Medical Genetics: Advances in Brief

Cytogenetic versus DNA diagnosis in routine referrals for fragile X syndrome


Diagnosing fragile X syndrome


Wang et al have compared cytogenetic versus molecular testing for fragile X in 525 routine referrals; 510 of these cases were negative by both methods. Hence the comparison of methodology relates to only 15 positive result situations. Of these, 12 were positive by both methods. There was a discrepancy in the remaining three (20% of the positive results). One of the three was a patient with positive cytogenetic analysis, negative for FRAXA by DNA, but DNA confirmed positive FRAXE by DNA. The other two cases were cases who tested positive for FRAXA by DNA but negative cytogenetically. The negative cytogenetic result would not be entirely unexpected in a female heterozygote and a male with an expansion in the premutation range, such as this pair of cases.

This paper is hampered by a shortage of real data, concealed in the inclusion of so much normal data. However, the value of the communication is to provide initial evidence for the rate of discrepancy between the two available options in testing for fragile X. The other important aspect is that 3.4% of cases referred for fragile X testing had a chromosomal aberration. As emphasised by Young in his commentary, routine chromosomal analysis must still be undertaken in children being tested for fragile X. This being the case, the cost effectiveness of undertaking parallel DNA testing for FRAXA needs further consideration. These aspects are of particular importance in the context of screening, which has to date only been targeted at known high risk populations. Awareness, which takes account of practical and ethical considerations in regard of more widespread screening has yet to emerge and further data in a much larger sample of positive results need to be generated before the merits and demerits of the two different methodologies as applied to large populations can be conclusively defined.

W REARDON

The fish odor syndrome: biochemical, familial, and clinical aspects


Sufferers from the fish odor syndrome secrete trimethylamine, which smells of rotting fish in their breath, sweat, urine, and vaginal secretions. One hundred and eighty seven subjects with suspected body malodour were ascertained through a newspaper article and 156 (19 males) had trimethylamine and its N oxide (which is odorous) analysed in a samples collected under normal dietary conditions and after an oral challenge with 600 mg trimethylamine. The syndrome was diagnosed in 11 subjects: the percentage of total trimethylamine excreted as the N-oxide was <55% under normal conditions and <25% after challenge compared to >80% in normal controls. Parents of six subjects had intermediate responses to the oral challenge suggesting that they were heterozygotes, and some affected subjects had an affected sibling, suggesting autosomal recessive inheritance. The condition causes psychosocial problems and the odour may be reduced by adopting a diet low in choline and fish.

A M NORMAN

Hemizygosity at the elastin locus in a developmental disorder, Williams syndrome


Williams syndrome (WS) has always been something of an enigma. Often overdiagnosed because of the rather subtle dysmorphic features, the ‘core’ group of WS patients do have a striking phenotype, which is succinctly summarised in this article. Although usually sporadically there have been sufficient cases of apparent dominant transmission to suggest a genetic aetiology. Previous attempts to identify the causative locus have focused on a variety of associated clinical abnormalities (in retrospect, some of these patients may not have had WS), linkage to calcitonin gene related peptide (because of the hypercalcaemia), and most recently, uniparental disomy. Now it seems that Ewart et al have the answer.

The work described here is the culmination of a series of recent papers describing, first, genetic linkage of dominantly inherited supravalvar aortic stenosis (SVAS) to proximal 7q, and subsequently a chromosome translocation involving 7q11.23 that bisects the elastin gene, in a family with SVAS. The frequent occurrence of SVAS in WS suggested the elastin gene as a candidate locus for WS, and this paper confirms that elastin is completely deleted in WS, whereas more subtle intragenic mutations may occur in isolated SVAS. The working hypothesis is that WS represents a true ‘contiguous gene deletion syndrome’ and that the CNS features are the result of deletion of genes neibouring that for elastin. Yet another dysmorphic syndrome is thus shown to have a genetic basis, and these findings should soon see application in routine molecular diagnostics.

A WILKIE

Wolfram syndrome: a mitochondrial-mediated disorder?


In the beginning there were monogenic diseases obeying mendelian inheritance, at least for the most part. Mitochondrially transmitted diseases came later and the full extent of their subtle phenotypic diversity was unrecognised. Now the phenomenon of ‘mitochondrially mediated’ diseases has to be considered. In this clear and accessible paper, Bu and Rotter briefly outline the range of mitochondrial transmitted diseases and go on to consider diseases which appear to be the result of simultaneous defects in the nuclear and mitochondrial genomes. This two locus model was already proposed by the authors in a large Arab-Israeli deaf pedigree showing maternal inheritance, on the basis of segregation analysis and biochemical studies. A mutation in mtDNA has since been shown, thus substantiating the two locus model. It is not surprising that further candidate diseases for mitochondrial mediated pathophysiology should be sought, even if the two locus interactive model does not seem appropriate. The candidate phenotype should suggest dysfunction of high energy dependent tissues, indicating a mitochondrionally ‘mediated’ pathophysiology. Such a condition is Wolfram (DIDMOAD) syndrome, a well recognised autosomal recessive condition with a known association with parental consanguinity. However, abnormal mitochondrial morpho-

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