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INVITED EDITORIAL
Williams Syndrome Starts Making Sense

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1996 may be marked as a transitional year in the study of Williams syndrome (WS), when the causes of this complex condition and a practical way to investigate it began to come into focus. WS presents a remarkable collection of symptoms that affect blood vessels, growth, intelligence, and behavior. WS commonly leads to infantile hypercalcemia, retardation of growth (Pankau et al. 1992), prematurely wrinkled skin, supraventricular aortic stenosis (SVAS), and sensitivity to loud noise. Children with this condition are often mentally retarded, with distinctive "elfin" facial features, a hoarse voice, and an "engaging" personality (Preus 1984; Ewart et al. 1993). Their cognitive deficits may be minimal or profound but typically involve a specific pattern of strengths and weaknesses, with better-than-average face recognition but little ability to recognize how parts of patterns that they see fit into a whole (Udwin and Yule 1991; Frangiskakis et al. 1996).

These defects are not present in all instances, and no single characteristic serves as a definition of WS. A diagnostic system for scoring the various manifestations of WS is used to provide a quantitative definition of classical or ambiguous cases (Preus 1984). Surprisingly, the most consistent of the symptoms may be the ones that are most complex to measure in the clinic: patients' cognitive and behavioral patterns. The so-called cocktail party pattern of conversation (i.e. , strings of meaningless pleasantries) is well defined in WS patients (Udwin and Yule 1991), and a distinctive cognitive profile can be measured by any of several diagnostic tests, apparently with concordant results (Frangiskakis et al. 1996). The diversity of WS symptoms, their subtlety, and their irregular presentation in individual patients have hampered efforts to dissect the condition genetically. In recent months, however, with the publication of several articles, including two in this issue of the *Journal,* the prospects for teasing apart the features of WS and developing a mechanistic understanding of some of them suddenly seem brighter.

The initial insights into the genetic basis of WS came with its localization to chromosome 7q11.23, in the vicinity of the gene for the extracellular-matrix protein elastin (*ELN*) (Ewart et al. 1993). The great majority of WS cases involve a deletion of this gene along with tightly linked markers, leading to hemizygosity for *ELN* (Lowery et al. 1995; Mari et al. 1995; Nickerson et al. 1995). The disease almost always occurs sporadically; in the few reported examples of familial transmission, the deletion acts as an autosomal dominant mutation (Ewart et al. 1993). Expression of half of the normal amount of elastin suggests a plausible explanation for a few WS symptoms, including SVAS. Because arterial lamina are normally rich in elastin, the aorta may become distended or fragile when this protein is expressed in limiting quantities. Similarly, the hoarse voice and rapidly sagging skin may occur in part because elastin is required for normal ultrastructure in the vocal ligaments and the skin. This deficiency does not readily account for the behavioral or cognitive WS symptoms, however, because elastin is not expressed at significant levels in the brain.

Direct evidence that hemizygosity at the *ELN* locus contributes to WS came with the report that reciprocal translocation t(6:7) (p21.1;q11.23), which disrupts *ELN,* segregates in a family with dominant autosomal SVAS (Curran et al. 1993; Morris et al. 1993). Most of the individuals who carry this allele are of normal mental abilities, and, although their facial features are somewhat reminiscent of those of WS patients, they are free from the other effects of WS. Subsequently, other studies have shown that a short deletion involving only *ELN* is linked to this simple form of SVAS (Olson et al. 1995), and Curran et al. (1993) mention unpublished cases of human SVAS with a single nonsense or missense mutation in elastin. It thus appears that *ELN* hemizygosity is necessary and sufficient for SVAS but is not sufficient for the other manifestations of WS, including, surprisingly, the vocal and growth- and skin-related symptoms of WS.

