abundant in the brain, normally hydrolyses the bonds between ubiquitin molecules or between ubiquitin and other molecules such as glutathione. The mutation detected by Leroy *et al.* leads to a decrease in the enzyme activity of UCH-L1. However, exactly how this produces PD is currently unclear, although a change in the state of ubiquitination of a key protein might be important. These results are analogous to those obtained from experiments on HD by Saudou *et al.* discussed above. However, it is also possible that the mutated UCH-L1 itself is prone to aggregate.

The widespread detection of α-synuclein-related peptides in aggregates and the ability to manipulate aggregate formation via changes in ubiquitination are certainly important. However, the precise role of aggregates in each of the diseases discussed still remains to be defined. Answers will certainly be forthcoming from current studies on the emerging sociology of macromolecules.

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PERSPECTIVES ON DISEASE

Bridging cognition, the brain and molecular genetics: evidence from Williams syndrome

Ursula Bellugi, Liz Lichtenberger, Debra Mills, Albert Galaburda and Julie R. Korenberg

Williams syndrome (WMS) is a rare sporadic disorder that yields a distinctive profile of medical, cognitive, neurophysiological, neuroanatomical and genetic characteristics. The cognitive hallmark of WMS is a dissociation between language and face processing (relative strengths) and spatial cognition (profound impairment). Individuals with WMS also tend to be overly social, behavior that is opposite to that seen in autism. A genetic hallmark of WMS is a deletion on chromosome band 7q11.23. Williams syndrome is also associated with specific neuromorphological and neurophysiological profiles: proportional sparing of frontal, limbic and neocerebellar structures is seen using MRI; and abnormal functional organization of the neural systems that underlie both language and face processing is revealed through studies using event-related potentials. The non-uniformity in the cognitive, neuromorphological and neurophysiological domains of WMS make it a compelling model for elucidating the relationships between cognition, the brain and, ultimately, the genes.

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THIS ARTICLE provides a multifaceted view of a unique neurobiological disorder by describing the cognitive, neuroanatomical, neurophysiological and molecular genetics probes used to improve understanding of the neurobiological bases of WMS. The unusual cognitive profile of WMS, with strengths and weaknesses in cognitive abilities, is currently being mapped out towards achieving this goal[1–10].

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Williams syndrome is rare, occurring in an estimated one in 20 000 to one in 30 000 live births. Diagnostic characteristics include specific facial and physical features: a constellation of cardiovascular difficulties, which include supravalvular aortic stenosis (SVAS); failure to thrive in infancy; transient neonatal hypercalcemia; delayed language and motor milestones, and abnormal sensitivities to classes of sounds (hyperacusis). It has been recently found that in well over 95% of the individuals who have been diagnosed clinically with WMS, there is a submicroscopic deletion of one copy of perhaps 20 contiguous genes, which include the gene for elastin, among others, on chromosome 7. The deletion of one copy of elastin has provided a new genetic marker for WMS (Refs 11,12).

Cognitive profile of WMS

Cognitive deficits

A hallmark of WMS is the dissociation between language (which is a strength in adolescents and adults) and spatial cognition (which is profoundly impaired), as shown in Fig. 1A. There are consistent cognitive deficits in WMS: in general, standard Full Scale IQ scores range from 40–100, with means of around 60 (Refs 2,13; Fig. 1B). Many individuals with WMS find aspects of general problem solving difficult; most are not able to achieve independent living[14] and typically experience difficulty when dealing with money or balancing a checkbook. However, within the context of their intellectual impairments, individuals with WMS display characteristic 'peaks' and 'valleys' in specific cognitive abilities. Complex expressive language abilities are relatively strong, spatial cognition is disproportionately impaired (particularly at the level of global organization) and face-processing abilities are remarkably strong. From studies across different populations, a characteristic WMS cognitive profile is emerging[2,6,8,15].

Expressive language abilities

One striking aspect of the WMS profile is the strength in language abilities in adolescence and adulthood, in contrast to the overall impairment seen in cognitive abilities. Although in the earliest stages of language development, children with WMS show significant delay[16], once language is acquired, this ability tends to become a relative strength in their cognitive profile. When adolescents and adults with WMS and Down syndrome (DNS), both syndromes of mental retardation that are genetically based, are matched in age and Full Scale IQ, the differences in language skills are evident at all levels (phonological, lexical, morphological and syntactic, as well as at levels of prosody, discourse and narrative). For example, adolescents with WMS score significantly higher on measures of receptive word knowledge than on measures of general cognitive functioning, and perform dramatically better than their counterparts with DNS (Ref. 17). On a word-fluency test, which asks subjects to name all the animals they can in 60 seconds, adolescents and adults with WMS score similarly to normal individuals at the same mental age. Moreover, the responses of the WMS group might include many atypical examples (for example, chihuahua, ibex, condor) as well as typical ones (Fig. 1C). As part of a basis for their language strengths, short-term memory for speech sounds or phonological working memory, a form of memory that is relevant to language learning and comprehension, is relatively preserved in the WMS population[6,18,19]. The strength in verbal memory seen in WMS is apparent when contrasted with another domain, that of spatial memory. Individuals with WMS show far better verbal memory than spatial memory, whereas individuals with DNS exhibit the opposite pattern (Fig. 1D)[2,20].

In general, compared with age-matched and Full Scale IQ-matched subjects with DNS, the subjects with WMS perform far better on a wide variety of grammar probes (reversible passives, negation, tag questions, sentence repetition, sentence completion, sentence correction, conditionals, etc.; see Fig. 1E)[2,3,17]. Thus, language at all levels in older individuals with WMS is a remarkable strength, in light of the level of cognitive deficits that they have generally[17]. In fact, because their language abilities are often at a level that is higher than their overall cognitive abilities, individuals with WMS might be perceived to be more capable than they really are. Although the domain of language is a strength of individuals with WMS, there are clues that language might develop in somewhat different ways than in normal children. Morphological errors abate more slowly in children with WMS than in normal children (but far more rapidly than in DNS)[21] and errors show some differences from those produced by normal children[6,15,22,23]. Studies are now showing that there are proportionately far more errors in the use of spatial prepositions and in the use of language about space by WMS individuals than found in the normal development (for example, when describing a picture of an apple in a bowl during an experimental task, WMS individuals made errors such as 'The apple is around the bowl', 'The bowl is in the apple' or 'The apple without the bowl')[23].

There are controversial issues raised by the research on WMS concerning the relationship between language and cognition, which are still a matter of debate[10,22–25]. Some researchers consider the syndrome to be a remarkable example of the modularity of language as a system that is separate from general cognitive abilities. Others argue that as adults with WMS are said to function in some ways at the five- to seven-year-old level, there is a sufficient substrate of cognitive abilities for the development of complex syntax, and that, thus, WMS does not represent a dissociation between language and general cognitive functions. There are unresolved issues about the relationship between syntax and semantics, and about the intactness of levels of language in WMS (Ref. 18), yet researchers agree generally that language (for example, morphology and syntax) is a relative strength in WMS, which is apparently different from other syndromes that can involve mental retardation[2,6,17,18,24].

