CATCH 22

This volume of the Journal of Medical Genetics includes a series of articles on 22q11 deletions. The acronym CATCH 22, suggested by the Newcastle upon Tyne group, not only helps to remember the features of concern (Cardiac, Abnormal facies, Thyroid hypoplasia, Cleft palate, and Hypocalcaemia) and the 22nd chromosome but also suggests the complexity which exists in 1993 with regard to defining the clinical features and understanding the genetic ramifications of a deletion from a specific area of a specific chromosome.

The history of the DiGeorge syndrome goes back to the mid 1960s when a group of clinical features were recognised to occur together frequently and became described as a specific disorder. The term syndrome is usually reserved for disorders in which all patients have one known cause, but the term 'syndrome' has stuck with everyone's facies, Thymic hypoplasia, cardiac anomalies, and became described as DiGeorge syndrome. With the recent development of molecular probes which allowed for precise areas of particular chromosomes that were different embryonic origins were demonstrated, the DiGeorge critical region (the boundaries of which are still being defined) was used to describe this type of small chromosomal deletion. It is estimated that to be a visible microdeletion something in the range of 4000 kilobases of DNA will have been lost, suggesting several genes will have been lost as well in the process. Interestingly, the clinically recognised deletion syndromes seem to map near the ends of chromosomes or near the centromere. This suggests that they occur in areas having to do with crossing over and raises the question as to whether crossing over is programmed in such a way as to predispose to segmental aneuosomy.

The original description of three different groups of patients now known to be involved with 22q11 deletions may well have occurred because of bias of ascertainment related to the area of interest of the original investigators – DiGeorge (immunological), Shprintzen (clefting), and familial conotruncal (cardiological). Overlap of features between these three groups of patients does exist but causal heterogeneity must exist as well. Using probes and cosmid from the DiGeorge critical region (the boundaries of which are still being defined) to perform DNA dosage analysis and FISH on appropriate patients, 83% of DiGeorge syndrome patients, 68% of Shprintzen syndrome patients, and 29% of sporadic non-syndromic conotruncal patients have been recognised to have deletions of 22q11. Time and lots of work will identify the other aetiologies. Fetal alcohol syndrome, retinoic embryopathy, maternal diabetes mellitus, and 10p deletions are likely candidates for the DiGeorge syndrome.

What fun it is to find that what were thought to be separate syndromes are now merging into one group, CATCH 22, while other patients who were thought to belong to those same previously separated syndromes are being excluded from that catchy acronymous group because they must have different mechanisms.

It would appear that there is a very important gene(s) having to do with conotruncal development of the heart in the 22q11 region. We tend to think that the heart is an organ which has been embryologically patched together from many different areas of the early embryo. The cells of the heart have come from many different embryonic origins and appear to have a 'memory' of their origins
which gives them a unique identity and hence unique abilities to express different genes. Most chromosomal anomalies are associated with cardiac defects of some kind, but this 22q11 deletion has a very specific effect on conotruncal development. Perhaps the collagen-like gene described by Wadlow et al will be the generator of that effect – if not, surely the next few years of the human genome project will uncover the responsible DNA sequence(s). The challenge then will be to figure out how 'it really works' – what the phenotypic-genotypic correlations are, what the control mechanisms are, and how the early embryonic environment orchestrates the interactions of gene products.

Finally a word about what these exciting papers are telling us about the natural history of 22q11 deletions. To family members the really important piece of information is what will happen with time? Are they going to get cancer? Why are some people with the genetic defect so much more severely affected than others? How can affected parents and children have such different problems? What will the children be like when they grow up? The natural history is beginning to emerge, but long term follow up is needed to flesh out the picture. One interesting problem is the relatively high rate of psychiatric problems among those with the deletion, suggesting that the deletion may affect brain function. In the family of Holder et al, quite different organ systems are involved in the mother and child leading the authors to suggest that all unusual families, with CATCH 22 features, even if they appear to have unconnected problems (for instance, congenital heart disease and mental retardation in one family member and immunodeficiency and psychiatric disorder in another), may benefit from molecular testing because the family could be segregating a 22q11 deletion. When the parents of affected children are tested, one quarter of the families show that one of the parents has the same 22q11 deletion as the child. So far germline mosaicism has not been observed.

Interfamilial differences are usually blamed on the differences in the size of the deletion between families, that is, which genes have been lost. However, it seems quite likely that epigenetic modification will be different in different families and thus that ethnic differences could exist as well. Intrafamilial differences (which seem to be very common) will almost surely have a number of different explanations: parental mosaicism, with no mosaicism in the more severely affected child; an unstable or expanding mutation which gets worse with each generation; parent of origin effects such that there is a difference in expression of genes when the deletion is transmitted by mother versus father; complementation, so that the defect is 'filled in' by copying the normal chromosome; environmental effects; modifying genes at separate loci, and others. Continuing careful studies of natural history will lay the ground work for understanding how the loss of these several genes leads to CATCH 22 in the way that it does.

By the time you have read these seven fascinating papers you won't forget the combination of clinical features, nor the challenges they present. CATCH 22 is a wonderful model for what is to come over the next 10 years of human genome work. We are very likely to end up with more questions to answer than when we started and with a more appropriate name, such as a DNA sequence designation. But for now the acronym CATCH 22 will help to focus on this fascinating problem.

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