Effects of Hemizygosity

Because these mutant *ELN* alleles do not obviously compromise expression of other genes linked to

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7q11.23, it appears that WS represents a contiguous-gene–deletion syndrome: other loci deleted in WS but not in SVAS are thus implicated in the nonvascular symptoms. In principle, the effect of such a deletion in a single copy of an autosome could be explained in several different ways. First, the deletion might uncover recessive mutations in the remaining allele. Second, the deletion might uncover imprinting of some loci. If, for example, a region of the maternally derived chromosome were silent because of imprinting, and if the paternal chromosome were to suffer a deletion covering the same region, expression of genes mapping to the deletion would be diminished or even abolished. Finally, the reduction of expression levels by a factor of two (haploinsufficiency) might cause phenotypic changes. If multiple loci are involved, the same mechanism need not apply to all, and the phenotype might be synthetic, reflecting functional interactions between the different genes in the deleted region.

In dominant autosomal SVAS, haploinsufficiency in *ELN* expression almost certainly explains the vascular symptoms. No parent-of-origin effects have been identified in *ELN* mutations in mice or humans, and the defect is found in unrelated families, arguing against the uncovering of recessive defects. In WS, however, the situation is less clear. Again, the large number of sporadic cases argues strongly against a common recessive defect being uncovered by deletion. Several groups have reported that the 7q11 deletion in WS is as likely to be maternally as paternally derived (Ewart et al. 1993; Gilbert-Dussardier et al. 1995; Urbán et al. 1996 [in this issue]). Still, with the complexity of the WS phenotype, the possibility of imprinted genes affecting some aspect of the phenotype remains.

Imprinting in WS

In this issue of the *Journal,* Pérez Jurado et al. (1996) now suggest that parental imprinting of a gene in the WS region accounts for some clinical findings. This group has studied 65 sporadic cases of WS cytologically and with a high-resolution linkage map and has scored many of the classical WS phenotypes. Of the quantitative and qualitative effects measured, the only one to show significant parent-of-origin effects was stature, measured on the basis of patient height, weight, or head circumference. Individuals who carry the WS deletion on the maternal copy of chromosome 7 are smaller than those with deletions on paternal chromosome 7. The authors suggest that one or more genes in the deleted region serve normally to promote growth but are silent when present on the paternal allele. (The data are also formally consistent with the presence of growth-*inhibiting* genes imprinted on *maternal* chromosome 7.) This parent-of-origin effect is unexpected and at least superficially at odds with previously published conclusions.

Imprinting in humans may be detected either because of deletions on a single chromosome or because of uniparental disomy (UPD) (Cassidy 1995; Ledbetter and Engel 1995). In UPD, two copies of a chromosome derive from one parent, and the other parent fails to contribute that chromosome. Typically, UPD is identified when recessive disorders appear in a person only one of whose parents carries a single mutant allele at the disease locus. However, once recognized, instances of UPD reveal the effects of imprinted loci elsewhere in the uniparental chromosome. Of the possible 47 classes of UPD, 25 have been reported, and there is evidence of imprinting at loci on at least five chromosomes. Perhaps the clearest examples of genomic imprinting are on chromosome 15, where maternal disomy leads to Prader-Willi syndrome and where paternal disomy leads to Angelman syndrome. These disorders more commonly arise when a lesion on one copy of chromosome 15 exposes the imprinted status of the remaining copy, rather than as a result of UPD. Thus, in both of the chromosome 15 disorders, having two imprinted alleles is functionally equivalent to having one imprinted and one defective allele.

Effects of UPD 7 on stature have been noted in several instances. Maternal disomy 7 has been observed in several independent reports. In each, subjects were ascertained because the disomy uncovered recessive mutations carried only by the patient's mother, leading to cystic fibrosis (Beaudet et al. 1991) or osteogenesis imperfecta (Spotila et al. 1992). In these reports, the subject was significantly shorter than average, with a proportionate build. However, in the single reported case of paternal disomy 7 (Höglund et al. 1994), the subject was of average height, suggesting that imprinting of paternal chromosome 7 does not silence genes required for growth, in contrast to the conclusion of Pérez Jurado et al. (1996). To reconcile these results, one might speculate that expression of the putative growth-regulatory gene at 7q23.11 is reduced but not abolished on the paternal allele. If so, one would expect that having two copies of the imprinted gene—as seen in UPD—would permit higher levels of gene expression and hence more normal growth than would be seen in individuals with only one imprinted chromosome. If the second imprinted copy were sufficient for the expression level to meet some threshold value, imprinted genes would go undetected in carriers of UPD7, but they still might be manifest when a deletion leads to paternal hemizygosity, as Pérez Jurado et al. (1996) observe.