Abnormally high linguistic affect

A distinctive facet of the language abilities of individuals with WMS is their ability to use their heightened linguistic skills to engage others socially. Many individuals with WMS display a strong impulse towards social contact[21,26] and affective expression, although their social behavior is not always appropriate[27,28]. The intersection of language behavior and social engagement in individuals with WMS has been investigated through a series of narrative tasks in which subjects are asked to tell a story from a wordless picture book[21,26]. Figure 1F shows examples of the expressive language found in subjects with WMS compared to subjects with DNS (Ref. 2). The most obvious distinction between subjects with WMS, and

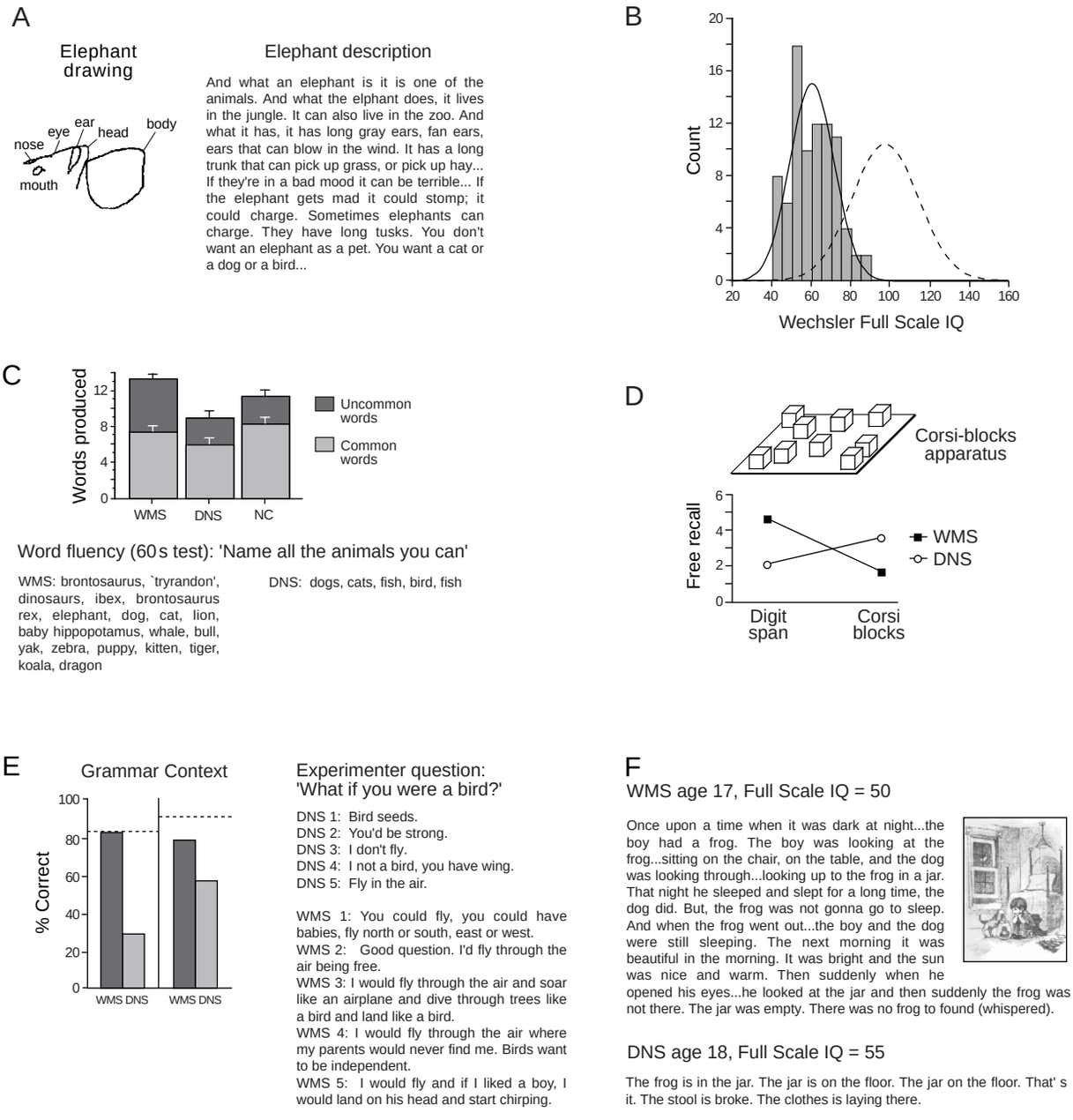

Fig. 1. ***Unusual language and cognitive profiles in Williams syndrome (WMS).*** *A characteristic of WMS is the dissociation between language and space.* **(A)** *shows a drawing and description of an elephant by a teenager with WMS, Full Scale IQ of 49, Verbal IQ of 52 and Performance IQ of 54. Note the difference between the impoverished drawing and grammatically complete language.* **(B)** *Wechsler Full Scale IQs range from 40 to 100 in WMS and are reasonably normally distributed, with a mean IQ of approximately 60 (solid line; SD = 11). Broken line shows population distribution of Full Scale IQs (mean = 100; SD = 11).* **(C)** *On a semantic fluency task, subjects with WMS give the same number of common responses but significantly more uncommon infrequent responses (for example, ibex, yak, dragon) than either matched subjects with Down syndrome (DNS) or normal subjects matched for mental age (NC;* n *= 10 in each group). The double dissociation between verbal and spatial short-term memory is shown in* **(D)***: age-matched and Full Scale IQ-matched individuals with WMS (*n *= 10) and DNS (*n *= 9) demonstrate a differential ability to remember a list of numbers in order (Digit Span) versus remembering location and order of blocks (Corsi blocks)*[2]*.* **(E)** *Individuals with WMS perform significantly better than individuals with DNS (age-matched and Full Scale IQ-matched) in syntactic processing tasks (for example, conditional sentences) on both grammar and content (for example, 'Good question. I'd fly through the air being free.'). Normal control results are shown by the broken line.* **(F)** *Individuals with WMS use more affective prosody, more audience 'hookers' and more linguistic affective devices than do normals or individuals with DNS at any age. Subjects are asked to tell a story from a wordless picture book and the WMS subjects tend to be dramatic story tellers. The figure shows samples of a story-telling task by age-matched and Full Scale IQ-matched individuals with WMS and DNS. The WMS individual shown is 17 years old, Full Scale IQ = 50, Verbal IQ = 54 and Performance IQ = 55; the DNS individual shown is 18 years old, Full Scale IQ = 54, Verbal IQ = 59 and Performance IQ = 53 (Ref. 2). (D)* and *(F)* reproduced, with permission, from Ref. 2.

subjects with DNS and age-matched normal controls, is in the use of narrative enrichment devices during this story-telling task by subjects with WMS. The enrichment devices (addition of affective qualities) are not found in the pictures themselves, but are added to the narrative by the subject as linguistic affect. Individuals with WMS show an abundance of affectivity in both prosody and lexical devices and appear to be able to manipulate affective linguistic devices for the purposes of story telling[21,26,29,30]. Affective prosody was measured by noting how frequently paralinguistic affective expression was used, including pitch change, vocalic lengthening and

