More than the sum of its parts: new mouse models for dissecting the genetic complexities of Williams–Beuren syndrome

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Psychiatric disorders are a common, severe and disabling group of diseases where progress in finding novel molecular targets has been slow. This is partly due to our lack of understanding of the molecular pathophysiology of these conditions as they play out in the brain (Insel & Scolnick, 2006). Since many of these diseases (such as schizophrenia, bipolar disorder or autism) are highly heritable, a genetic approach to dissecting the risk architecture is a promising avenue for molecular medicine; however, variants in single genes frequently present in the population have only small to moderate effects on complex behavioural phenotypes (O’Donovan et al, 2008).

In this setting, microdeletion disorders, in which a known group of genes is heterozygously deleted due to misalignment during meiosis, are fascinating and instructive accidents of nature. In these a known genetic “lesion” can be related to a neurobehavioural phenotype, offering chances to identify not only distinct, but also interacting contributions of genes in the microdeleted region to brain development, structure and function (Meyer-Lindenberg et al, 2006). This is especially topical since copy number variants and microdeletion syndromes have recently been implicated in the genetics of common psychiatric disorders as well (International Schizophrenia Consortium, 2008).

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An excellent example for this strategy is given by studying the Williams–Beuren syndrome (WBS), a neurodevelopmental disorder afflicting as many as one out of every 7500 (Strømme et al, 2002) births. WBS is caused by a hemizygous deletion of approximately 1.6 megabases (Mb), containing ~25 genes, on chromosome 7q11.23 (see Fig 1), caused by unequal homologous recombination at flanking repeats during meiosis (Urban et al, 1996).

More than 80% of individuals with WBS have cardiovascular abnormalities. Other common somatic symptoms include endocrine and orthopaedic problems (Morris et al, 1990). Neurological problems include developmental delay, coordination difficulties and nystagmus (Chapman et al, 1996), hearing loss and hypersensitivity to sound (Committee on Genetics, 2001).

In cognition, WBS is associated with a distinctive cognitive profile (Mervis & Klein-Tasman, 2000; Mervis et al, 2000), and this weakness, together with a relative strength in verbal short-term memory and language (Farrran & Jarrold, 2003; Mervis et al, 2000), differs significantly from other syndromes. A particularly striking feature of children with WBS is their high sociability (Bellugi et al, 1999; Klein-Tasman & Mervis, 2003) and their empathy for others. Individuals with WBS typically are socially fearless and engage eagerly and often impulsively in social interaction even with strangers (Bellugi et al, 1999). Intriguingly, this remarkable hypersociability is coupled with strong non-social anxiety (Dyken, 2003; Klein-Tasman & Mervis, 2003). In some sense, the clinical opposite of WBS is exhibited in a first reported case of a duplication of the WBS region (Somerville et al, 2005), which showed severe speech and expressive language delay but visuospatial construction skills that were similar to those of other family members.

In previous work, the cardiovascular defects observed in WBS have been linked to haploinsufficiency for elastin (ELN), as have been many of the facial features (Morris et al, 2003). Single gene contributions to behavioural phenotypes for genes in the WBS region including Limk1 and Ciln2 (Hoogenraad et al, 2002; Meng et al, 2002), frizzled-9 (Zhao et al, 2005) and Gtf2ird1 (Durkin et al, 2001; Tassabehji et al, 2005) have also been described. However, it has been noted (Karmiloff-Smith et al, 2003) that, apart from ELN and the cardiovascular...
aspects of WBS, no other part of the phenotype has been recognized as an isolated Mendelian dominant character in families with a point mutation in one of the critical genes.

This emphasizes a major opportunity for translational work that had not been used, namely, the fact that the WBS region in mice, on chromosome 5, shows a considerable degree of conserved synteny with the human region (Bayarsaihan et al, 2002; DeSilva et al, 2002). In this issue of EMBO Molecular Medicine, Li et al have taken advantage of this fact to create a new generation of mouse models. They created two half-deletions of the conserved syntenic region (see Fig. 1), proximal deletion (PD) mice, which were missing Gtf2i to Limk1, and distal deletion (DD) mice missing Limk1 to Fkbp6, and also studied double heterozygotes (D/P) which model the complete human deletion with the exception of Limk1, which was included in both DD and PD and was therefore much more strongly deleted in D/P than expected for the WBS hemideletion. Since the orientation of the mouse region is reversed with respect to the centromere, this means that PD mice correspond to a telomeric small deletion syndrome in humans, and DD mice to a deletion of genes centromeric and up to Limk1. It is therefore intriguing to compare these ‘mouse small deletion syndromes’ to the phenotype of known human families where only a part of the region is WBS deleted (see Fig. 1). If the ELN gene is affected, many of these individuals require medical attention for cardiovascular abnormalities. This is also found in the present paper, where such abnormalities are found for the DD region, which includes ELN. A further general conclusion that reassuringly

