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Williams Syndrome: Use of Chromosomal Microdeletions as a Tool to Dissect Cognitive and Physical Phenotypes

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Summary

In Williams syndrome (WS), a deletion of ~1.5 Mb on one copy of chromosome 7 causes specific physical, cognitive, and behavioral abnormalities. Molecular dissection of the phenotype may be a route to identification of genes important in human cognition and behavior. Among the genes known to be deleted in WS are *ELN* (which encodes elastin), *LIMK1* (which encodes a protein tyrosine kinase expressed in the developing brain), *STX1A* (which encodes a component of the synaptic apparatus), and *FZD3*. Study of patients with deletions or mutations confined to *ELN* showed that hemizygosity for elastin is responsible for the cardiological features of WS. *LIMK1* and *STX1A* are good candidates for cognitive or behavioral aspects of WS. Here we describe genetic and psychometric testing of patients who have small deletions within the WS critical region. Our results suggest that neither *LIMK1* hemizygosity (contrary to a previous report) nor *STX1A* hemizygosity is likely to contribute to any part of the WS phenotype, and they emphasize the importance of such patients for dissecting subtle but highly penetrant phenotypes.

Introduction

Many human chromosomal-abnormality syndromes include specific cognitive and behavioral components. Children with Prader-Willi syndrome, who lack a paternally derived copy of the proximal long arm of chromosome 15, eat uncontrollably (Sarimski et al. 1996). People with Smith-Magenis syndrome, caused by a microdeletion of chromosome 17p11.2, have bizarre and specific self-mutilating and aggressive behavior, sleep disturbances, and indifference to pain (Greenberg et al. 1996). A deletion of 22q11 can be associated with obsessive behavior and schizophreniform disorders (Ryan et al. 1997). Identification of the genes located on the relevant chromosomal segments may allow us to characterize genes that contribute to specific features of human cognition and behavior.

This strategy faces three main difficulties. First, it is not sufficient simply to enumerate the deleted genes, because, for most genes, a 50% decrease in gene dosage has no phenotypic effect. Second, mouse knockouts are of limited use for confirmation that a gene causes human cognitive or behavioral effects, making it difficult to test the hypotheses generated. Finally, the gene-dosage effects that cause these phenotypes are often dependent on genetic background, reducing the value of single clinical cases and making cross-species comparisons particularly unreliable. Williams syndrome (WS) provides a good example of the progress and problems in the use of microdeletion phenotypes to define genes affecting human cognition and behavior.

WS (MIM 194050) is rare (frequency 1/20,000), with particularly striking cognitive and behavioral features (Morris et al. 1988). The full intelligence quotient (IQ) of persons with WS is usually in the 50s to 60s (range 40–85). However, this camouflages a very uneven cognitive profile: people with WS show relatively good verbal abilities alongside very deficient visuospatial abilities (Udwin and Yule 1991; Bellugi et al. 1994; Jarrold et al. 1998). This differential pattern of abilities has been termed the "WS cognitive profile" (WSCP) (Frangiskakis et al. 1996; Mervis et al., in press). The formal definition of WSCP is shown in the Appendix; note that it is independent of IQ or overall ability levels. Furthermore, despite low IQ, the ability of individuals with WS to recognize faces falls within the normal range on certain standardized tests, such as the Benton Face Processing Task (Bellugi et al. 1994) and the Rivermead Face Memory Test (Udwin and Yule 1991). However, the cognitive process by which these behavioral scores are achieved may, in fact, be different in persons with WS versus normal controls (Karmiloff-Smith 1997). Children and

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Figure 1 *A,* Patients PM (*left*) and TM (*right*) with their father, from whom they inherited their deletion. *B,* Patient CS. All subjects lack the dysmorphic features typical of WS.

adults with WS also have characteristic personality traits, preferring the company of adults to that of peers and lacking shyness toward strangers (Einfeld et al. 1997; Karmiloff-Smith et al. 1995). Physically, there is growth retardation, a characteristic face, a high frequency of supravalvular aortic stenosis (SVAS), and, sometimes, severe infantile hypercalcemia and hyperacusis.

