Medical genetics: advances in brief

Limb defects and chorionic villus sampling: results from an international registry, 1992-94
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Commentary. Limb defects and chorionic villus sampling

Following the reports of limb defects in babies born after chorionic villus sampling (CVS) was carried out during pregnancy, the World Health Organization set up an international registry of cases. Froster and Jackson present the results of the registry for a two-year period from 1992 to 1994. Seventy seven cases of limb defects were noted after CVS in a series of 1388 pregnancies (1/1738). Strict definition criteria were used for inclusion matching those used in a population survey of limb defects from British Columbia in 1993. Abnormalities consistent with recognised genetic syndromes were excluded. The pattern of abnormality was also noted and compared to that in the population study. Overall the incidence of limb defects was lower than in the population study and there were no marked differences in the pattern of abnormality. The CVS group had fewer right sided defects and more limb defects without abnormalities in other organs, but it is suggested that these results occur because of the differing ascertainment of the data. The authors also assessed the frequency of limb defects at CVS procedures at differing gestational ages and could not show an effect of the timing of the procedures (1/1738).

Prevalence and origin of de novo duplications in Charcot-Marie-Tooth disease type 1A: first report of a de novo duplication with a maternal origin

Charcot-Marie-Tooth (CMT), or hereditary motor and sensorial neuropathy, is the commonest inherited peripheral neuropathy, and may be inherited as an autosomal dominant, autosomal recessive, or X linked disorder. CMT1, with severely slowed nerve conduction velocities, is the commonest subtype, CMT1A, in a autosomal dominant, with a locus on 17p11.2 (other loci for CMT1A include 1q21.2-2q5 and Xq11.2-21.1). In the majority of CMT1 cases there is a 1.5 Mb DNA duplication on 17p11.2, and in sporadic cases this duplication has been recognised since the 19th century. In order to ascertain the prevalence of de novo CMT1A duplications, the authors examined 118 duplication positive families. In 10 of these the disease was shown to have arisen as a de novo mutation, representing 8.5% of families. However, this may be an underestimate of the incidence of new mutations because in the authors' cohort the biased sporadic cases are less likely to be diagnosed, and of the families studied were recruited initially because they were suitable for linkage studies. The CMT1A duplication is probably the product of unequal crossing over between parental chromosome 17 homologues during meiosis. Polymorphic markers from within the duplicated region were used to determine the parental origin of the de novo duplication in eight informative families. Seven were of paternal origin, and one of maternal origin, the first report of a de novo duplication with a maternal origin. Recombination fractions for the duplicated region are larger in females than in males, suggesting that oogenesis may have greater protection from misalignment during synopsis. However, a de novo deletion of maternal origin has been reported previously in hereditary neuropathy with liability to pressure palsies (HNPP), a clinically distinct neuropathy in which the 1.5 Mb DNA deletion occurs at the same genetic locus as CMT1A.

Partial deficiency of surfactant protein B in an infant with chronic lung disease

Surfactant protein B (SP-B) is one of the components of pulmonary surfactant, a hydrophobic protein which reduces surface tension at the air–liquid interface within the alveolus. Deficiency of SP-B is a cause of death from respiratory distress syndrome (RDS) in term neonates, and gives the pathological appearances of congenital pulmonary alveolar proteinosis. Treatment for this condition is by supported ventilation or extracorporeal membrane oxygenation (ECMO) and then lung transplantation. Glucocorticoids and artificial surfactant have been of limited use initially in some cases. Surfactant protein B deficiency is inherited in an autosomal recessive fashion, a mutation occurring in the SP-B gene in several affected people have now been identified. The commonest mutation is a frameshift mutation designated 121ins2. Infants homozygous for this form have presented with respiratory distress at birth. In this report, Ballard et al describe a term infant who presented with respiratory distress owing to SP-B deficiency but had a milder course than previously reported infants. He was found to be a compound heterozygote for the 121ins2 mutation and for a different mutation, R236C. He was found to have low levels of expression of SP-B, whereas the 121ins2 homozygotes do not express this protein. The authors conclude that there are some forms of inherited SP-B deficiency which run a milder course, with longer survival (although the long term outlook without transplantation is still not good). Expression of the SP-B gene is under developmental regulation and probably contributes to the development of RDS in premature neonates. RDS is unusual in term babies and its occurrence should prompt investigation for SP-B deficiency, especially in familial cases. In describing this case of partial SP-B deficiency, the question arises as to whether milder mutations in the SP-B gene may give rise to other respiratory problems and it would seem prudent to look for SP-B mutations in all children with unexplained chronic lung diseases. It is also interesting to note that within the family of the child with partial SP-B deficiency there may have been relatives who had suffered from chest problems, one dying at the age of 41 from asthma. Could the discovery of mutations within this gene have even wider implications?

Friedreich's ataxia: autosomal recessive disease caused by an intronic GAA triplet repeat expansion

Friedreich's ataxia (FRDA) is an autosomal-recessive neurodegenerative disorder with a prevalence of 1 in 50,000. Onset of ataxia is typically at puberty and complications may include hypertrophic cardiomyopathy, diabetes mellitus, optic atrophy and sensori-neural deafness. Linkage to a locus on chromosome 9 (q13-q21.1) was established after a long search in 1988 and subsequently narrowed by this international team to a 150 kb internal. The results reported in this paper began with the construction of the cDNA sequence of a candidate gene X25 in which only three heterozygous point mutations were found in five out of 18 affected FRDA subjects. Southern analysis of fragments containing exon 1, however, led to the discovery of an expanded (GAA), triplet repeat tract in intron 1 of this X25 gene. Among 79 FRDA patients, all five with point mutations had heterozygous expansions, 71 had expansions on both chromosomes 9, and only three had heterozygous expansions without a repeat. The identified candidate gene, FXII, is an uncharacterised gene whose length in normal controls was seven to 22 units while the expanded alleles ranged from 200 to 900 repeats. Expanded repeats were transmitted from asymptomatic parents of both sexes, no examples of marked expansion or reversion have been detected.
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