The Extent and Origin of WS Deletions

Cytological and linkage analyses in the study by Pérez Jurado et al. (1996) show a consistent deletion of ~2 cM in their group of WS individuals. This deletion is detectable by chromosome banding. Among 61 WS pa-

tients with a deletion at the elastin locus, there was no sign of variability in deletion length. This result is consistent with the recent report by Urbán et al. (1996), who find that most WS deletions affect *ELN* and one marker 3′ to this gene, corresponding to a deletion in the range of 0.9–2.5 cM. They also identify ≥4 of their 31 patients who carry a somewhat larger deletion. Taken together with the data on the *ELN* deletion in SVAS, these results suggest that there is at least one major and several minor patterns of deletion in the WS region. Deletion and translocation events (Curran et al. 1993) may be mediated by *Alu* repeats, which are present at high frequency in and near the *ELN* gene (Frangiskakis et al. 1996). Urbán et al. (1996) have followed the linkage of highly polymorphic markers mapping near the deletion. They observe that, wherever the markers used were informative with regard to chromosomal phase, there is evidence for meiotic recombination between markers proximal to and markers distal to the deletion, suggesting that the deletions arise from unequal meiotic crossovers.

It is worth noting that the diversity seen in deletion size probably represents an underestimate of this value. This is true both because linkage data are necessarily of relatively low resolution and because of probable biases in ascertaining WS patients who fit the WS profile closely. By focusing on WS cases that match strict diagnostic criteria, one may systematically disregard those patients in whom deficits are less profound because of relatively small chromosomal deletions. The converse strategy of looking to mild or nonclassical WS cases (Nickerson et al. 1995) to refine the map of the WS region has been applied successfully in the recent paper of Frangiskakis et al. (1996). By the estimate of these authors, deletions in most WS individuals extend >500 kb, consistent with the distances of >1 cM cited above (Pérez Jurado et al. 1996; Urbán et al. 1996); in two families described by Frangiskakis et al. (1996), however, the deletions are ~300 and 84 kb.

Affected individuals in these two nonclassical WS pedigrees have some of the facial features of WS that are seen in the classical form of the disease, but their score on this scale is comparable to that seen in SVAS individuals. Their performance on cognitive tests is also distinctive. Whereas mental retardation is nearly always found in the classical WS, affected members of these two families are similar in general intelligence to their unaffected kin. However, they display a marked deficiency in a specific cognitive skill, described as visuospatial construction. This is the ability to comprehend the relationship between parts of a diagram; in practical terms, it corresponds to the ability to assemble a structure from components when one is given a pattern to follow. It is remarkable that this specific cognitive capacity is cleanly separable from general mental ability, and it is more remarkable still that this distinction should correlate with chromosomal deletion size. In the two kindreds examined, 12 of 13 affected individuals were of normal general intelligence, and 11 displayed the visuospatial cognitive defect. By the same tests, all classical WS patients had both visuospatial difficulties and mental retardation, and SVAS individuals were uniformly free of both conditions (Frangiskakis et al. 1996).