WS is caused by a chromosomal deletion at 7q11.23 (Lowery et al. 1995; Nickerson et al. 1995). This chromosomal region is highly repetitive, and the deletion arises from recombination between misaligned repeat sequences flanking the WS region (Baumer et al. 1998). The deletion breakpoints cluster within the repeats, so that most patients with WS have similar, although not identical, deletions of ~1.5 Mb (M. Tassabehji, unpublished data). The first deleted gene identified in the critical region was that for elastin (*ELN*) (Ewart et al. 1993*a*). Studies of patients having deletions or point mutations confined to this gene show that hemizygosity for *ELN* causes SVAS but not the other typical features of WS. Several other genes have now been identified (Osborne et al. 1996, 1997; Peoples et al. 1996; Tassabehji et al. 1996; Wang et al. 1997) that are deleted in most patients with WS, but no phenotype has been assigned to them; these include *LIMK1* (Tassabehji et al. 1996), which codes for a protein tyrosine kinase expressed in the developing brain; that for syntaxin 1A (*STX1A*) (Osborne et al. 1997), which encodes a component of the synaptic apparatus); *RFC2* (Peoples et al. 1996), which codes for a subunit of the replication factor–C complex involved in DNA replication; and *FZD3* (Wang et al. 1997), which is homologous to the *Drosophila* tissue-polarity gene, "*frizzled.*" To define the roles of these other genes in the WS phenotype, we performed molecular and psychometric analysis of several persons with partial WS deletions that cause hemizygosity for only some of the genes deleted in WS. Frangiskakis et al. (1996) have reported that patients from two families with deletions of only *ELN* and *LIMK1* show the characteristic WSCP, generally without mental retardation, and the main objective of our study was to test the generality of this observation. Thus, our psychometric testing followed exactly the same procedures as those reported by Frangiskakis et al. (1996), apart from necessary adjustments to allow for testing of British rather than American subjects (see the Patients and Methods and Discussion sections). We found no evidence to support the claim that haploinsufficiency for *LIMK1* (or for any of the other genes that we tested) is implicated in the WSCP as defined by Mervis et al. (in press). We were also able to investigate the contribution of haploinsufficiency of *ELN* to the physical WS phenotypes.

Patients and Methods

Patients

PM was seen at age 29 years (fig. 1*A*). He belongs to a family showing autosomal dominant uncomplicated SVAS, which he inherited from his father. A cardiac murmur was noted at age 3 mo. Echocardiography had shown mild SVAS, and he was no longer under followup. He had no history of hypercalcemia, and hearing and vision were normal. Bilateral inguinal-hernia repairs were done at age 3 years. Early developmental milestones were normal, although he attended special education classes and obtained no formal qualifications. He is employed in manual work. His growth was normal, and he has no dysmorphic features. Voice quality was normal, and there was no subjective hyperacusis. There was no history of joint problems.

TM (the brother of PM) was seen at age 26 years (fig. 1*A*). A cardiac murmur was noticed shortly after birth and subsequently was diagnosed as mild SVAS. He had no history of hypercalcemia, and developmental milestones were within normal limits. He attended mainstream school but left without formal qualifications. He had no history of hyperacusis or joint problems, and eyesight, voice quality, and hearing were normal. He had an inguinal-hernia repair as an adult. Benign glycosuria had been noted on a number of occasions, but he was otherwise in good health. Growth was normal, and there were no dysmorphic features.

CS was seen at age 7 years 8 mo (fig. 1*B*). She was born at term and weighed 2.7 kg. Although she was constipated as an infant, there was no documented history of hypercalcemia, hyperacusis, or joint problems. Developmental milestones were within normal limits. Her mother tongue is English, but at the time of examination she was attending mainstream school in France and was functioning bilingually, with lessons conducted in both English and French. She underwent surgery, at age 4 years, for severe SVAS and peripheral pulmonary arterial stenosis but had otherwise been in good general health. At the time of examination her height was at the 3d–10th centile, and head circumference was at the 10th centile. She did not have the dysmorphic features of WS, and, apart from her surgical scar, examination results were normal. Her parents did not report problems with hyperactivity or concentration.

HG, a Greek university student, was seen at age 19 years. He had a normal birth, but SVAS had been diagnosed during childhood and had been surgically repaired at age 7 years. He had no other medical problems. Growth, development, and hearing were normal, and there were no dysmorphic features. There was no history of hyperacusis, and voice quality was normal. For a full description of this subject, see the report by Frysirra et al. (1997). Although we were unable to complete psychometric testing on subject HG, he was included in the study for purposes of investigating the physical phenotype of WS.

