MEDICAL GENETICS: ADVANCES IN BRIEF

Cytogenetic versus DNA diagnosis in routine referrals for fragile X syndrome

Wang Q, Green E, Barnicoat A, *et al.* *Lancet* 1993;342:1025-6.

Diagnosing fragile X syndrome

Young ID. *Lancet* 1993;342:1004-5.

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 subsequently confirmed positive FRAXE by DNA. The other two discrepant 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. A consensus 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

Diagnosis of human genetic disease using recombinant DNA. Fourth edition

Copper DN, Schmidtke J. *Hum Genet* 1993;92:211-36.

These authors present what will be their last hard copy update of this useful database. Its major feature is a tabular list of genetic conditions giving disease, McKusick number, gene name code, probe, distance between probe and genetic locus, method of detection, nature of the mutation, and recent references up to and including 1992. Over the two years since the last edition, the number of conditions for which analysis is possible has risen from 300 to 441. The vast majority of identified gene defects remain point mutations and

deletions with only a relatively minor contribution from insertions, duplications, or other gene rearrangements. Despite the tremendous progress in identifying the specific cause of many of the major genetic diseases, there is a growing number of conditions which can be approached only through linkage analysis (113 from the current list). This series has fulfilled its aim in providing genetic counselors, clinical geneticists and others with a quick reference to relevant publications and thereby to groups working on a specific disease; for future advances we are referred to the electronics of online *Mendelian Inheritance in Man* available through all good Human Genome Database terminals.

J C K BARBER

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

Ayesh R, Mitchell SC, Zhang A, Smith RL. *BMJ* 1993;307:655-7.

Sufferers from the fish odour 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 odourless) analysed in urine 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 sib, 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

Wolfram syndrome: a mitochondrial-mediated disorder?

Bu X, Rotter JI. *Lancet* 1993;342:598-600.

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 subtleties probably remains unappreciated. 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 mitochondrially 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 mtrRNA has since been shown, thus substantiating the two locus model. It is not surprising that further candidate diseases for mitochondrially 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 mitochondrially '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 morphology and biochemistry have been observed in the condition, as has a mitochondrial deletion of mtDNA, in a single case. The authors submit that Wolfram syndrome is a genetically heterogeneous condition which may be caused by both mitochondrial and nuclear mutations mediating a disturbance in mitochondrial function which underlies the recognised phenotype.

W REARDON

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

Ewart AK, Morris CA, Atkinson D, *et al.* *Nature Genet* 1993;5:11-16.

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 sporadic, 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 chromosomal 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 supra-valvular 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 intra-genic 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 neighbouring 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.

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