

MEDICAL GENETICS: ADVANCES IN BRIEF

Parental origin and germline mosaicism of deletions and duplications of the dystrophin gene: a European study

van Essen J, Abbs S, Baiget M, *et al.* *Hum Genet* 1992;88:249-57.

One third of all cases of Duchenne muscular dystrophy (DMD) are new mutations; however it has been shown in some cases that a new mutation has not occurred as a single gamete but as a germline mosaic, thus further complicating risk calculations. This report provides evidence that germline mosaicism is far from rare. Twelve out of 52 cases of new DMD mutations, consisting of partial gene duplications or deletions, were found to involve maternal germline mosaicism. The study excluded the approximately 25% of cases which are probably caused by point mutations or very small deletions in the dystrophin gene, and the authors note that the risk of mosaicism for these types of mutation may be different. The study also shows no significant deviation from a 1:1 ratio of male to female origin of partial gene deletions. The authors also point out that haemophilia A studies suggest that point mutations arise preferentially in males. In conclusion, this study highlights the possibility that germline mosaicism may be a more important factor than has previously been thought in genetic disease.

D O ROBINSON

Levels of naturally occurring DNA polymorphism correlate with recombination rates in *D melanogaster*

Begun DJ, Aquadro CF. *Nature* 1992;356:519-20.

In the rush to sequence individual genes, there is a tendency for the unifying principles of genome design (if there are any) to be forgotten. Why do linear chromosomes show regular variations in nucleotide composition, gene density, repeat sequence content, and many other properties, and what are the causes? The various genome projects will generate the data necessary to address these 'global' issues. This paper is an early attempt to examine one such problem, the variation in amount of naturally occurring DNA polymorphism in different parts of the genome. The authors collated data for the fruitfly *Drosophila melanogaster*, and found that local levels of nucleotide diversity correlated with the local recombination rate. There was no corresponding relationship between sequence divergence with a closely related species, *D simulans*, and the local recombination rate, excluding a direct effect of recombination on mutation rate. The authors interpret their findings in terms of the 'hitch-hiking' of DNA flanking hypothetical advantageous mutations that have become fixed in the population. The lower the recombination rate, the wider the zone of linkage disequilibrium around the mutation, hence the lower the level of polymorphism. These are pre-

liminary but interesting data, and in time a more rigorous analysis will be possible in a variety of species including the human.

ANDREW WILKIE

Characteristics and prognostic implications of myosin missense mutations in familial hypertrophic cardiomyopathy

Watkins H, Rosenzweig A, Hwang D, *et al.* *N Engl J Med* 1992;326:1108-14.

Autosomal dominant hypertrophic cardiomyopathy (HOCM) is characterised by variable myocardial hypertrophy and symptoms such as effort pain, dyspnoea, syncope, and sudden death. Linkage has been established between HOCM and markers on 14q, and genes encoding α and β isoforms of cardiac myosin heavy chains have been mapped in tandem to the same region, making them candidate genes for HOCM. In 1990 Geisterfer-Lowrance *et al* found a β cardiac myosin heavy chain gene missense mutation in a HOCM family. Watkins *et al* have developed a ribonuclease protection assay which they used to screen β cardiac myosin heavy chain genes of probands from 25 unrelated HOCM families. Seven mutations were identified in 12 of the 25 families and nucleotide sequencing showed these were all missense mutations (that is, single amino acid substitutions) clustered in the head and head-rod junction regions of the molecule. Six mutations changed the charge of the amino acid. In these families mean age at death was 33 years, whereas in those with the neutral mutation survival was nearly normal. Different missense mutations can now be identified in the β cardiac myosin heavy chain gene in approximately half of HOCM families, allowing definite diagnosis in members of such families and suggesting better estimation of prognosis in future.

ANDREW NORMAN

Girls with fragile X syndrome: physical and neurocognitive status and outcome

Hagerman RJ, Jackson C, Amiri K, Cronister Silverman A, O'Connor R, Sobesky W. *Pediatrics* 1992;89:395-400.

This paper uses physical examination, behavioural assessment, and intelligence testing to compare 32 girls (1 to 18 years of age) who showed the fragile X chromosome on cytogenetic testing with 19 of their sisters who did not. Only three of the FRAX positive girls in the study were probands; the remaining girls were tested after the diagnosis was made in a male relative. There were no significant differences between the groups in height, weight, or head circumference. However, there were highly significant differences in the mean IQ score between the FRAX negative (109) and FRAX positive (80) girls; 25% of the FRAX girls were functioning in the mentally retarded range and 28% in the

borderline range. In the FRAX girls with learning disabilities, mathematics was the weakest academic area. The most distinguishing physical feature in the FRAX girls was prominent ears. Hand biting and hand flapping were observed in about a quarter of the FRAX girls. Other common features in the FRAX girls were shyness, poor eye contact, and attention deficit hyperactivity disorder (DSM-III-R criteria). Interestingly, the degree of cognitive defect in the FRAX girls did not correlate with percent fragility. The authors recommend cytogenetic testing of female relatives of a male with FRAX as this may lead to the early identification and treatment of learning and/or behaviour difficulties.

DAVID FITZPATRICK

Attitudes toward presymptomatic testing and prenatal diagnosis for adrenoleukodystrophy among affected families

Costakos D, Abramson RK, Edwards JG, Rizzo WB, Best RG. *Am J Med Genet* 1991;41:295-300.

This paper reports questionnaire responses of 136 subjects (18.4% affected, 72.8% first degree relatives) with a family history of an X linked disorder. The clinical spectrum of adrenoleukodystrophy ranges from rapidly fatal neurological degeneration to asymptomatic 'gene carriage' in most females and some males. Respondents were asked about their attitudes to prenatal and presymptomatic diagnosis under conditions of no therapy and a 'hypothetical' therapy. The following results are highlighted. Unaffected subjects were more likely to seek presymptomatic than prenatal testing, but availability of therapy made little difference to the 'predicted' uptake of either test, despite maximising intervention being the main motivation for these requests; 55 to 59% would terminate an affected male and 13 to 14% a carrier female. This compared to 35 to 43% of 'affecteds' who would terminate an affected male. The reason for termination of carrier females was to alleviate future suffering or transmission. The authors suggest "the value of prenatal testing needs to be explored", as many subjects would not terminate an affected fetus. More striking was that 95 to 100% of all responders would request carrier testing for daughters. The results are obviously hypothetical, and in practice, as in Huntington's disease, the response may be different. However the results question many principles of genetic counselling, such as the freedom of choice for possible carriers of X linked disorders and the role of presymptomatic testing, in minors, for conditions without therapy. Are geneticists out of touch with reality? Are families in need of further counselling on the genetics, benefits, and consequences of their decisions? Perhaps the answer lies somewhere in between.

T R P COLE



Medical genetics: advances in brief: Girls with fragile X syndrome: physical and neurocognitive status and outcome

David Fitzpatrick

J Med Genet 1992 29: 598
doi: 10.1136/jmg.29.8.598-c

Updated information and services can be found at:
<http://jmg.bmj.com/content/29/8/598.4.citation>

Email alerting service

These include:

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
<http://group.bmj.com/group/rights-licensing/permissions>

To order reprints go to:
<http://journals.bmj.com/cgi/reprintform>

To subscribe to BMJ go to:
<http://group.bmj.com/subscribe/>