Microsatellite Analysis

Standard PCR conditions were applied: 2 min of denaturation at 94°C, followed by 27 cycles of 94°C for 1 min, 55°C for 1 min, and 72°C for 1 min, with a 5-min extension at 72°C. Reactions (25 μl) were set up with 50 ng of genomic DNA, 10 pmol of each primer, and 0.5 U *Taq* polymerase (BCL) in the manufacturer's buffer. The PCR products were run on an 8% polyacrylamide gel (acrylamide:N,N methylene bisacrylamide 19:1, 300 V, 2 h), then were visualized by silver staining.

FISH Using Cosmid Clones

Metaphase spreads of chromosomes from patients TM, PM, CS, and HG were prepared from Epstein-Barr virus–transformed lymphoblastoid cell lines, by standard techniques. FISH was performed as described elsewhere (Tassabehji et al. 1996), with cosmid probes containing *ELN, LIMK1,* and *STX1A.* A cosmid mapping to chromosome 7p was used both to identify the chromosome 7 homologues and as an internal control in each case.

Somatic Cell Hybrids

Hybrid cell lines were isolated after lymphoblastoid cells from the patients were fused with mouse BW5147 cells, as described elsewhere (Tassabehji et al. 1996). The presence of a single chromosome 7 in all cell lines was verified by FISH analysis of interphase nuclei, by means of a chromosome 7–specific centromeric probe (Oncor), and on metaphase chromosomes, by means of a human chromosome 7–specific paint (Cambio). Hybrids containing normal and deleted chromosomes were differentiated by FISH (WSCR elastin probe; Oncor) and microsatellite typing, by means of *LIMK1GT* (Mari et al. 1998), with D7S653 as a control.

Deletion Mapping of Hybrids by PCR

Primers were designed for PCR analysis of somatic cell hybrids by means of the published *ELN* (Tassabehji et al. 1997), *LIMK*1 (Tassabehji et al. 1996), *STX1A* (Osborne et al. 1997), and *FZD3* (Wang et al. 1997) cDNA sequences, as well as D7S489 (Gyapay et al. 1994). We used 50 ng of DNA, 10 pmol of each primer, and 0.5 U of *Taq* polymerase (BCL) with the manufacturer's buffer, in a 20-μl reaction. PCR conditions were as follows: 2 min denaturation at 94°C, followed by 30 cycles of 94°C for 1 min, 60°C for 1 min, and 72°C for 1 min, with a 5-min extension at 72°C.

Cognitive/Behavioral Assessment

For psychometric testing, we used the British Abilities Scale (BAS-II) (Elliott 1997). We used six core subtests (matrices, quantitative reasoning, similarities, word definitions, recall of designs, and pattern construction) plus digit recall. These are the same tests as had been used

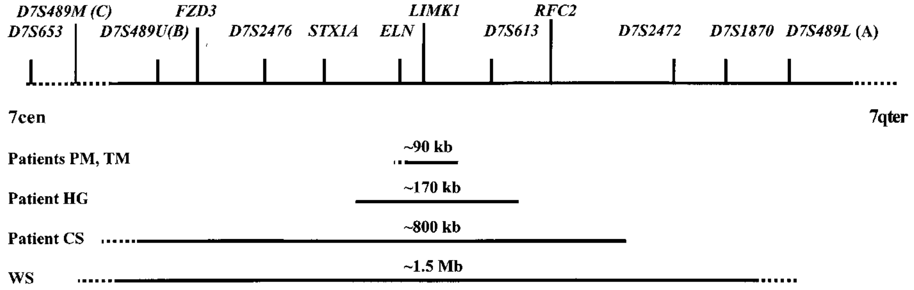

Figure 2 Map of WS critical region, showing approximate size and extent of deletions in the patients with SVAS and in typical subjects with WS. The distance between D7S653 and D7S489A is ~2.5 Mb.

by Frangiskakis et al. 1996). As in their study, for subjects >18 years old we used the norms for the oldest age group in the standardization sample (17 years 6 mo–17 years 11 mo). This is consistent with the procedure for the determination of subscale standard scores for the adult version of the Wechsler (1981) test. Raw scores were converted to *T* scores.

