Monozygotic twins with chromosome 22q11 deletion and discordant phenotype

I believe that the recent description by Goodship et al of discordance in monozygotic twins with a 22q11 deletion raises some interesting issues. The likelihood of a heart defect in a person with a constitutional 22q11 deletion cannot currently be estimated, as ascertainment of such patients is usually on the basis of the presence of a heart lesion. In addition, the true prevalence of 22q11 deletions is not known, although a low limit of 1:4000 has been quoted on the basis of children presenting with congenital heart defects.1 Thus, until prospective studies are carried out to allow complete ascertainment of subjects with a 22q11 deletion, irrespective of phenotype, this question cannot be answered. Variability of phenotypic expression among people with presumably identical deletions (that is, familial cases) strengthens the concept that a 22q11 deletion merely increases the likelihood of certain anomalies being present but does not guarantee them.2 It is clear, therefore, that the association of heart disease with this deletion is far from deterministic.

The discovery of monozygotic twins with a 22q11 deletion who are discordant for heart disease should, therefore, come as no surprise. Although this report, which describes a “genetic background” could never be ignored.3 While it is clearly true that the phenotype in these twins could not have been predicted on the basis of their identical (germline) genotypes, it is not necessarily true that the discordance cannot be attributed to genetic differences between the two. If, in the above paper, the words “chromosome 22q11 deletion” had been replaced by “germline mutation in the retinoblastoma gene”, little surprise would have been expressed, and the discussion would have focused on the chance element involved in the “second hit” genetic mutations now known to be necessary for phenotypic expression in retinoblastoma.4 The concept of a “second hit” in congenital malformations, however, is not widely accepted. The disorganisation gene in the mouse is an example of a dominant mutation that increases the risk of a wide variety of congenital malformations, from cleft palate to accessory limbs.5 Analysis of the likelihood of one, two, or three malformations in this mouse is consistent with the Krudnow “second hit” hypothesis, although little can be said about the nature of these secondary somatic events, only that they occur independently of each other.6 They may be genetic or epigenetic and are likely, in any event, not to occur at the Ds locus itself. Thus, it is likely that the disorganisation gene is important in development of many organ systems but that abnormalities of these systems result from random somatic events, as yet unidentified.7 Of note is the fact that the majority of mice with the Ds mutation are phenotypically normal, having presumably escaped secondary somatic events occurring at an early stage of development.8 With this mechanism in mind, it is possible that a secondary somatic event is required for the manifestation of some features known to be associated with a 22q11 deletion.

The velocardiofacial syndrome is remarkable for its array of non-phenotypic manifestations and is best thought of as comprising features that are relatively constant (facial features, developmental delay), features that are common but not universal (conotruncal heart defects, immunological abnormalities), and features that are only found rarely (upper lip malformations, meningomyelocele,5 cerebellar atrophy), although this analysis is of necessity biased as the number of relatively normal subjects who harbour 22q11 deletions is not known. While it is likely that haploinsufficiency alone may be sufficient to explain the dysmorphic faces and developmental delay, it is not clear that this is true for the found other common but not universal features. While somatic events may play a role, it is possible that haploinsufficiency may simply increase the statistical likelihood of other malformations in a way that is unpredictable, maybe even in principle. The association of rare anomalies with 22q11 deletions may result from a number of general mechanisms.

(1) Uncovering recessive events. The deletion uncovers a recessive mutation present on the non-deleted chromosome. The frequency of such features in the “22q11 deletion” population should mirror the frequency of heterogeneous mutation in the population for the relevant recessive disorder (for example, Bernard-Soulier phenotype). A careful search for rare interactions in “microdeletion syndromes” may be helpful in mapping recessive phenotypes.

(2) A second hit, either on the contralateral 22q11 or elsewhere in the genome, may give rise to the relevant (uncommon) abnormality. This mechanism, as described above for the Ds gene, has been invoked to explain vertical transmission of conditions that give rise to “phenotypic mosaicism” and which had hitherto been thought of as resulting from genetic mosaicism (for example, ILVEN).9 In this model, the presence of a germline mutation in a large number of subjects does not, of itself, result in the phenotype; in a small proportion, however, the germline mutation occurring at an early stage in development will result in the relevant abnormality, which will generally appear mosaically. There will be few such subjects as the chance that the second hit will occur in the right cell type and early enough in development is very low. The majority of such subjects will therefore occur sporadically and be deemed to represent new postzygotic mutations. The discovery, however, of even one example of a parent-child combination, both displaying “phenotypic mosaicism” must force a re-evaluation of the original hypothesis. The report of unilateral preaxial polydactyly in a child with a 22q11 deletion, for example, would be consistent with a somatic event occurring early and affecting a cell line about to be involved in formation of the distal limb bud.10

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Large inv dup(15) chromosome in two generations

Inv dup(15) is a relatively common chromosomal abnormality, which does not appear to account for approximately half of all small supernumerary marker chromosomes detected.1 The phenotype is highly variable ranging from apparently unaffected persons to those who are severely retarded. According to several authors the severity of the phenotype typically correlates with the size of the marker. Webb,1 in her review article, suggests that cytogenetic division of inv dup(15) markers into three groups according to size. The majority of patients with a marker equal to or larger than a G group sized chromosome were found to be mentally retarded. Robinson et al argued that the number of copies of the Prader-Willi syndrome/ Angelman syndrome (PWS/AS) region present in the marker may be directly related to the severity of the retardation. To our knowledge, no non-mosaic inv dup(15) carriers without mental retardation have been described, who appeared to have extra copies of the PWS/AS region, as shown by molecular techniques.1

We report a family with inv dup(15) in two generations. The proband, a girl ascertained shortly after birth, was the first child of healthy, non-consanguineous parents. She was born at term but was small for gestational age with borderline microcephaly, bilateral epicanthus, and frontal bossing. Feeding was poor owing to hypotonia. Apart from an unusual head retraction reflex when tapped on the nose, to other abnormality was noted at birth. At the age of 16 months she was not able to sit without support, did not attempt to speak, and had developed seizures. A G group sized inv dup(15) supernumerary marker chromosome was found in all cells ana- lysed. Subsequent fluorescent in situ hybridisation (FISH) analysis (centromeric D15S1 probe and B25E9,16 as well as

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