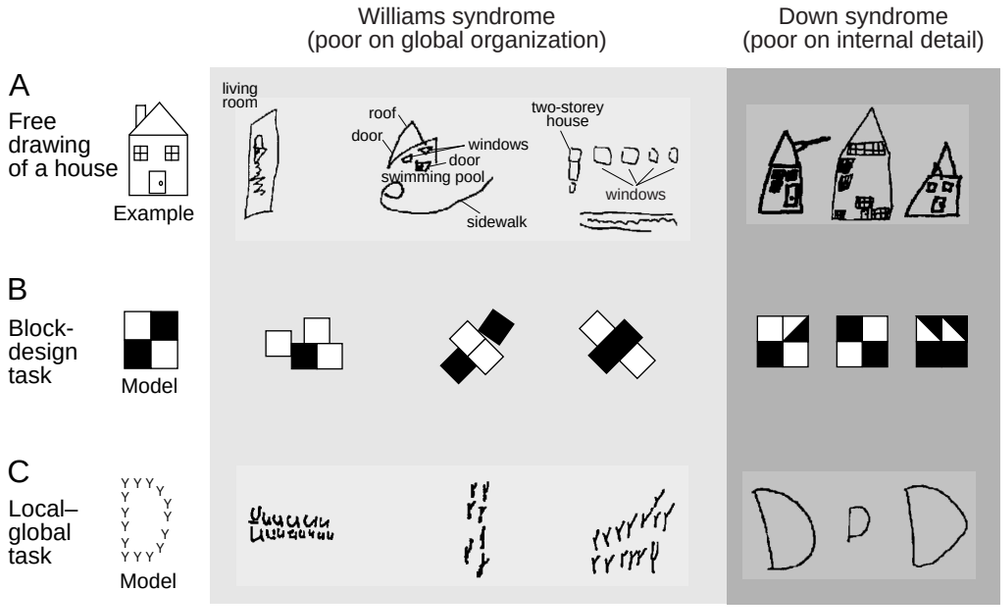

Fig. 2. ***Different spatial deficits in Williams syndrome (WMS) and Down syndrome (DNS).*** **(A)** *The drawings by adolescents and adults with WMS contain many parts of houses but they are not organized coherently. In contrast, the drawings of age-matched and Full Scale IQ-matched DNS adults are simplified but have the correct overall gestalt.* **(B)** *In the block-design task both subjects with WMS and subjects with DNS fail (scaled scores more than 2 SD below normal), but they fail in very different ways: adolescents and adults with WMS show disjointed and fragmented designs, while age-matched and Full Scale IQ-matched DNS subjects make errors in internal details while maintaining the overall configuration.* **(C)** *In the Delis hierarchical processing task, subjects are asked to copy a large global figure made of smaller local forms (a 'D' made out of 'Y's). Again, both groups fail but in significantly different ways: subjects with WMS tend to produce the local elements sprinkled across the page, whereas age-matched and Full Scale IQ-matched subjects with DNS tend to produce only the global forms.*

modifications in volume. Affectivity in lexical devices is noted in the frequency of exclamatory phrases and other audience engagement devices (for example, 'Suddenly splash! The water came up'; 'Lo and behold' or 'Gadzooks! Guess what happened next!'). This pattern of increased linguistic affectivity is strikingly different from subjects with DNS, as well as from normal individuals at any age or other contrast groups (for example, individuals with early focal brain lesions)[31–33].

Thus, in adolescents and adults with WMS, expressive language is typically a great strength and is used effectively (and sometimes effusively) in social situations. This is exemplified by the WMS teenage girl who said, 'Everyone in the world is my friend'. Individuals with WMS, therefore, exhibit a striking contrast to the social and language profiles of individuals with other disorders such as autism[31].

Strengths and deficits in visually based cognition in WMS

In studies that examine spatial cognition, as opposed to language, subjects with WMS are significantly more impaired than subjects with DNS across all age ranges examined[3,34,35]. Indeed, individuals with WMS performed more poorly in our studies than children with early right-hemisphere lesions[36]. Difficulties with spatial cognition in WMS seem to be especially acute with respect to the global, rather than the local, level of spatial organization across tasks. Lack of cohesion or global organization is typical in drawings by subjects with WMS, while subjects with DNS tend to show a different effect[37,38]. For example, a subject with WMS might draw a house with windows and a door as separate entities from the house itself, thus lacking global organization (Fig. 2A). By contrast, a typical drawing by a subject with DNS might be simplified yet exhibit proper gestalt relationships among elements. On block-design tasks, both WMS and DNS subjects perform poorly, but in different ways, with WMS subjects typically unable to organize the blocks into a global pattern, and DNS subjects instead making errors of internal detail (Fig. 2B). Difficulties with integration of simple shapes have also been shown on tasks that require subjects to copy a drawing of geometric forms from a model[2,3]. When asked to reproduce a large figure made up of smaller figures (for example, a large 'D' made of small 'Y's), subjects with WMS tend to produce primarily the local constituent forms sprinkled across the page and fail to reproduce the global form, whereas subjects with DNS tend to show the opposite pattern[2,37] (Fig. 2C).

Face processing is a remarkable strength in individuals with WMS, in great contrast to their other visual–spatial cognitive deficits[2,39]. This contrast is highlighted when comparing two tasks, each of which requires only pointing to the correct answers: one involves judging the orientation of lines (a spatial task) and the other involves

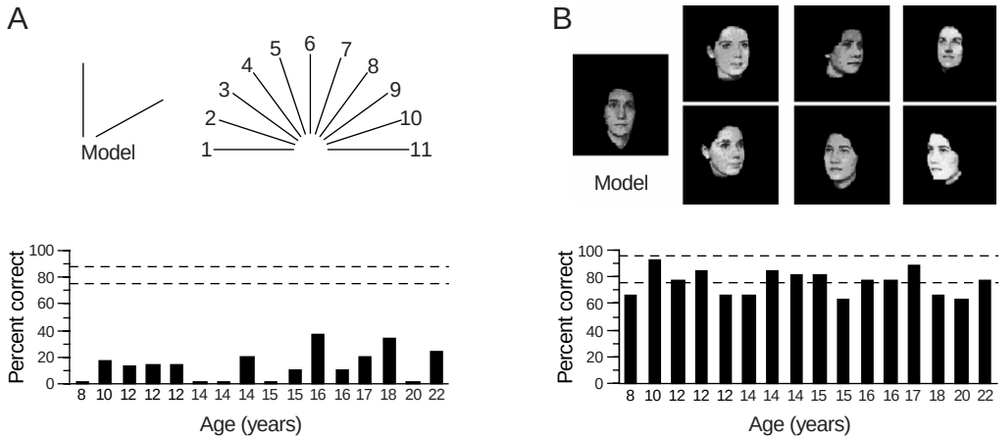

Fig. 3. ***Spatial cognition (impaired) and face processing (relatively spared) in Williams syndrome (WMS).*** *The strengths and weaknesses in visuo–spatial processing in WMS show an unusual profile. The results from two tasks that are both visuo–perceptual tasks, sensitive to right-hemisphere damage, where the correct answer requires only pointing are shown. The results for the same subjects are shown for each task. Note that the same subjects with WMS perform very differently on the two tasks.* **(A)** *Subjects with WMS perform very poorly on judging the orientation of lines (Benton judgement of line orientation), in keeping with their spatial deficit. Several subjects cannot even pass the warm-up items.* **(B)** *In great contrast with this, exactly the same subjects with WMS perform remarkably well on a very difficult face discrimination task (Benton face recognition), which involves recognizing the same individual under different conditions of lighting, shadow and orientation. In both parts, the performance of normal subjects is indicated by the broken line.*

discrimination of unfamiliar faces in different conditions of lighting and orientation (a face-processing task). Individuals with WMS show extreme difficulty with the spatial task and obtain scores in the range considered to be severely deficient; sometimes they are not even able to do the simplest items. In contrast, the same WMS individuals show a remarkable strength in the ability to recognize faces[40,41] (Fig. 3). Across different face-processing tasks (recognition, classification, memory), individuals with WMS show strong performance[41].

Different trajectories in cognitive domains

What is interesting about individuals with WMS is that there are areas of serious deficits (general intelligence, visuo–spatial abilities) but also areas of relative strengths (face processing, expressive language). Questions about the relationships between the deficits and strengths emerge from the research findings on WMS: do the different cognitive abilities depend on one another or can they be dissociated from one another? Do they change throughout development? What are the underlying brain systems for these strengths and deficits in abilities in cognitive domains? The associations between and within different types of abilities have been examined through correlational studies. In WMS, correlations between measures of face processing are strong, but measures of different aspects of language functioning and visuo–spatial abilities are not correlated with face-processing abilities[34,41,42]. Across three cognitive domains, distinct trajectories of development are found in studies involving individuals with WMS between the ages of 5 and 29 (n = 71). In WMS, there are clearly different trajectories across the three domains reported (lexical knowledge, spatial cognition and face processing) (Fig. 4A). In contrast, individuals with DNS show essentially uniformly depressed development (Fig. 4B). In a lexical knowledge task, children with WMS begin with very low scores, but show a sharp increase with age (unlike DNS children). On a standard drawing task, individuals with WMS score consistently lower than individuals with DNS at all age levels and reach a plateau early in development. On a face-processing task, individuals with WMS tend to perform very well, even at a relatively early age, and continue to do well throughout development[35]. Overall, subjects with WMS perform significantly better during development than DNS subjects on face-processing and language tasks, but significantly less well than DNS subjects on visual–spatial tasks[35] (see Fig. 4C).

