NEWS AND COMMENTARY

Deletions Revealing Recessive Genes

Deletions that reveal recessive genes

David J Coman and RJ McKinlay Gardner

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Recessive genes, by definition, recede. Mostly, what brings them out into the open is the homozygous state. But in rare instances, the heterozygote can display the particular phenotype; and one mechanism allowing this is the 'deletion that reveals'. A deletion on the normal chromosome, removing the normal allele, can thereby expose the recessive mutation on the other chromosome to the full light of the day. In such a case, there will be two phenotypes combining: the clinical consequences of the deletion on the normal chromosome, typically due to haplo-insufficiency of dosage-sensitive genes within the deleted segment; and the recessive syndrome itself, normally seen only in the homozygote. The clinician will need to display a level of astuteness to recognise the differing component parts that a patient may display, and to suspect the possibility that there may be two separate pathogenetic mechanisms operating.

An elegant example of this phenomenon is given in Flipsen-ten Berg *et al.*¹ on page xxx of this issue. The authors describe a fascinating patient in whom the clinical phenotype suggested Wolf-Hirschhorn syndrome (OMIM 194190), with a typical deletion of chromosome 4p being demonstrated, and who also developed clinical features in keeping with Wolfram syndrome (WFS, OMIM 222300). A nonsense mutation was identified in the *WFSI* gene, which lies within the same region of chromosome 4p, the hemizygous deletion rendering the patient functionally homozygous for a deficiency of *WFSI*. Beware the hemizygous deletion unmasking heterozygous mutations on the alternative allele!

The concept illustrated by Flipsen-ten Berg *et al.*¹ is certainly not novel, albeit sparsely reported in the medical literature; and we note a number of examples. Lee *et al.*² reported a patient with Prader-Willi syndrome (PWS, OMIM 176270), with the typical deletion of paternal chromosome 15q11–q13, plus oculocutaneous albinism. The PWS deletion led to the patient being hemizygous for a maternally inherited mutant allele of the *P* pigmentation gene.²

Phenotypic discordance between monozygous twins with 22q11 deletion syndrome (OMIM 192430) has been recorded twice in the literature.^{3,4} Although the most probable explanation may be that there have been differing stochastic influences and environmental factors during *in utero* existence, another theoretical possibility is the unveiling of a somatically arising autosomal recessive locus on the non-deleted allele.

Mutations in the *COMP* gene on chromosome 19p13.1 have been shown to be causative in pseudoachondroplasia (PASCH, OMIM 177170). Ikegawa *et al.*⁵ reported a patient with PASCH and a *de novo* del(11)(q21q22.2), and postulated that the deletion removed other genes that might have modified the PASCH phenotype. The genes in this region are not good candidates for PASCH, and the patient's clinical and radiographic phenotype did not deviate from that expected in PASCH, and thus, this suggestion must remain speculative at this time.

Mutations in *MYO15A* are responsible for DFNB3 autosomal recessive deafness, which maps to 17p11.2. Hemizygous deletions of 17p11.2 cause Smith–

Magenis syndrome (SMS, OMIM 182290), which is characterised by multiple congenital anomalies, intellectual impairment, and often severe pervasive developmental disorders. Hearing impairment is common in SMS and is often multifactorial in origin. Liburd *et al.*⁶ reported a patient with SMS and severe sensorineural hearing loss secondary to a hemizygous missense mutation of *MYO15A* on the alternative allele.

Hermansky–Pudlak syndrome (HPS, OMIM 203300) is an autosomal recessive disorder characterised by oculocutaneous albinism, a bleeding diathesis, granulomatous colitis, and pulmonary fibrosis. Griffin *et al.*⁷ described a patient with HPS in whom a large deletion unmasked a hemizygous deletion on the normal chromosome.

Thrombocytopenia-absent radius syndrome (TAR, OMIM 274000) is characterised by hypomegakaryocytic thrombocytopenia, and bilateral absence of the radius. Numerous modes of inheritance have been proposed. Klopocki *et al.* identified a microdeletion on chromosome 1q21.1 in all of their affected TAR cohort and in 32% of unaffected family members.⁸ The inference they drew was that this deletion is necessary but not of itself sufficient to cause TAR syndrome, with a second common polymorphism or mutation elsewhere in the genome.

