

Quick guide

Williams Syndrome

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Williams syndrome...people with intact language, intact face processing and very low IQ, right? Wrong! That's the propagated myth because, if it were true, it would be such an elegant example of innate modularity at the genetic, brain and cognitive levels. But numerous labs across the world have shown that although vocabulary levels can be surprisingly high in Williams syndrome children, they are rarely if ever age-appropriate, with quite shallow semantics. Even claims about very low IQ turn out to be exaggerated. Williams syndrome IQ ranges from 48 to 85. True, people with Williams syndrome are often very loquacious and usually have better language than spatial skills, but the profile of the syndrome is unscientifically exaggerated by secondary sources. The syndrome actually illustrates the tight relationship between language and intelligence

But what about their face processing, that's relatively intact, isn't it? I'm always amused by such theoretically loaded expressions as 'relatively intact'. It's like being 'relatively pregnant'! It's a fact that face-processing studies originally showed that people with Williams syndrome score in the normal range — another potentially preserved module! But subsequent, in-depth work showed that, while control subjects process faces configurally (their brains rapidly compute the distances between eyes, nose, mouth), at best people with Williams syndrome process faces holistically as an overall Gestalt, and most research indicated that they process faces featurally.

Moreover, brain imaging studies showed that, whereas in controls it is predominantly the right hemisphere that is activated during face processing, and they display a difference between the processing of faces and cars, in people with Williams syndrome the activation is bilateral, and there are no clear differences in the temporal dynamics of processing faces or cars. Furthermore, in normal children the so-called 'inversion effect' (a decrement in performance when faces are upside down) gradually emerges over developmental time, but this does not occur in children with Williams syndrome. So, while behavioural scores can fall in the normal range, the cognitive and brain processes underpinning the behaviour are far from normal. People with Williams syndrome don't have an intact face-processing module; they fail to display the progressive localisation/specialisation of function that is the brain signature of normal development.

But we're sure they have an uneven cognitive profile, with serious spatial deficits, right? And don't we know which gene causes the spatial problems? If only biology were that simple: one gene/one function! People with Williams syndrome do have quite proficient language abilities compared with their serious spatial impairments — these are less severe in perceptual tasks but a major problem in spatial construction tasks. And there was a lot of excitement when it seemed that one of the 28 genes in a chromosome 7 deletion associated with Williams syndrome might be directly linked to the spatial impairments typical of Williams syndrome. Researchers found individuals with just two of the 28 Williams syndrome genes deleted: *Limkinase1* and *Elastin*. The *Elastin* deletion seemed to be involved in the facial dysmorphology and some other physical symptoms (aortic and renal stenoses) of Williams syndrome. *Limkinase1*, which is

expressed in the brain, encodes a protein tyrosine kinase that phosphorylates and inactivates the actin-binding protein cofilin, so defects could affect axonal guidance during CNS development. Because these partial deletion patients have spatial problems, the *Limkinase1* deletion was hailed as a direct contributor. Media sources even claimed: "the discovery of the gene for intelligence"! Rather premature on all fronts... Subsequent work on other partial deletion patients revealed no spatial deficits despite deletions of *Limkinase1*, and no facial dysmorphology despite deletions of *Elastin*. The only clear genotype/phenotype correlation turned out to be between *Elastin* and the stenoses. More recent work on yet other partial deletion patients (with more than two genes deleted within the Williams syndrome critical region) has identified some 10 telomeric genes, several of which are transcription factors, as the more likely seat of those contributing to full-blown Williams syndrome.

But isn't there a Williams syndrome Limkinase1 mouse model, which really clarifies the genotype/phenotype debate? Again, it's just not that simple. Animal models are really important, but need to be interpreted with caution. First, Williams syndrome is a contiguous gene syndrome and hitherto all the Williams syndrome knockout models involve single genes. Second, in the *Limkinase1* knockout mouse, the comparison made was between human tasks involving spatial relations between objects where the participant remains seated at a table, whereas the mouse tasks involved spatial navigation in which the mouse has to constantly represent and update its changing position in space. Hardly comparing like with like!

Just now you mentioned the facial dysmorphology: don't individuals with Williams syndrome look like elfins?

I find such expressions quite unpleasant for families. There are more detailed clinical descriptions of the distinctive facial appearance — flat nasal bridge, anteverted nares, wide mouth with fleshy lips, long filtrum, periorbital fullness, epicanthic folds, flat malar region, small mandible and prominent cheeks — but nowadays we have more scientifically constrained ways of assessing facial dysmorphology. For instance, three-dimensional face images can be captured with photogrammetric devices, yielding 4,000–20,000 three-dimensional points on the facial surface. Dense surface models can then be built using specially designed computer programs that enable researchers to compare very fine details of faces within and across syndromes and, for example, to pinpoint localized dysmorphologies of subtle facial features in partial deletion patients, which the naked clinical eye cannot detect.

Could we say that Williams syndrome is the opposite of autism? No, that would be overly simplistic. For instance, featural processing is characteristic of both Williams syndrome and autism. Second, even though people with Williams syndrome seem extraordinarily friendly, their social behaviour is as inappropriate as that of individuals with autism. Those with Williams syndrome cannot judge social situations, fail to modulate their behaviour properly between strangers and friends, and tend to stare and invade the personal space of others. Interestingly, this inappropriately friendly Williams syndrome behaviour even emerges in Japan where such immediate intimacy is culturally sanctioned. But the Williams syndrome brain is indeed very different from the autistic brain, so cross-syndrome comparisons may yield some interesting insights into gene–brain–cognition–behaviour relations.

It all seems so complex: shouldn't researchers simply give up or study a syndrome caused by only one gene instead of 28? Fragile X is no simpler to study than Williams syndrome. The resulting phenotype is very complex even when a single gene is involved. In my view, Williams syndrome constitutes a challenging and exciting detective story! We still need to understand the full developmental trajectory from infancy onwards, and how initially small perturbations can have cascading effects on the emergent outcome.

Where can I find out more?

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