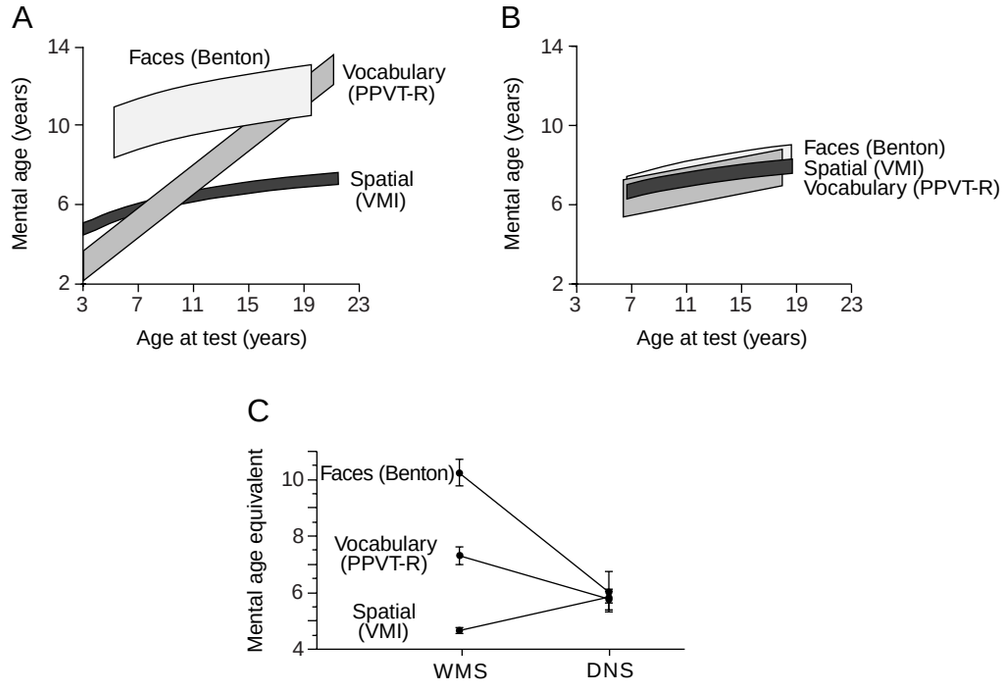

Fig. 4. ***Three domains of cognition in Williams syndrome (WMS) but not in Down syndrome (DNS).*** **(A)** *Developmental trajectories of contrasts between language, face and space processing in WMS are shown. Subjects of all ages with WMS show distinctly different trajectories in three cognitive domains: lexical knowledge, spatial cognition and face processing. On a standardized test of vocabulary [the Peabody picture vocabulary test-revised (PPVT-R)], subjects with WMS start with low scores and then show a sharp increase in score with age. On a probe of spatial cognition that involves copying geometric shapes [the developmental test of visual moror integration (VMI)], the performances of subjects with WMS are consistently below those of subjects with DNS, and plateau at an early age. On a task of face processing (the Benton test of facial recognition), subjects with WMS perform extremely well even at very young ages.* **(B)** *Subjects with DNS show essentially the same developmental trajectory across the three domains. In contrast, subjects with WMS show three distinctly different trajectories.* **(C)** *Planned contrasts show that performance on the three tests differs significantly within the WMS group, even when controlled for age. No between-test differences are found in the DNS group. A 2 × 3 (WMS, DNS × Benton, VMI, PPVT-R) analysis of covariance with chronological age entered as the covariate revealed a significant group–test interaction (*$P < 0.0001$*).*

The neurophysiological profile of WMS

The neurobiological profile of individuals with WMS is being revealed through studies of brain function [event-related potentials (ERPs)], brain structure 3D computer-graphic analyses of MRI) and brain cytoarchitectonics in autopsy brains. Initial proposals about how the cognitive and brain profiles might be linked are presented in this article.

Studies using ERP techniques are useful in assessing the timing and organization of the neural systems that are active during sensory, cognitive and linguistic processing in subjects with WMS (Refs 43–48). Event-related potentials provide information about the timing and temporal sequence of neural events and, to some extent, the location of neural activity. Electrodes are placed on the scalp over specific brain areas while subjects are processing information, which, thus, allows the monitoring of the time course of neural activation on a millisecond to millisecond basis. The recorded activity occurs before subjects make an overt response. Studies of brain-wave activity during language and face-processing paradigms in individuals with WMS and normal individuals are reported in this article.

A neurophysiological marker for auditory language processing

The morphology of ERP components to auditory words was dramatically different in individuals with WMS from normal controls. Event-related potentials were recorded as subjects listened to sentences that were presented one word at a time. The final word in each sentence either provided good closure or was semantically anomalous (for example, 'I have five fingers on my moon'). The results revealed that the morphology of

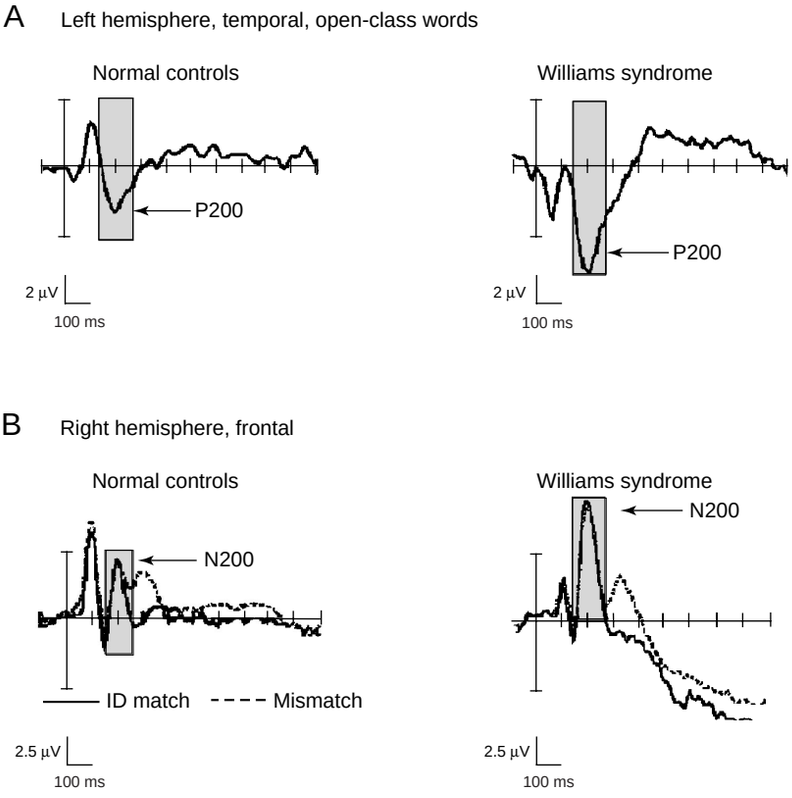

Fig. 5. ***Neurophysiological markers for Williams syndrome (WMS) in language and face processing.*** **(A)** *In event-related potential (ERP) recordings of online processing of grammatical and semantic information in sentences, subjects listened to sentences that ended either in a semantically probable way or in an anomalous way. In normal individuals, there is a left-hemisphere asymmetry for closed-class items and a difference between open- and closed-class items. In contrast, subjects with WMS do not show the left-hemisphere asymmetry for words, nor do they show the typical difference between open- and closed-class words (not shown). The unusual wave form to auditory words exhibited by all subjects with WMS and none of the normal controls, involving a large positivity at 200 ms (P200), which is particularly evident over left temporal regions is shown here. This is a candidate neurophysiological marker for WMS.* **(B)** *ERP recordings were made as subjects watched photographic pairs of faces presented sequentially on a computer monitor. The subject's task was to indicate whether the second face in the pair was that of the same or a different person as in the first photograph, some presented as upright faces, some as inverted. The response when the second face was the same as the first (ID match) and when the second face is different (mismatch) is indicated. In normal individuals, there is a right-hemisphere asymmetry for processing faces, but this is not found in subjects with WMS. The abnormally large negativity at 200 ms (N200) in subjects with WMS but not in normal controls or other groups tested, which occurs over brain regions is shown in this figure. This is also a candidate neurophysiological marker for WMS.* Reproduced, with permission, from Ref. 1.