Results

Deletion Mapping Using Microsatellite Markers

Microsatellite mapping of the DNA of patients with SVAS and of their parents, by use of nine markers spanning a distance of 3 cM (seven Généthon primers [Gyapay et al. 1994] plus microsatellites from intron 18 of *ELN* [Foster et al. 1993] and from intron 13 of *LIMK1* [Mari et al. 1998]) allowed the initial definition of the deletion breakpoints. Patients PM and TM were heterozygous for all of the markers tested, apart from *LIMK1* and *ELN,* suggesting that any deletion was very small. Subjects CS and HG had larger deletions compared with those in TM and PM (fig. 2). The sizes of the deletions were estimated by use of markers from a physical map of the region (M. Tassabehji, unpublished data).

Deletion Analysis by FISH

FISH analyses were done on subjects PM, TM, CS, and HG by use of cosmids containing *LIMK1, ELN,* and *STX1A* (data not shown). One copy of *LIMK*1 was deleted in all four subjects. *ELN* was deleted in HG and CS, but in PM and TM both chromosomes gave a FISH signal, suggesting that the gene was either not deleted or only partially deleted. *STX1A* was deleted only in CS.

Deletion Mapping by PCR of Somatic Cell Hybrids

Because partially deleted genes can give detectable FISH signals, somatic cell hybrid lines were made from cells of subjects CS, HG, and TM, to allow their deletion breakpoints to be more finely mapped. The normal and deleted copies of chromosome 7 were segregated, and stable cell lines were established. Hybrids containing the deleted chromosome 7 from each person were tested for the presence of *FZD3, STX1A, ELN, LIMK1,* and *RFC2,* by PCR using primers designed to amplify the 5′

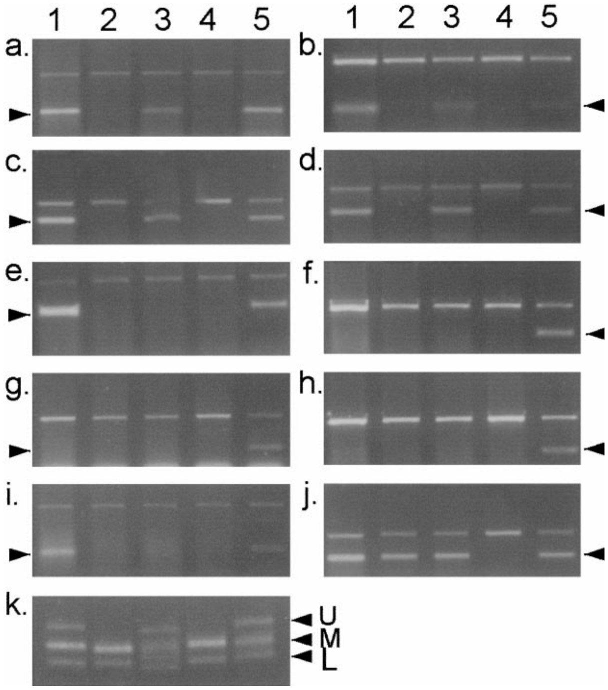

Figure 3 PCR analysis of hybrids for deletion of genes in the WS region. *a, FZD3 5′* end. *b, FZD3 3′* end. *c, STX1A 5′* end. *d, STX1A 3′* end. *e, ELN* exon 1. *f, ELN* exon 34. *g, LIMK1 5′* end. *h, LIMK1 3′* end. *i,* D7S613. *j,* D7S2472. *k,* D7S489 (repeated at three loci on 7q; the order is cen–D7S489M,D7S489U,D7S489L–tel). Lanes 1, PM. Lanes 2, CS. Lanes 3, HG. Lanes 4, Typical patient with WS. Lanes 5, Control. An internal PCR control was included in each reaction (*upper band*). In each gel, the PCR product expected is indicated by an arrowhead. CS is deleted for D7S489U, *FZD3, STX1A, ELN, LIMK1,* and D7S613; PM is deleted for *LIMK1* and part of *ELN;* HG is deleted for *ELN, LIMK1,* and D7S613.

