-kinase 1 (LIMK1), wherein a nucleic acid probe or primer specific for LIMK1 is hybridized to said individual's nucleic acid, wherein hemizygosity of LIMK1 is indicative of impaired visuospatial constructive cognition.
2. The method of claim 1 wherein said zygosity is measured by in situ hybridization.
3. The method of claim 1 wherein said zygosity is measured by fluorescent in situ hybridization.
4. The method of claim 1 wherein said zygosity is measured using a polymerase chain reaction.
5. The method of claim 1 wherein said zygosity is measured using a DNA fingerprinting technique.
6. A method for determining the presence of a partial Williams syndrome profile, said method comprising determining the presence of a complete deletion of LIM-kinase 1 (LIMK1) and a deletion of at least a 3' terminal region of elastin (ELN) on one chromosome, wherein said presence of a complete deletion of LIMK1 and a deletion of at least a 3' terminal region of ELN, said deletion of a 3' terminal region of ELN comprising a region from exon 28 through the stop codon of ELN, on one chromosome and further wherein no more than about 100 kb 3' to LIMK1 is deleted on said chromosome is indicative of the presence of a partial Williams syndrome profile.

7. The method of claim 6 wherein said method comprises in situ hybridization.
8. The method of claim 6 wherein said method comprises fluorescent in situ hybridization.
9. The method of claim 6 wherein said method comprises a polymerase chain reaction.
10. The method of claim 6 wherein said method comprises a DNA fingerprinting technique.
11. A method for distinguishing whether an individual has supravalvular aortic stenosis (SVAS), partial Williams syndrome profile or Williams syndrome (WS), said method comprising analyzing an individual's chromosomes for deletions of portions of chromosome 7 wherein a deletion of elastin (ELN) but not LIM-kinase 1 (LIMK1) is indicative of SVAS, a deletion of ELN and LIMK1 but no more than about 100 kb 3' to LIMK1 is indicative of partial Williams syndrome, and a deletion of ELN, LIMK1 and greater than 300 kb 3' of LIMK1 is indicative of WS.
12. The method of claim 11 wherein said analyzing comprises in situ hybridization.
13. The method of claim 11 wherein said analyzing comprises fluorescent in situ hybridization.
14. The method of claim 11 wherein said analyzing comprises a polymerase chain reaction.
15. The method of claim 11 wherein said analyzing comprises a DNA fingerprinting technique.

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