WMS individuals' ERP components to auditory words was different from normal controls[46,47]. A unique pattern of ERPs that includes prominent positivities at 50 and 200 ms (called the P50 and P200 components) and a smaller than normal negativity at 100 ms (the N100 component), was most striking over temporal brain regions. This pattern of components, that is, abnormally large P50, a smaller-than-normal N100 and a large P200, was found in all subjects with WMS (Fig. 5A), and was not found in normal school-age children or adults[43], which suggests that this pattern might emerge as a marker for WMS.

In age-matched normal controls, there are differences in ERP responses to open- and closed-class words. Open-class words, which typically convey meaning (for example, nouns, verbs and adjectives), elicit a negativity at 400 ms that tends to be larger in posterior regions of the right hemisphere. Closed-class words, which typically convey information about grammatical relations (for example, articles, prepositions, conjunctions), elicit a negativity that peaks somewhat earlier and is largest over anterior regions of the left hemisphere in normal subjects. Unlike normal subjects, individuals with WMS do not show ERP differences to open- and closed-class words, nor do they show the normal left-hemisphere brain asymmetries to closed-class words. In normal individuals, the semantically anomalous final word elicits an N400 component (negativity that peaks at 400 ms) that is larger from the right than the left hemisphere. The N400 effect is larger over the left hemisphere in individuals with WMS than in normal control individuals. This larger semantic anomaly might be related to the unusual semantic proclivities shown by subjects with WMS in lexical tasks. Thus, the results that show ERP differences between subjects with WMS and normal subjects in language processing suggest that the neural organization of these aspects of language might be different between these groups despite the apparent relative sparing of language abilities in subjects with WMS (Refs 45,47).

A neurophysiological marker for face processing

Face-processing ERP data on ten subjects with WMS and 20 normal controls were obtained from the task described in Fig. 5B. Results showed that both the WMS and normal control groups displayed ERP differences to matched versus mismatched upright faces, which consisted of a negativity to the mismatched faces approximately 320 ms after the onset of the second stimulus[43]. However, the normal subjects showed the largest N320 component over anterior regions, which was greater over the right hemisphere than the left; the subjects with WMS did not show this asymmetry. In contrast to the normal adults, the subjects with WMS also displayed an abnormally large negativity (at 200 ms) to upright faces (approximately four times the amplitude of the N200 component to faces in normal adults; see Fig. 5B), but not to pictures of objects. These results appear to be specific to WMS and might be related to the increased attention paid to faces by individuals with WMS. The abnormally large negativity at 200 ms, which occurred in all subjects with WMS but not in other groups, could be suggestive of a brain-activity marker that is linked to the noted strength in face-processing abilities found in individuals with WMS (Ref. 43). Neurophysiological indices that relate brain and behavior, and that might be phenotypic markers for WMS are suggested by these neurophysiological studies. Unique brain-wave markers, one found during face processing and a different one found during language processing, could be characteristic of individuals with WMS but not of other groups[43,45]. Taken together, these findings suggest that in individuals with WMS the neural systems that subserve higher cognitive functions, such as language and face processing, are different from normal individuals.

Neuroanatomical characteristics from structural MRI

Neuroanatomical studies that contrast WMS and DNS subjects with normal controls have been undertaken to investigate the neural systems that mediate the cognitive profile of individuals with WMS (Refs 49–51). The results characterize some of the overall gross morphological differences between the two syndromes and also provide data on more specifically targeted morphological underpinnings of the uneven

cognitive profile of individuals with WMS (Refs 2,3,34,41,42).

Three groups, WMS, DNS and normal controls, were studied using MRI (Fig. 6 displays some of the results)[49–51]. The frontal cortex of individuals with WMS has an essentially normal volume relationship with the posterior cortex but in DNS the frontal cortex is disproportionately reduced in volume (Fig. 6A). Limbic structures of the temporal lobe (including uncus, amygdala, hippocampus and parahippocampal gyrus) are proportionately spared in subjects with WMS relative to other cerebral structures, while these limbic structures are dramatically reduced in volume in DNS (Fig. 6B). Additionally, cerebellar size is reduced in subjects with DNS but is entirely normal in subjects with WMS. Importantly, in WMS, while paleocerebellar vermal lobules subtend a smaller area on midsagittal sections than in normals, neocerebellar lobules are actually larger[49,51]. In a separate study involving MRI images from 11 subjects with WMS, seven subjects with DNS and 18 normal controls (aged 10–20 years), neocerebellar tonsils of WMS subjects were found to be equal in volume to those of controls and significantly larger than those of subjects with DNS. In proportion to the cerebrum, tonsils in subjects with WMS are larger than in both these groups[44]. In contrast, in subjects with DNS, the mean volume of subcortical areas, which include lenticular nuclei, is proportionally large when compared with those areas in individuals with WMS and controls (Fig. 6C). Quantitative volumetric analysis of Heschl's gyrus, an area in the primary auditory cortex, shows that in the WMS group the absolute volume of Heschl's gyrus does not differ from normal control subjects despite the significant cerebral hypoplasia evident in the WMS group. However, compared to subjects with DNS, matched for supratentorial volume, Heschl's gyrus is significantly larger in the WMS group[48].

The differences within cerebral and cerebellar structures suggest that relatively intact linguistic and affective functions in subjects with WMS might rely upon the relatively normal development of some limbic, frontal cortical and cerebellar structures[2,3,52]. The relative sparing of frontal and cerebellar structures in subjects with WMS might contribute to their relative linguistic competence. The significantly better spatial and motor abilities in subjects with DNS might rely on the proportional preservation of subcortical structures in that group.

A significant correlation was found between standardized language measures and a measure of inferior frontal cerebral volume normalized by total supratentorial volume in nine subjects with WMS, which supports this brain–behavior relationship[34]. Similarly, face processing is also strongly correlated with brain morphology; specifically, performance on the 'Benton Faces' task is correlated to volume of grey matter in inferior posterior medial cortex[34]. Furthermore, the volumetric findings on Heschl's gyrus in subjects with WMS (relative to DNS and normal controls) are striking, given that the subjects with WMS showed not only a normal volume for this region, but also, in proportion to surrounding areas, showed an enlargement of this area. These findings in WMS subjects might perhaps be relevant to the strength in auditory short-term memory, language and music[9,53].