The 84-kb deletion found in the nonclassical WS individuals harbors one other known gene. Frangiskakis et al. (1996) have shown by sequencing the entire deleted region that the gene for a protein kinase, LIM kinase 1 (*LIMK1*), is deleted along with *ELN*. *LIMK1* has been identified independently as a locus within 36 kb of *ELN* and is found to be deleted in each of 20 WS individuals hemizygous for *ELN* (Tassabehji et al. 1996). No other sequences that are strong candidates to be expressed exons are present in the 84-kb deleted region, suggesting that all the symptoms of nonclassical WS may be ascribed to haploinsufficiency at these two loci. The imprinted status of *LIMK1* has not been addressed, but the pedigrees of the nonclassical WS patients show both maternal and paternal transmission of the visuospatial cognitive deficit (Frangiskakis et al. 1996).

Although LIMK1 is known to be expressed widely in the adult nervous system (Bernard et al. 1994; Proschel et al. 1995), the role of this kinase in normal brain development and function is not understood. The structure of this molecule is distinctive; except for its close homologue, LIM kinase 2, no other protein kinase is known to contain the double zinc-finger limb motif LIM (Freyd et al. 1990). LIM kinases 1 and 2 have been cloned from human and rodent tissues (Mizuno et al. 1994; Okano et al. 1995), and a chick homologue of LIM kinase 2 has been found (Ohashi et al. 1994), but there are no reports of homologues in invertebrates. LIM kinase 1 autophosphorylates in vitro on serine, threonine, and tyrosine residues (Proschel et al. 1995), and it coprecipitates from cell lysates with a single phosphoprotein that may be one of its substrates (Okano et al. 1995).

Such biochemical and expression data, although vital, seem unlikely to provide critical insights into the specific cognitive defects in WS. Genetic analysis may be a more promising approach, but it is unclear how much more detail can be gleaned from the phenotypic analysis in humans. Certainly, it will be valuable to identify more individuals or families with short deletions covering *LIMK1*, ideally in deletions that leave ELN intact. The approach of seeking out individuals with some but not all of the classical WS symptoms may well provide better definition of chromosomal regions, and eventually of the genes, associated with the different phenotypes in WS.

Kinases and Cognition in Model Systems

With the publication of the report by Frangiskakis et al. (1996), the popular press announced that for the

first time a single-gene defect could be associated with a specific cognitive deficit. Although this is almost certainly correct with regard to human cognition, it is also true that molecular neurobiologists working in other systems have linked particular mutations to some surprisingly specific physiological and behavioral phenotypes. This suggests an alternative approach to elucidate the cognitive role of LIMK1—namely, by disrupting expression of this protein in model organisms, most likely mice. A number of other genes expressed in nervous tissue have been disrupted by homologous recombination; the consequences for the behavior and the learning and memory of the mutant animals have generally been measurable but subtle and specific.

Because the hippocampus is implicated in spatial learning, the phenotype of mice with targeted mutations in hippocampal protein kinases may be quite relevant to the effects of *LIMK1* defects. Spatial learning is generally studied in some variant of the Morris water maze, where animals must swim to a platform to get out of a tank of water. Once trained to find the platform in a particular location, normal animals will use visual cues to find the platform in its normal location even if the platform itself is not visible to them. This protocol allows one to determine animals' short-term memory and long-term memory (LTM) of training sessions and to distinguish between different strategies that the animals use to find a hidden platform. In such experiments, mice with a mutation in α-calcium-calmodulin–dependent protein kinase II can, like wild-type mice, become increasingly efficient at finding the platform as they undergo training in the maze (Silva et al. 1992*a*). Thus they appear to be normal with regard to both swimming ability and desire to escape the water, and they can remember and learn from prior experience. However, whereas wild-type animals apparently make use of spatial cues to find the platform, mutants develop other strategies and never become as proficient at this task as do the wild-type animals. These experiments suggest that the kinase-deficient animals are unable to learn certain kinds of spatial associations but have no general defect in intelligence or memory. This learning deficit correlates with differences in long-term potentiation in hippocampal slices examined ex vivo. The ability of hippocampal neurons to alter their pattern of synaptic transmission in response to direct stimulation is compromised in mutant animals (Silva et al. 1992b). Because the structure of the hippocampus is not obviously affected by the mutation, these behavioral and electrophysiological differences probably do not result from changes in brain anatomy. Targeted disruption of other kinases (Abeliovich et al. 1993*a*, 1993*b*) or membrane channel proteins (Sakimura et al. 1995) causes similar phenotypes, although some mutations may act in part through effects on hippocampal neuroanatomy (Grant et al. 1992).

