Medical genetics: advances in brief

Growing interest in overgrowth

T Cole. *Arch Dis Child* 1998;78:200-3.

This annotation addresses the classification of the overgrowth syndromes (OGSs), reviews the molecular genetic basis for overgrowth in Beckwith-Wiedemann (BWS) and Simpson-Golabi-Behmel syndromes (SGBS), and comments on the overlapping clinical features in other overgrowth disorders, for which the molecular basis is unknown at present. Historically OGSs have been classified into two main groups. The first includes those conditions in which overgrowth is a primary phenomenon or major intrinsic component of a malformation syndrome. The London Dysmorphology Database lists 283 syndromes which are candidates for inclusion in this group and examples include Marfan syndrome, Sotos syndrome, BWS, and SGBS. The second group consists of those conditions where overgrowth has taken place as a result of known endocrinological or metabolic disorders. Often the aetiology of the overgrowth is clear, such as, in untreated congenital adrenal hyperplasia, the production of excess 7-hydroxyprogesterone and androgenic steroids results in increased growth from birth and precocious puberty. The author indicates this separation may be too simplistic with the advent of new insights into the genetic basis of OGSs; in the future a more specific system may be necessary. A third separate group are those conditions exhibiting regional or tissue specific overgrowth; they are not discussed in the annotation. Because the more common primary overgrowth disorders share similar features, differentiating between them is often difficult and requires considerable experience. Follow up examination and assessment of bone age may be helpful in establishing a diagnosis. BWS (abdominal wall defects, macroglossia, high birth weight) is a relatively common OGS and has provided many insights into molecular mechanisms in overgrowth in recent years. BWS has been linked to the chromosome region 11p15.5, including insulin-like growth factor II (IGF II). Paternal duplications, maternal translocations, and paternal uniparental disomy of this region all result in BWS, the likely mechanism being overexpression of IGF II. In addition, mutations in the maternal alleles of two proximal genes, p57 and KVQLT1, also result in the BWS phenotype, probably by alteration of IGF II expression. These imprinting effects have been the subject of intense investigation and may provide insights into the pathophysiology of other disorders. SGBS results from mutation in the gene encoding glypican 3. The ligands of this protein cross react with IGF II receptors, which provides some evidence for a "final common pathway" in the abnormal expression of these genes and may explain the similarity in phenotype of BWS and SGBS. In summary, the author points out that while there are clearly well described,

discrete conditions within the OGSs, their relationship to each other is still unknown. Different genetic mechanisms may be at work, for example, somatic mosaicism in Proteus syndrome and autosomal dominant inheritance with variable penetrance in familial macrocephaly. It is possible that some of these disorders are allelic, or result from different genes, but involve similar interactions at the functional protein level.

SARAH SLANEY

Diagnosing Friedreich's ataxia

N Wood. *Arch Dis Child* 1998;78:204-7.

This review provides a succinct summary of the clinical and genetic criteria for diagnosing Friedreich's ataxia (FA), now known to be the most common of the inherited ataxias and affecting approximately 1 in 50 000 people. The clinical features of FA are relatively homogeneous, with the onset of progressive ataxia of gait and limbs before the age of 25 years, absent tendon jerks, dysarthria, and an axonal picture on neurophysiology. The clinical diagnostic criteria were defined in three groups (essential, present in 100% of cases, additional in 66%, and others in less than 50%) by Harding in 1981 and these were used for the inclusion of patients in genetic linkage studies before the identification of the FA gene. It is important to recognise that patients with FA, as well as the ataxia may present with pyramidal tract signs, including muscular weakness in the legs sometimes leading to paralysis and extensor plantar responses. The most significant non-neurological feature of FA is cardiomyopathy. About 65% of patients with FA have ECG changes, most frequently T wave inversion in the inferolateral chest leads. Echocardiogram often shows concentric ventricular hypertrophy. Cardiac arrhythmias may occur although heart failure is usually a late event. Other system involvement in FA includes scoliosis, pes cavus, optic atrophy, deafness, and diabetes mellitus. In the differential diagnosis of FA, it is important to exclude vitamin E deficiency. The gene for FA was linked to 9q13 in 1988 and identified in 1996 by an international collaborative study. The transcript of this gene was called X25 and the predominant mutation was a trinucleotide repeat (GAA) in intron 1. In the vast majority of FA patients studied, there was an expansion in both alleles, although in three cases there was a point mutation in one allele. Although the exact structure of the gene is not known, the protein produced from the X25 transcript is called frataxin and is expressed in the tissues involved in FA. The putative function of frataxin is in mitochondrial iron transport. The identification of the gene has allowed genotype-phenotype correlation studies with two main outcomes. Firstly, it is now clear that a few cases of FA may "escape" the essential diagnostic criteria of 1981 by

retaining tendon reflexes until a late stage in the disease. Secondly, there is a correlation between the size of the expansion and the age at onset of FA. In summary, the molecular genetic advances in FA have been a very valuable contribution to the diagnosis by providing a direct test. However, the clinical criteria for diagnosis still remain very important. It is hoped that further understanding of frataxin may allow the possibility of therapeutic intervention in the future.

SARAH SLANEY

Short GCG expansions in the PABP2 gene cause oculopharyngeal muscular dystrophy

Brais B, Bouchard J-P, Xie Y-G, *et al.* *Nat Genet* 1998;18:2:164-7.

Autosomal dominant oculopharyngeal muscular dystrophy (OPMD) is a late onset disease presenting with progressive dysphagia, ptosis, and proximal limb weakness. Brais *et al* have identified a GCG repeat sequence that encodes part of a polyaniline repeat domain in the poly(A) binding protein 2 gene (PABP2) on chromosome 14q11. An increased number of repeat units from the normal (GCG)₆ to (GCG)₈-(GCG)₁₁, is associated with dominant OPMD in all patients studied, including cases from Europe, America, Armenia, Israel, and Japan. More severe phenotypes were found in cases with compound heterozygosity for the (GCG)₈ and (GCG)₉ alleles, (GCG)₇ being found in about 2% of the French-Canadian population studied. Interestingly, homozygosity for the (GCG)₇ allele leads to recessive OPMD. This is the first description of a short trinucleotide repeat causing a disease in humans. These expansions are different from other trinucleotide repeat expansions in that they are short, meiotically stable, and there is a clear difference between the normal and abnormal alleles. The common allele found in 98% of French Canadians is (GCG)₆, so the addition of just two repeats is sufficient to cause the dominant disease with a single (GCG) expansion being a recessive mutation. The authors suggest that a gain of function of PABP2 may cause the accumulation of nuclear filaments seen in OPMD and that the polyaniline tract plays a role in polymerisation. PABP2 oligomers composed of mutated molecules might accumulate in the nuclei by forming undegradable polyaniline rich macromolecules. The difference between the dominant and recessive inheritance patterns may be because of the rate of accumulation, which in turn depends upon the ratio of mutated and normal molecules and the nature of the mutation. Future studies may provide insight into why certain muscle groups are more affected even though the gene is expressed in all.

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