The functional distinctions between ventral and dorsal cortical systems (particularly within the visual system) might be especially relevant to the contrast between brain-anatomical profiles of subjects with WMS and DNS. The ventral visual system, with predominant input from the parvocellular pathway, has been associated with form, color and face-processing functions. Dorsal extra-striate systems in the temporo–parietal junction (related to the magnocellular pathway) have been associated with spatial-integrative and motion-processing functions. The relatively spared and impaired visual–spatial functions in subjects with WMS appear to respect these dorsal–ventral distinctions (for example, face processing is relatively

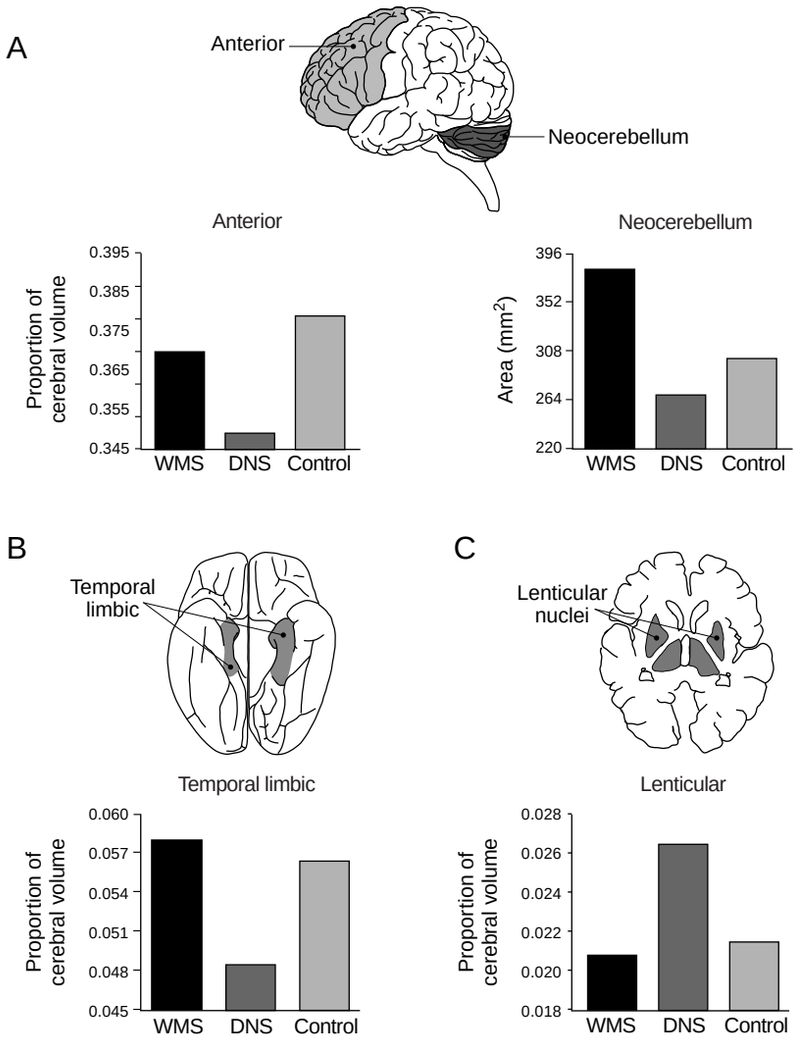

Fig. 6. ***The distinctive brain morphology in Williams syndrome (WMS) and Down syndrome (DNS).*** In vivo *MRI studies involving computer-graphic analysis of the brains of individuals with WMS suggest an anomalous morphological profile that consists of a distinct regional pattern of proportional brain volume deficit and preservation. For the anterior, temporal limbic and lenticular nuclei regions, their volumes are expressed as a proportion of the total volume of cerebral gray matter (%); for the neocerebellum, the measure of its area is given. Subjects between ages 10 and 20 with WMS (*n *= 9) and DNS (*n *= 6), and normal controls (*n *= 21) were studied using MRI.* **(A)** *There is relative preservation of the anterior cortical areas and enlargement of neocerebellar areas in WMS subjects. These are the two areas that have undergone the most prominent enlargement in the human brain relative to the brain of primates. Such emerging evidence is consistent with a model where language functions might be subserved by a fronto–cortical-neocerebellar system.* **(B)** *There is relative preservation of the mesial temporal lobe in WMS subjects. In conjunction with certain areas of frontal cortex, this area is thought to mediate important aspects of affective functioning.* **(C)** *In DNS individuals there is relative preservation of the subcortical areas (lenticular nuclei) that is not seen in WMS subjects, which is perhaps relevant to the significantly better motor skills in DNS subjects.* Reproduced, with permission, from Ref. 2.

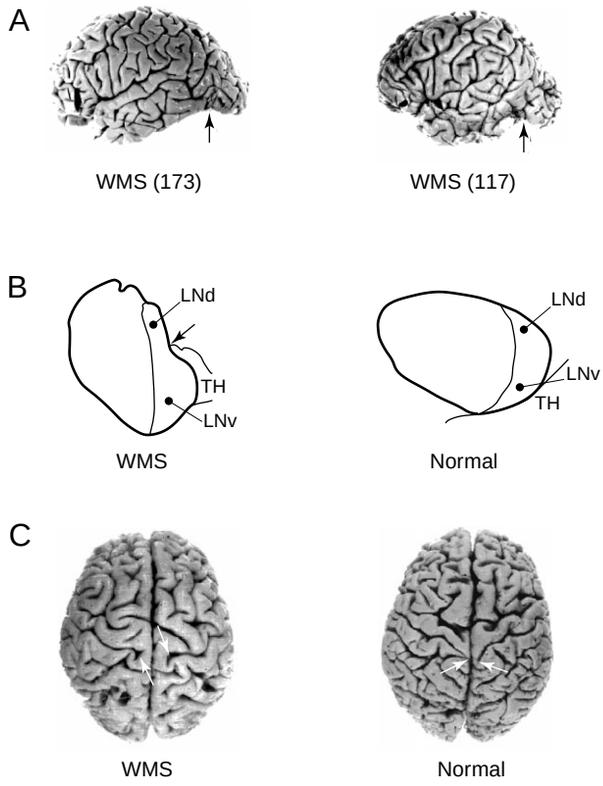

Fig. 7. ***Brain cytoarchitectonic in Williams syndrome (WMS).*** **(A)** *The arrows indicate a marked indentation of the temporo–parietal regions in the area of the sulcus. The whole posterior-parietal regions and occipital regions are small.* **(B)** *Amygdalar nuclei in WMS and normal brains, showing that in WMS the dorsal portion of the lateral nucleus (LNd) appears to be reduced and has an unusual shape. The arrow indicates a curtailment in the lateral nucleus of the amygdala. In this specimen, the nucleus was estimated to be about half the size of the average amygdala in normal subjects. Also, note that the temporal horn (TH) is placed more dorsally in WMS individuals than in normal subjects.* **(C)** *Unlike in the normal brain, where the central sulcus reaches to the interhemispheric fissure and proceeds a variable distance along the medial surface of the hemisphere (arrows), the central sulcus in the WMS brain ends substantially before it reaches the midline (arrows). Abbreviation: LNv, ventral lateral nucleus.*

spared, while spatial-integrative functions are markedly impaired). Perhaps cortical systems that subserve the slower, but higher resolution, processes associated with the parvocellular pathway are selectively spared in WMS, while in DNS the two pathways could both be affected[54].

Brain cytoarchitectonic findings in WMS

An opportunity to link brain findings with cognitive deficits can also be found in the study of focal cognitive deficits of individuals with WMS at the level of brain cytoarchitectonics. Four autopsy brains of individuals with WMS have been studied by Galaburda and colleagues[55–57] (see Fig. 7). Microencephaly and the relative curtailment of the occipital and posterior-parietal areas were evident in three of the brains (Fig. 7A). One of the four brains showed a marked reduction in the size of the parietal, posterior-temporal and occipital regions in comparison with the more rostral portions of the hemispheres. These abrupt and dramatic reductions led to the brain appearing as though a band had constricted its posterior portions[55]. Another brain showed dramatic reduction in the size of the amygdala (Fig. 7B), which could be associated with abnormal social behavior that occurs in subjects with WMS. The MRI data also corroborated the general finding of a reduction in the size of posterior areas. Curtailment of the dorsal-parietal regions and posterior-temporal areas might indeed be relevant to the extreme visuo–spatial deficits seen in individuals with WMS. The four brains show largely normal overall sulcal patterns, except for some simplification of tertiary sulcation and a consistently non-opercularized dorsal central sulcus. The central sulci in normal brains reach all the way to the interhemispheric fissure and then a short distance further onto the medial surfaces of the hemispheres, but in all the available WMS cases the central sulcus ends no less than a centimeter lateral to the interhemispheric fissure (Fig. 7C). This finding could indicate abnormal development of the medio–dorsal cortices, which have been associated with visuo–spatial functions.