The deficit in visuospatial cognitive skills that is associated with hemizygosity at the LIMK1 locus is undoubtedly different from the spatial learning defects in these mouse models. Still, it may be possible to modify these animal learning experiments to test visuospatial cognition more specifically. Thus, one might train normal and mutant animals to recognize shapes as visual cues and might test their response to more complex shapes incorporating the simpler ones, probing their capacity to recognize the part in the whole. The idea that this locus will have a similar role in cognitive function in two different species is, of course, radically reductionist and may well prove naive. Precedent for this suggestion, however, arises from comparisons between two even more divergent species, mice and fruit flies. One of the most dramatic examples of conservation in neurobiology concerns the mechanism of LTM in these distantly related species (Frank and Greenberg 1994).

The phenotype of mice with a targeted mutation in the cAMP response-element–binding protein (CREB) gene suggests a role for this class of molecule in associative learning in mammals (Bourtchuladze et al. 1994). CREB proteins regulate patterns of transcription in response to cellular levels of cyclic AMP. CREB-deficient mice can be trained to associate a tone with a painful shock and will learn to flinch when they hear the tone alone. For as long as 30 min after they receive this training, they respond to the stimulus just as wild-type mice do. However, by 60 min they appear to have largely forgotten this association, and they fail to respond to the tone; in contrast, wild-type animals remember their training for ⩾24 h.

Like mice and other vertebrates, fruit flies exhibit associative learning and can be trained to avoid a conditioned stimulus—an odorant—by use of electric shock as a negative stimulus. Many mutations have now been isolated that affect the rate at which flies learn or forget such associations, and some of these are beginning to be understood at a molecular level. For flies to maintain memory of learned associations over a period of hours, they need to have multiple training sessions, with a space between sessions (Yin et al. 1994, 1995). The number of training sessions is less important than the space between them, and, during this delay, animals must not be treated with inhibitors of transcription. This observation has been made in other systems and is taken to indicate that, unlike initial learning and the formation of short-term memory, the consolidation of memory into LTM requires new RNA and protein synthesis.

The genes that need to be expressed to induce LTM are not known, but transcription factors of the CREB family are key mediators of memory consolidation. In flies, the CREB proteins include isoforms that serve either to activate or to repress LTM. Flies expressing a dominant-negative form of CREB2 can be trained, but, unlike normal flies, they fail to consolidate the memory

of their training over a period of a day (Yin et al. 1994), a finding that is directly analogous to the results in CREB-deficient mice. Even more significantly, when flies express an activator isoform of CREB2, they do not require multiple spaced training periods to consolidate their learned association into LTM. A single training period suffices for maximal LTM (Yin et al. 1995). This suggests that spaced training periods serve as an opportunity for the animal to forget associations that might not continue to correlate in its later experience. With the dominant activator protein expressed, this default forgetting pathway is inactive, and all learned associations become permanent.

The role of CREB proteins suggests that aspects of LTM are astonishingly well conserved in the brains of mammals and invertebrates. It is of course uncertain that higher cognitive processes such as visuospatial construction are conserved in a similar manner, but it is reassuring to consider the relatively short evolutionary time that separates humans from other mammalian species. The recent developments in the understanding of WS have built on insights from very disparate sources, from detailed clinical, behavioral, and cytogenetic descriptions to the high-resolution genetic maps now available, as well as the technological advances permitting large-scale DNA sequencing. These resources will continue to be important for specifying the roles of different genes affected in this contiguous-gene–deletion syndrome. Further advances may require a still broader approach, drawing on reverse genetics and on insights into the molecular basis of memory and cognition developed in model genetic organisms.

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