Table 1

Psychometric Test Results for Subjects TM, PM, and CS

	PM	TM	CS
	Score[a]		
Subtests:			
Recall of designs	38	49	57
Pattern construction	49	52	54
Matrices	27	57	67
Quantitative reasoning	20	57	55
Similarities	40	50	53
Word definitions	58	45	60
Mean	38.7	51.7	57.7
Digit recall	32	48	49
Standard tests:			
Verbal	98	96	110
Nonverbal reasoning	55	111	118
Spatial	88	100	115
GCA	77	103	115
	Fit to WSCP		
Criterion:			
1	No	No	Yes
2	No	No	No
3	No	No	No
4	Yes	Yes	Yes

[a] Results of testing using BAS-II; for subtests, *T* scores are given.

and 3′ regions of the genes. A marker, D7S639, known to map outside the deleted region was included as a positive control in the PCR reaction. Mouse DNA was also included as a control, to show that the PCR-amplification products were human specific.

The results (fig. 3) show that the entirety of *LIMK1* is deleted in each subject, confirming the FISH results. In TM, the deletion included part of *ELN* from exon 10 onward but did not include either *RFC2* or *STX1A*. HG has a larger deletion that includes the entirety of both *ELN* and *LIMK1* but none of either *RFC2* or *STX1A*. CS has a larger deletion that includes *FZD3, STX1A, ELN, LIMK1,* and *RFC2;* her deletion extends to D7S489U(B). The marker D7S489 is present at three loci on chromosome 7q (D7S489M[A], D7S489U[B], and D7S489L[C]), and D7S489U(B) is deleted in most patients with WS (fig. 2). The deletion in CS thus appears to include all of the WS critical region proximal to *ELN*.

Cognitive/Behavioral Assessment

Subjects were tested by means of BAS-II (Elliott 1997). Because valid administration of BAS-II tests requires meticulous adherence to protocols and timing, we were unable to obtain data for HG, the Greek student, whose English was very poor despite his high intelligence. Table 1 shows the results of the BAS-II subscales for the remaining three subjects—PM, TM, and CS. We used the same tests (six core subtests plus digit recall) as had been used by Frangiskakis et al. (1996). These tests included two spatial-construction tasks (recall of designs and pattern construction), two nonverbal-reasoning tasks (matrices and quantitative reasoning), and two verbal tasks (similarities and word definitions). Figure 4 illustrates the performances of CS and TM on the recall-of-designs task, compared with two age-matched patients with WS.

Globally, PM performed more poorly than did either TM or CS. In view of the differential abilities and the four criteria (Appendix) that are combined to specify the WS cognitive/behavioral profile, only CS met criterion 1. No subject met either criterion 2 or criterion 3. All subjects met criterion 4, as expected of normal subjects. Thus, none of our three subjects met the WSCP, despite their *LIMK1* deletions. BAS-II allows standard scores (mean 100, SD 15) to be derived both for clusters of subtests (verbal, nonverbal reasoning, and spatial) and overall (the latter is termed "general conceptual ability" [GCA]). GCA is close to what other tests call "IQ." The standard scores are also shown in table 1. Subject PM's GCA is at the low end of the normal range, because of poor nonverbal nonspatial reasoning. When his verbal and spatial scores are compared, he does not have the WSCP. It is not likely that his overall poor score is in any way related to his chromosomal deletion, because none of the other subjects scored poorly.

Discussion

Chromosome 7 deletions causing WS remove a number of genes; but determining which gene is responsible for which part of the phenotype is not simple. Mouse knockouts may not be very informative, because there is not always a consistent homology between mouse and human phenotypes for haploinsufficiency syndromes, whereas genetic background often has a large modifying effect. For example, haploinsufficiency for *PAX3* causes dystopia canthorum; pigmentary abnormalities of the skin, hair, and eyes; and frequent hearing loss in humans (type 1 Waardenburg syndrome); however, the same genetic change in mice causes no hearing loss and just a white belly splotch (Read et al. 1997). When the phenotype in question is behavioral, the difficulties are compounded. Thus, unraveling the cognitive and behavioral components of WS is likely to rely heavily on studies of individuals with partial deletions and/or partial WS. In the present study, such persons were identified on the basis of a single feature of WS—SVAS—which demonstrates a general strategy for disentangling the components of complex phenotypes.

