Williams–Beuren Syndrome

More or less? Segmental duplications and deletions in the Williams–Beuren syndrome region provide new insights into language development

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The wealth of data arising from high-throughput global analysis of the human genome sequence has uncovered a large number of interspersed and tandem segmental duplications of the human genome. Indications are that ~5% of the human genome has been duplicated within the past 40 million years and this provides us with a snapshot of ongoing genome evolution.[1] Segmental duplications play an important role in disease because they create genome instability that can lead to genomic rearrangements in important regions with consequential dosage imbalance or misregulation of gene(s) necessary for normal human development.[2–6] Abnormal gene dosage is involved in the aetiology of many genetic disorders such as Charcot-Marie-Tooth type 1A (CMT1A, caused by *PMP22* gene duplication)[2] or Williams–Beuren Syndrome (WBS, caused by a contiguous gene microdeletion)[3] which is the focus of this commentary.

Research into the molecular pathology of WBS and efforts to link phenotypic features with specific genes in the deleted segment on 7q11.23 has been slow partly due to the homogeneous nature of the deletion which occurs by nonallelic homologous recombination between flanking low copy repeats (LCRs or duplicons) during meiosis.[4] It has long been predicted that a reciprocal duplication of the region should occur at the same frequency as the deletion, especially since matching duplications have been defined for other microdeletion disorders with similar genome architecture. The reciprocal duplications of the Smith–Magenis syndrome (SMS) deletion on 17p11.2 is one example[5] and the duplication in the VCFS-DGS (DiGeorge/Velocardiofacial syndrome) region on 22q11.2 another.[6] Now, at last, Somerville *et al*[7] and Kriek *et al*[8] report patients with what appears to be a reciprocal duplication of the WBS deletion and, tantalisingly, both key patients have significant speech delay. This is in direct contrast to WBS patients where one of the most interesting features displayed is their fluent expressive language alongside poor visuospatial skills.

WBS patients have a very distinctive phenotype including a dysmorphic facial appearance (full cheeks, periorbital puffiness, a short upturned nose), frequent cardiac defects (often supravalvular aortic stenosis, SVAS), short stature and infantile hypercalcemia and most are clinically diagnosed in infancy. They also exhibit a characteristic cognitive profile with a discrepancy between relatively strong verbal and poor spatial abilities; in fact early reports drew attention to their 'cocktail party' pattern of speech emphasising strong verbal abilities but lack of depth in understanding. The first gene to be linked to a specific component of the phenotype was *elastin*, which was disrupted in a family with dominant SVAS[9] and was subsequently found to be mutated in patients with SVAS without a family history of cardiac disease.[10] Further genotype–phenotype correlations have been aided by detailed analysis of a few atypical patients with partial deletions of the region and mouse models.[11] Although no further absolute associations have been established with single genes, *LIMK1*, *CYLN2* and *GTF2IRD1* have all been linked to aspects of the cognitive and craniofacial pathology.[11–14] As yet no specific gene(s) have been assigned to the unusual language pattern.

Recently, Somerville *et al*[7] reported a proband with a *de novo* duplication of the WBS region. He displayed severe expressive language delay (not present in his parents or sister), mild developmental delay and attention deficit-hyperactivity disorder (ADHD), shared with some family members. Published photographs show a relatively normal looking boy whose features are not really distinctive although he does have a small chin and mild facial asymmetry. His short stature is common to other family members. The report demonstrates convincingly that the duplication is reciprocal to the common WBS deletion, however, attempts to show the phenotype is reciprocal to that of WBS are less convincing other than in the fields of language development. Kriek *et al*[8] detected their duplication patients by screening a cohort of 105 patients with developmental delay and/or congenital malformations. Genetic variations were sought within 63 duplicon-flanked regions (selected from targeted hot spots of genomic instability including some from known disease loci) as well as in 58 genes from outside the duplicons. They demonstrated that such imbalances were more frequent within duplicon-containing regions and their Multiplex Amplifiable Probe Hybridisation (MAPH) assay successfully identified six cases with duplications, which were verified and characterised using a combination of FISH, MLPA and array-CGH techniques. Two of the duplications involved the WBS region, one of which appears to be a reciprocal duplication of the whole region encompassing the genes from *FKBP6* to *GTF2I* (1.4–1.7 Mb), although the breakpoints were not defined. Phenotypically, the patient had undergone reconstruction of his skull due to synostosis of the metopic suture and had 'mild developmental delay, especially delay in speech

development'. His father who, apart from syndactyly of the hands and feet, is not reported to have other problems also carried the duplication, which was *de novo* in him. It would be interesting to obtain more detailed analysis of the speech dyspraxia in the proband and to know if his father displayed similar but perhaps more subtle problems. The second patient with coronal and lambdoid suture synostosis, facial asymmetry, a severe congenital heart defect and a finger-like thumb, but normal development carried a much smaller duplication (0.3–0.4 Mb) involving the *FKBP6* gene, which is not thought to be a key factor in the development of the WBS pathology.[11] Again this duplication was inherited (maternally) therefore warrants further investigations to determine if it is a benign polymorphism and whether the proband harbours an additional genetic abnormality at another locus. The lack of a phenotype in the 'unaffected' parents (with duplications) is interesting and implies that, in addition to gene dosage, other mechanisms such as genetic and/or environmental interactions may be important in determining the phenotypic outcome of patients with these genetic aberrations.

What all this new information shows is that microduplications of 7q11.23 do exist but the paucity of reported cases in contrast to microdeletions probably reflects a combination of ascertainment bias, milder and less distinct phenotypes and limitations in the diagnostic technology. Future high-resolution screening of large cohorts using microarrays should resolve this latter shortcoming and identify changes in the genome on a global scale. In addition, the question of copy number polymorphisms will be addressed as genome-wide analyses uncover more variations in normal populations.[15]

The clinical presentation associated with reciprocal WBS duplications certainly seems to be milder and facial features are different and less distinct than those of WBS so many more patients probably exist but remain undiagnosed. However, the 'outing' of the duplication phenotype should increase the detection of more cases. This situation is mirrored in other genomic disorders where milder pathological consequences tend to arise with gene duplications compared with the reciprocal deletions, for example duplications *versus* deletions of 22q11.2.[6] In the extreme case, monosomy 21 is probably lethal and consequently not detected, whereas trisomy 21, which causes Down's syndrome is compatible with survival. It is intriguing that a very distinctive part of the phenotypes in both WBS deletions and duplications concerns speech which suggests that specific gene(s) in the region are exquisitely sensitive to dosage changes, and upsetting the balance can affect human speech and language as well as visuospatial capabilities. Developmental disorders of speech are known to have a genetic component and *FOXP2*, a member of the forkhead transcription factor family, was the first gene associated with the development of speech and language in humans.[16] Now, in the WBS region, we have another locus which offers a unique entry point for further investigations into the neurological and molecular mechanisms influencing human speech and language acquisition■

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