

## Invited Comment

# Precision in Phenotyping and Genotyping

The report by Moncla et al. [this issue] describing a patient with an occult 4;18 translocation brings up several interesting points which warrant additional discussion. First, these authors point out the clinical similarity of their patient to those of the multigenerational family reported by Rasmussen et al. [1979] and the individual reported by Julia et al. [2002]. The patient of Julia et al. was described by the authors as having Rasmussen syndrome and was later determined by Veltman et al. [2003] to have an 18q terminal deletion of approximately 5 Mb. The relevant point is that this is an example of a clinically defined syndrome resulting from a microdeletion lying within a region associated with a well-known cytogenetically detectable chromosome abnormality.

As techniques improve for screening and detecting smaller and smaller genomic deletions and duplications, clinically defined dominant syndromes will undoubtedly be identified as resulting from microdeletions and microduplications. These hold great potential to help elucidate the sub-phenotypes that comprise the composite phenotypes of the cytogenetically detectable chromosome abnormalities. The case report is a good example of the power of genomic microarray technology to elucidate the genotype of conditions not previously thought to be genomic as well as their importance in piecing together the components of the composite phenotypes associated with larger chromosome abnormalities.

This new technology also holds great potential for creating much cleaner datasets by identifying translocations that were previously occult. In this case and the similar case reported by us [Gunn et al., 2003], the failure of G banding to identify an abnormality coupled with the abnormal FISH indicated that a more complex rearrangement was involved. However, to efficiently sort out the precise nature of the defect, a whole genome approach was required. We had shown previously [Brkanac et al., 1998] by performing 18q telomere FISH that 14% of the cases referred to us with a cytogenetic diagnosis of a terminal 18q deletion actually had more complex rearrangements. The use of high resolution genomic array techniques will increase the power to detect additional rearrangements and, thereby, increase the percentage of cases found to have more complex rearrangements.

In order to determine the role of individual genes on the composite phenotype associated with chromosome abnormalities, precise phenotype and genotype information will be critical. Individuals with rearrangements involving additional chromosome segments, such as the case reported by Moncla et al., need to be identified and eliminated from the analysis. Even when the appearance of such a child is similar to that of a patient with a simple deletion, the contribution of the other genomic segment must be considered. Additionally, it seems unwise to use such a patient to define the phenotype of the simpler deletion. This is a bit like using the definition of a mansion to define a house.

Based on the present case, no conclusion can be drawn about the phenotype of individuals with 18q-subtelomeric deletions

due to the more complex rearrangement. Additionally, of the other cases cited as examples, two [Slavotinek et al., 1999; Rosenberrg et al., 2001] also reported cases with more complex rearrangements and the third [Rio et al., 2002], actually had a 12 Mb deletion that was apparent on re-inspection of the G banding. This is not a case of a subtelomeric microdeletion. Drawing conclusions about the phenotype require inclusion of only those with the simple genotype.

The clinical gestalt provides intuitive guidance of what to look for genotypically, as demonstrated in this case. But gestalt is not phenotype any more than cytogenetic evaluation is genotype. Now that we have sophisticated molecular level genotyping, we need to employ equally sophisticated phenotyping. Only when both are employed with equal precision, will progress be made toward linking specific genes to specific phenotypes.

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