Haploinsufficiency for elastin accounts for the SVAS in patients with WS. Keating's group showed that dominant isolated SVAS maps to 7q11 (Ewart et al. 1993*b*). Subsequently, they and we have described loss-of-function mutations in *ELN* in many persons with uncomplicated SVAS (Li et al. 1997; Tassabehji et al. 1997). Although it had seemed plausible that a deficiency of

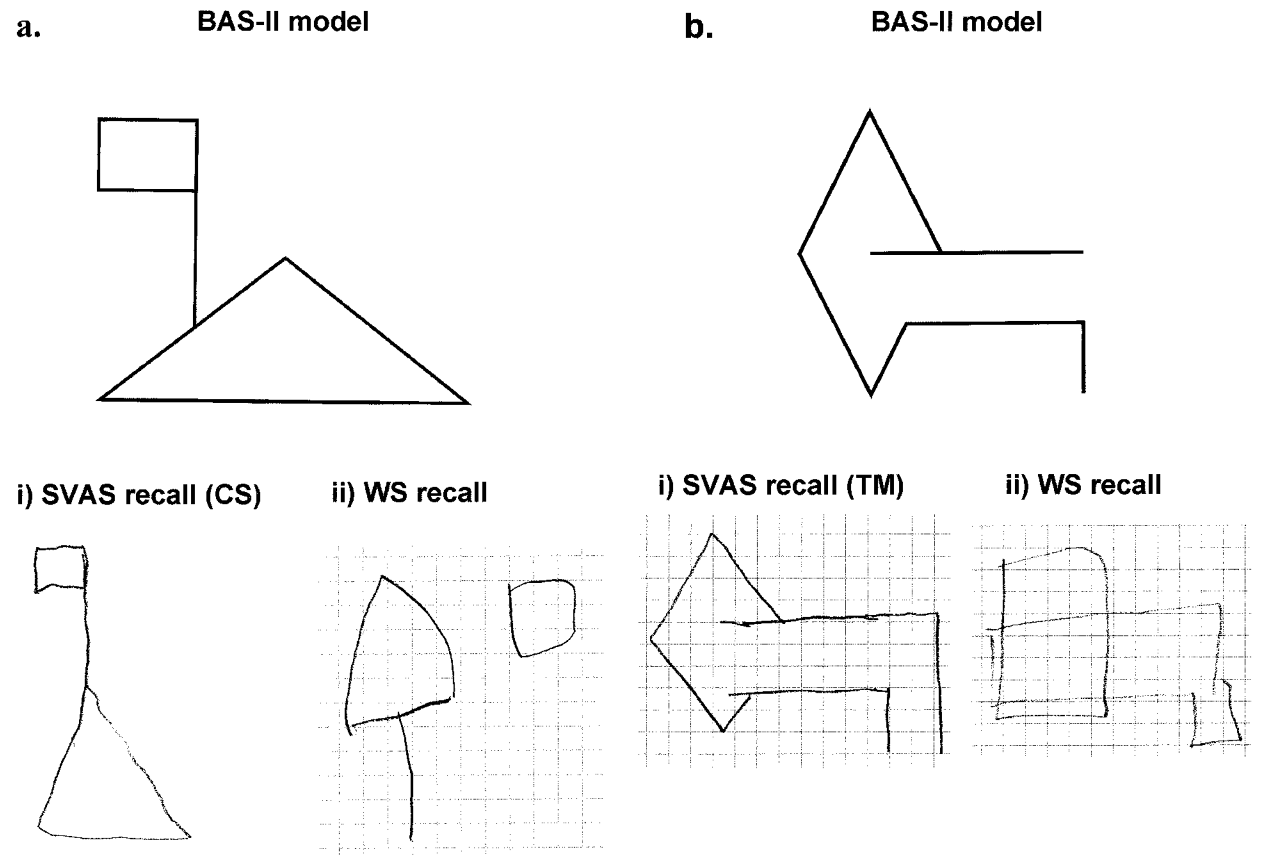

Figure 4 Examples of visuospatial deficiency in patients with WS and of its absence in subjects CS and TM. Subjects were shown a drawing (BAS-II model) and were asked to reproduce it immediately afterward, from memory (BAS-II recall-of-designs task). *a,* Reproductions by CS (i) and by a linguistically able patient with WS, age 9 years 10 mo (ii). *b,* Reproductions by TM (i) and by a linguistically able patient with WS, age 29 years 7 mo (ii).

this connective-tissue protein might also cause the characteristic WS face, patients with mutations or deletions of *ELN* do not have this appearance (fig. 1), which must therefore be caused by other genes within the WS deletion. In the present study, two of the four patients with SVAS had inguinal hernias, and, since hernias occur in $\sim$30% of our patients with WS (K. Metcalfe, unpublished data), it is possible that haploinsufficiency for elastin may be responsible for this. No other WS feature is seen in patients with isolated *ELN* deficiency.