The blocks of the cerebral cortex of WMS individuals that have been examined show well-developed cytoarchitectonic areas with all main divisions identifiable. However, there are subtle distortions in the architecture. Morphometric studies suggest that neuronal-cell-packing density is diminished with a concurrent increase in glial numbers, which possibly indicates a substantial decrease in total number of neurons. The observed cell numbers and cell-packing densities suggest early developmental arrest (for example, prenatally or before the second year of age), or regressive events that occur postnatally into the middle of the first decade of life[55]. Research that involves establishing links between the genomic changes and the changes in production of mRNA and protein that lead to the unusual development of the WMS brain, might shed light on normal brain and behavioral development[56,57]. In general, these findings provide unusual opportunities for linking brain findings to cognitive deficits and their neural underpinnings.

A molecular-genetic profile for WMS

Williams syndrome is caused by a microdeletion on chromosome 7 that involves the gene encoding elastin (*ELN*)[58] and perhaps 20 other genes, including the human homolog of the *Drosophila* gene, *frizzled* (*FZD3*)[59], LIM-kinase 1 (*LIMK1*)[60], syntaxin 1A (*STX1A*)[61], replication factor C2 (*RFC2*)[62], *CLYNZ* (Ref. 63), *FKPB6* (Ref. 64), *WSTF* (Ref. 65), *WS-bTRP*, *WS-bHLH*, *BCL7B* (Ref. 66), and a duplicated gene, *GTF2I* (general transcription factor 2I)[67]. Korenberg and colleagues are constructing a physical map of the deleted region of chromosome 7 band 7q11.23 by using multi-color fluorescence *in situ* hybridization (FISH) of bacterial artificial chromosomes (BACs) on metaphase and interphase chromosomes, large-fragment library screening, genomic Southern blot and pulsed-field-gel analyses, STS (sequence tagged site) and polymorphic-marker analyses. Bacterial artificial chromosomes were chosen to construct the physical map because they are cloned in a stable vector and contain large genomic fragments of up to 300 kb that are stable and readily manipulated. Therefore, they are suitable for gene isolation and DNA sequencing. These map reagents were used to investigate the size and extent of the deletions in individuals with WMS in whom subsets of features, including neurocognitive profiles, brain structures and brain functions, were determined simultaneously[68–70].

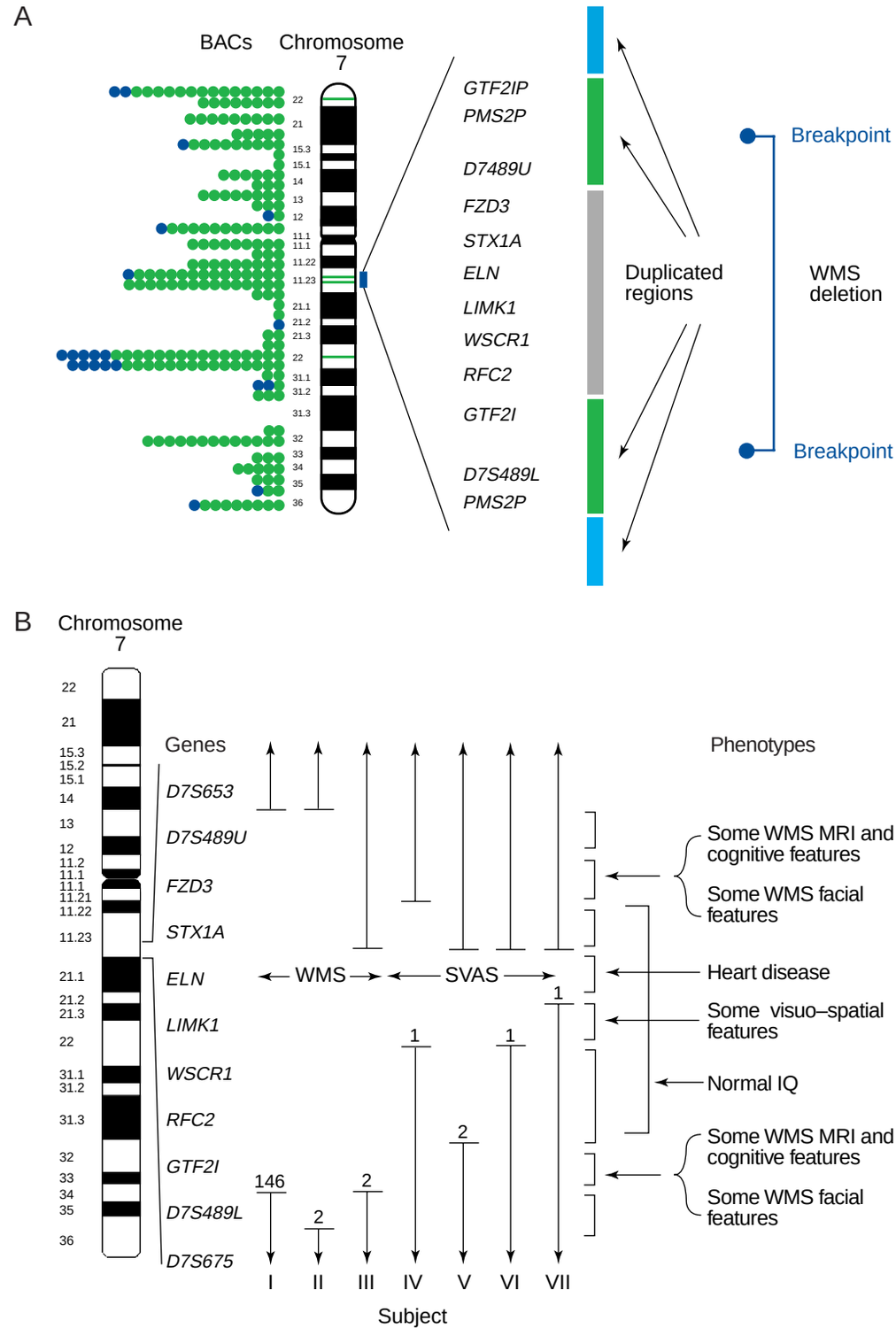

Fig. 8. ***The molecular-genetic basis of Williams syndrome (WMS).*** **(A)** *The region of chromosome 7, band 7qll.23, that is commonly deleted in WMS is represented by the dark-blue box in the ideogram. This region is expanded to the right to illustrate its genomic organization, a region of mainly single copy genes – the homolog of the* Drosophila *gene,* frizzled *(*FZD3*), syntaxin 1A (*STX1A*), elastin (*ELN*), LIM-kinase 1 (*LIMK1*),* WSCR1*, replication factor C2 (*RFC2*) – flanked by a series of genomic duplications (green, pale blue) containing genes (for example,* GTF2I*), pseudogenes (for example,* GTF2IP, PMS2P*), and duplicate markers (for example,* D7S489L*). The regions used in the common breakpoints are indicated by dark-blue bars. The map positions of independent bacterial artificial chromosomes (BACs) used in part for this analysis are shown as green dots to the left of the ideogram.* **(B)** *Vertical lines indicate the regions deleted and the number of subjects carrying the common WMS deletion, which are associated with some of the typical facial features, mental retardation and heart disease, or carrying smaller deletions, including subregions of* STX1A *through to* RFC2*, which are associated with only the typical heart disease, SVAS. Subject VI also has a subtle defect in visual–spatial processing. Small square brackets indicate deleted regions that differ among subjects and, therefore, provide the potential deletion to assign specific WMS features to single regions or genes. The large square brackets indicate regions that, from the current data, are likely to contain a gene or genes that when deleted contribute in some measure to the characteristic features of WMS. The significance of these data is that deletion of* STX1A, ELN, LIMK1, WSCR1 *and* RFC2 *do not appear to be associated with the characteristic facial features or mental retardation seen in WMS, although they could contribute. This is the first step in defining single genes whose deletion is ultimately responsible for the distinctive cognitive features of WMS. Subject I is a typical WMS individual[67,68,71,74,75], subject II has a larger deletion than a typical WMS individual[71,76], subject III can be found in the Italian cases detailed in Ref. 69, details of subjects IV and V can be found in Ref. 77, and details of subjects VI and VII can be found in Refs 78 and 60, respectively.*