Balanced reciprocal translocations unmasking autosomal recessive phenotypes are also occasionally reported in the medical literature. Only two balanced reciprocal translocations have directly led to the discovery of a new autosomal recessive gene. The first was a patient with Alstrom syndrome (OMIM 2038000) in whom a 46,XY,t(2;11)(p13;q21)mat translocation disrupted the *ALMS1* gene, and an intragenic mutation was identified on the other allele.⁹ Baala *et al.*¹⁰ have described a large consanguineous Moroccan family, in whom four males were found to be homozygous for a 46,XY,t(3;10)(p24;q23) translocation, expressing a clinical phenotype of microcephaly, structural brain malformations, and severe global developmental delay. The breakpoint on chromosome 3p silenced the *EOMES* gene (also known as T-box-brain2), which created the clinical phenotype in the ensuing homozygous (not hemizygous, in this instance) state.

As well as these two translocations having pointed the way to the discovery of a recessive gene, numerous other examples (and including the X chromosome) are on record, including: Duchenne muscular dystrophy (OMIM 310200), Diamond–Blackfan syndrome (OMIM 205900), Cam-pomelic dysplasia (OMIM 114209), Ehlers–Danlos type II syndrome (OMIM 130010), Smith–Lemli–Optiz syndrome (OMIM 270400), and Menkes disease (OMIM 309400).

The work presented by Flipsen-ten Berg *et al* reminds us of these rare genetic mechanisms, and raises the question: are such cases under-diagnosed? In any patient with a cytogenetic deletion (and especially one of the more common deletions), and in whom the clinical picture is not typical, the possibility of an unmasked recessive gene needs to be borne in mind. For example, in one of the most frequently seen deletion syndromes, the 1p36 deletion, the 5,10-Methylenetetrahydrofolate reductase (OMIM 236250) enzyme, involved in folate, homocysteine, and one-carbon metabolism, maps to 1p36.3. As many as 5–10% of the population are homozygous for a common thermolabile mutation, 677C>T, which predisposes to thromboembolic sequelae secondary to platelet dysfunction induced by the elevated homo-

cysteine levels. Might a functional homozygosity for this gene in an individual with a 1p36 deletion lead to further damage of an already compromised brain? ■

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David J Coman and RJ McKinlay Gardner are at the Department of Paediatrics, University of Melbourne, Genetic Health Services Victoria, Royal Children's Hospital, Melbourne, Victoria, Australia.
Tel: +61 3 8341 6201;
Fax: +61 3 8341 6390;
E-mail: david.coman@ghsv.org.au

References

- 1 Flipsen-ten Berg K, van Hasselt PM, Eleveld MJ *et al*: Unmasking of a hemizygous WFS1 gene mutation by a chromosome 4p deletion of 8.3 Mb in a patient with Wolf–Hirschhorn syndrome. *Eur J Hum Genet* 2007; (e-pub ahead of print).
- 2 Lee ST, Nicholls RD, Bunday S *et al*: Mutations of the P gene in oculocutaneous albinism, ocular albinism, and Prader–Willi syndrome plus albinism. *N Engl J Med* 1994; 330: 529–534.
- 3 Goodship J, Cross I, Scambler P, Burn J: Monozygotic twins with chromosome 22q11 deletion and discordant phenotype. *J Med Genet* 1995; 32: 746–748.
- 4 Yamagishi H, Ishii C, Maeda J *et al*: Phenotypic discordance in monozygotic twins with 22q11.2 deletion. *Am J Med Genet* 1998; 78: 319–321.
- 5 Ikegawa S, Ohashi H, Hosoda F *et al*: Pseudoachondroplasia with *de novo* deletion [del(11)(q21q22.2)]. *Am J Med Genet* 1998; 77: 356–359.
- 6 Liburd N, Ghosh M, Riazuddin S *et al*: Novel mutations of MYO15A associated with profound deafness in consanguineous families and moderately severe hearing loss in a patient with Smith–Magenis syndrome. *Hum Genet* 2001; 109: 535–541.
- 7 Griffin AE, Cobb BR, Anderson PD *et al*: Detection of hemizygosity in Hermansky–Pudlak syndrome by quantitative real-time PCR. *Clin Genet* 2005; 68: 23–30.
- 8 Klopocki E, Shulze H, Strauss G *et al*: Complex inheritance pattern resembling autosomal recessive inheritance involving a microdeletion in thrombocytopenia-absent radius syndrome. *Am J Hum Genet* 2007; 80: 232–240.
- 9 Hearn T, Renforth GL, Spalluto C *et al*: Mutation of ALMS1, a large gene with a tandem repeat encoding 47 amino acids, causes Alstrom syndrome. *Nat Genet* 2002; 31: 79–83.
- 10 Baala L, Briault S, Etchevers HC *et al*: Homozygous silencing of T-box transcription factor EOMES leads to microcephaly with polymicrogyria and corpus callosum agenesis. *Nat Genet* 2007; 39: 454–456.