![Figure 1. Genetics of WBS (modified with permission from Meyer-Lindenberg et al (2006)).
A. Chromosomal location of the hemideleted region.
B. Map (Tassabehji et al, 2005) of the region in humans (centre) and the homologous region in mice (top). PD and DD mouse deletions from Li et al.’s paper, this issue, marked in red; low copy repeat regions marked by arrows labelled A, B, C.
C. Extent of typical WBS deletion and examples of small (atypical) deletions. Dash means exact extent unknown. Letters refer to the following papers: B, Botta et al (1999) and Heller et al (2003); H, Heller et al (2003); KS, Karmiloff-Smith et al (2003); M, Morris et al (2003); F, Frangiskakis et al (1996); T, Durkin et al (2001) and Tassabehji et al (2005).]
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Studying the behaviour, Li et al present strong data showing that a social phenotype reminiscent of the reduced social fear and gregariousness found in WBS maps predominantly to the PD, which would implicate genes including and telomeric to ELN in humans. This should help identifying single genetic contributions, for example in Cyln2 or Gtf2i, to these social phenotypes.

These new mouse models should also afford an excellent opportunity to study the hallmark cognitive symptom of WBS, a severe impairment in the visuospatial domain (Mervis et al., 2000). Three human individuals have been described who showed the cognitive phenotype and had mental retardation, but had atypical centromeric breakpoints resulting in smaller deletions. In these cases, STX1A and the genes proximal to it were not deleted (Botta et al, 1999; Heller et al, 2003). These cases thus argue against a major role for genes centromeric to ELN in the behavioural abnormalities observed in WBS, as does the description of a highly intelligent individual lacking cognitive symptoms, who had an atypical 850 kb deletion which included these genes, but not genes telomeric to RFC2 (Karmiloff-Smith et al, 2003). Since these deletions correspond to a subset of the genes deleted in DD mice, mapping visuospatial deficits, a difficult but potentially tractable problem in mice, would implicate either genes from Stx1a to Limk1 or genes telomeric to Limk1 in this behavioural phenotype. The human literature is not consistent regarding the Limk1 involvement in the visuospatial constructive cognition phenotype (Franciskakis et al, 1996; Morris et al, 2003; Tassabehji et al, 1999) and unfortunately these mouse models cannot settle this debate, as both PD and DD mice have this gene disrupted, and D/P mice therefore have a stronger reduction of Limk1 than the one seen in human WBS.

Both from human data and the animal model results presented by Li et al, it should be clear that the WBS regions, and probably other clinically significant microdeletions, are more than ‘the sum of their parts’. For example, abnormalities in sensorimotor processing in prepulse inhibition and GAP processing tasks were found both in PD and DD mice, but not in the D/P deletion encompassing both. This situation highlights the existence of as yet not understood epistatic and complementing effects within these regions that will probably be important in understanding the emergence of neurobehavioural phenotypes.

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The new mouse models will also be invaluable to refine our understanding of the neural intermediate phenotypes of WBS and their molecular underpinning. In humans, profound abnormalities of hippocampal function (Meyer-Lindenberg et al, 2005b), amygdala regulation (Meyer-Lindenberg et al, 2005a) and parietal lobe processing of visual stimuli (Meyer-Lindenberg et al, 2004) have been described and linked to the core behavioural and cognitive abnormalities of WBS (Meyer-Lindenberg et al, 2006), and it will be of great interest to see the corresponding studies performed in DD and PD mice. Encouragingly, gross abnormalities in neuroanatomy, such as brain volume reduction, were found recapitulated by Li et al in their models, although several other aspects of regional anatomical abnormalities, such as cerebellar volume, ventricular volume or the microscopic anatomy of somatosensory cortex, differ from the human literature, which however has its own share of inconsistent findings (Meyer-Lindenberg et al, 2004; Reiss et al, 2004). One clear finding emerging from the present study is a definite impairment of brain maturation in DD mice, which would again implicate genes between Stx1a and Limk1 in the context of the phenotype exhibited by human small deletion cases (Botta et al, 1999; Heller et al, 2003).

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In addition to the results already presented in this communication, the new models described by Li et al should be invaluable for pushing further our understanding of interacting genetic effects—by adding genes back into the regional deletions and studying their effects on neural or behavioural phenotypes, achieving a new degree of modeling validity that can also be hoped to help translational efforts in finding drug targets addressing specific aspects of WBS, a condition where specific pharmacological interventions are currently absent.

The authors declare that they have no conflict of interest.

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