A working model of the genome organization that characterizes chromosome band 7q11.2 and incorporates other maps[71,72] was developed[73] and it suggests that this region includes highly homologous chromosomal duplications that are also characterized by a number of repeat-sequence families, genes and pseudogenes. The totality is organized as a nested repeated structure that surrounds the largely unique region occupied by elastin and the other deleted genes (Fig. 8A). This suggests that the region of DNA deleted in WMS individuals is located within an apparently single copy region of chromosome 7 that appears to be surrounded by a series of genomic duplications, some of which must be recent and others of which might have been duplicated earlier in primate evolution. Meiotic mispairing of subsets of the numerous repeated sequences might ultimately contribute to the deletion[71]. Therefore, it is not unexpected that the deletion breakpoints in WMS occur largely in common regions and most, though not all, individuals with WMS have the same genes deleted[68,71,74].

However, it is studies of the uncommon individuals with smaller deletions that are beginning to provide clues to the genes responsible for the subsets of WMS features. For example, from studies of individuals with isolated deletions and mutations of elastin, it appears that the absence of one copy of the gene is probably responsible for the heart defect, SVAS, that is typically found in

WMS (Refs 77,79). However, although absence of one copy of *LIMK1* had been implicated in the spatial deficit characteristic of WMS (Ref. 60), recent work unexpectedly revealed that the deletion of this gene and others in the region was compatible with normal function[77]. Further, preliminary analyses of individuals with the facial, cardiac and mental retardation features of WMS but with a smaller deletion, indicate that the region of the *FZD3* gene might not be essential for the development of these typical diagnostic features[69]. In summary, using this approach, it is now becoming possible to link aspects of the phenotypic profile (specific cognitive functions, facial features, sociability and spatial deficits) to their genetic origins (Fig. 8B).

Important issues revolve, in part, around the definition of the remaining genes in the common deleted region[69,76,77]. Furthermore, it is essential to dissect WMS cognitive features further and to determine the contributions of single genes and their interactions with others in the deleted regions, to each of these features and to the other characteristic embryological, neuroanatomical, physiological and functional landmarks of WMS, as well as to the genetic origins of variability in these phenotypes. Future studies will focus on those genes mapping to regions that, when deleted, are not compatible with normal phenotypes, but rather generate subsets of the features of particular interest in WMS. Animal models of the WMS deletion will be useful but it is expected that understanding many aspects of human cognition and its genetic underpinnings will ultimately rest on studying humans. Such human studies might depend on the need to define further rare individuals with WMS and small deletions, and to combine their molecular structures with a sophisticated understanding of their neurocognitive and behavioral phenotypes. Although many genes probably contribute to the mental retardation, it will without doubt be of interest to determine whether specific genes could be responsible for hypersociability, visual–spatial deficits or to the characteristic ERPs that might be markers for WMS. Hopefully, these new studies will provide the tools for investigating human evolution and, ultimately, the clues to the pathways that lead to the cognitive features of WMS and underlie normal human cognition[80–82].

Concluding remarks

One of the greatest challenges faced in understanding the brain and cognition is the need to link investigations across disciplines within the neurosciences. Until now, this goal has remained unachievable. The studies reviewed here using a specific neurogenetic disorder, which presents unusual dissociations in higher cortical functioning, might provide opportunities to explore some of the central issues of cognitive neuroscience that tie cognitive functions to brain organization and, ultimately, to the human genome.

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LETTERS TO THE EDITOR

What is the amygdala? A comparative approach

In their exciting and provocative article[1], Swanson and Petrovich consider the term 'amygdala' to be an arbitrary name describing a series of structures that are heterogeneous from both anatomical and functional viewpoints. Functionally, they see the amygdala as being made up of nuclei that belong to the autonomic nervous system (central nucleus), the vomeronasal system (medial, posteromedial cortical and posterior nuclei), the olfactory system (the cortical olfactorecipient nuclei, the basomedial nucleus and the posterior part of the basolateral nucleus) and the frontotemporal cortical system (lateral nucleus and anterior basolateral nucleus). Anatomically, they consider the amygdala to be composed of traditional cortical (cortical nuclei and areas receiving direct olfactory input), claustral (basolateral amygdala) and striatal elements (central and medial nuclei).

In the past, a combination of different methods has demonstrated the role of the basolateral and central amygdala in fear conditioning and emotional learning[2–4]. Therefore, the basolateral amygdala (frontotemporal) and the central amygdala (autonomic) appear to constitute a single functional system that, according to anatomical data from reptile studies[5–7], appears to have been well conserved during vertebrate evolution. Although the remaining amygdaloid nuclei certainly belong to the main and accessory olfactory systems (in view of the large number of afferents from the olfactory bulbs), even Swanson and Petrovich recognize that they have a set of intricate interconnections with the central and basolateral amygdala. The activity in the chemosensory amygdala must, therefore, have a strong influence on the basolateral and central amygdala, which suggests a functional interdependence of all the amygdaloid nuclei.

Additionally, as is emphasized by the authors[1], their structural classification of the amygdala coincides essentially with that proposed by Johnston in 1923 (Ref. 8). Using a comparative perspective, Johnston divided the amygdala into a primitive group of nuclei, which includes the 'striatal' and 'olfactory' nuclei, and a phylogenetically new group of nuclei, the 'claustral' amygdala. However, recent connectional and neurochemical studies have revealed the presence of a putative homologue to the mammalian basolateral amygdala in the dorsal ventricular ridge (DVR) of the reptilian brain[5–7], which, following the view held by Swanson and Petrovich, would be claustral and, therefore, isocortical in nature. Were this true, the DVR would represent the reptilian counterpart of the claustrum[9] and other derivatives of the cortical cell plate (layer VIb), even though the remaining layers of the isocortex are absent in the reptilian brain. However, the reptilian DVR has a subcortical origin[10,11] and occupies a subventricular position in the adult. This strongly suggests that the basolateral amygdala is not a cortical (claustral) structure. Data on the expression of genes that control regional specification, morphogenesis and differentiation in the forebrain of embryonic vertebrates are urgently needed in order to clarify this issue.

The major legacy of Johnston's work on the amygdala is not the compartmentalization he proposed but the use of a comparative perspective, which is essential to elaborate solid hypotheses concerning the anatomical and functional organization of the brain.

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Reply

Lanuza and his colleagues address two fundamental problems in their letter[1]: how are neural systems defined and is there a basic plan of the vertebrate brain? Their exciting work on the connections of what appears to be the amygdala in reptiles refers to the latter, classical problem, which has been reviewed thoroughly quite recently[2].

What is a neural system? Perhaps the best way to approach this problem is through a simple example. Essential