The most intriguing feature of WS is the cognitive and behavioral phenotype, which is striking and highly penetrant. The WSCP is one aspect of this. The WSCP describes the relative levels of several abilities, not their absolute level, and is defined in terms of relative performance on different subtests of the Differential-Abilities Scale (DAS) (Elliott 1990), on the basis of the four criteria listed in the Appendix (Frangiskakis et al. 1996; Mervis et al., in press). The BAS-II scale that we used is the British equivalent of the DAS. The main difference between the two scales is in the verbal-similarities subtest, where items relevant to American culture are replaced with items relevant to British knowledge; both types of items have been normed on large American and British populations, respectively. These tests are designed both to provide specific information about strengths and weaknesses in different areas and to give an overall performance level, and they can furnish differential scores even for patients performing at low levels. Moreover, whereas, on the Wechsler intelligence scale, individuals with WS do not always show an advantage of verbal IQ over performance IQ (Wechsler 1981; Udwin et al. 1987; Bellugi et al. 1994; Karmiloff-Smith et al. 1997), the DAS and BAS-II are particularly sensitive to the cognitive imbalance typical of WS.

Frangiskakis et al. (1996) have identified the WSCP in 11 of 13 people who have deletions of just *ELN* and the neighboring *LIMK1*. Most were of normal intelligence. Thus, the level of *LIMK1* product might govern specific features of cognition, rather than merely cause mental retardation as do so many other gene defects. *LIMK1* encodes a protein tyrosine kinase that phosphorylates and inactivates cofilin, a protein that is required for turnover of actin filaments (Arber et al. 1998; Yang et al. 1998). Actin depolymerization and recycling are required at the leading edge of a moving cellular process, so that defects in actin turnover could affect axonal guidance during CNS development. Since *LIMK1* is expressed at high level in the CNS (Okano et al. 1995), it is a promising candidate for mental aspects of the WS phenotype. However, our psychometric testing of subjects PM, TM, and CS showed no evidence of the WSCP. As explained above (see the Cognitive/Behavioral Assessment subsection in the Results section), we were unable to obtain valid BAS-II scores for the Greek subject, HG, because of his poor command of English.

Our data suggest either that *LIMK1* deletion is irrelevant to the WSCP or that, at most, it is necessary but not sufficient. It could be argued that WSCP, as a haploinsufficiency effect, is likely to have reduced penetrance, but, in patients with WS, the penetrance is not low; the WSCP is a near-universal feature of WS. This is not an artifact due to biased ascertainment: patients with WS are identified on the basis of various combinations of heart problems, hypercalcemia, developmental delay, and facial appearance but not on the basis of their cognitive profile, which emerges only after careful psychometric testing. Yet, almost every person diagnosed with WS has the WSCP. The cases reported by Frangiskakis et al. (1996) all came from two families, so they represent the effects of only two different deletions. The determinant of the WSCP must map within the WS critical region, since deletion of this region is the only genetic factor common to all patients with WS. Thus, it is possible that the WSCP could cosegregate in a family with a *LIMK1* deletion, without the deletion itself being the cause. Perhaps this unstable chromosomal region is prone to complex rearrangements, including noncontiguous deletions.

One patient, CS, also had deletions for *FZD3, STX1A,* and *RFC2,* suggesting that the determinants of all aspects of the WS phenotype, apart from SVAS, lie telomeric to *RFC2*. However, identification of further individuals with partial deletions would provide a valuable resource to confirm this and to help delineate the full spectrum of genes that contribute to the WS phenotype.

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Appendix

Criteria for WSCP

1. Pattern-construction *T* score less than mean *T* score for six core subtests
2. Pattern-construction *T* score less than digit-recall *T* score
3. Pattern-construction *T* score below the 20th percentile
4. *T* score, for either digit recall, naming-definitions, or similarities, above the 1st percentile

The WSCP is defined in terms of the relative, not absolute, levels of abilities and is independent of general intelligence. WSCP is present if all four criteria are met; normal subjects are expected to fulfill only criterion 4.

Electronic-Database Information

Généthon, http://www.genethon.fr (for microsatellite markers)
Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim (for WS [MIM 194050])

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