Medical genetics: advances in brief

Population genetics of BRCA1 and BRCA2

Most of the May 1997 edition of the American Journal of Human Genetics is devoted to a series of eight original articles about the population genetics of inherited variation in BRCA1 and BRCA2. Both genes have undergone multiple mutations, the resultant alleles have migrated with the people in which they occur, and disease associated mutations have persisted because they generally have little impact on reproductive fitness. The proportion of high risk families with BRCA1 or ovarian cancer attributed to BRCA1 mutations varies considerably, being highest in Russia (79%), with Israel (47%) and Italy (29%) following. Two alleles are common in Russia, and one of these (5382insC) is also the commonest in Europeans. The other common Russian mutation (4153delA) has not been detected elsewhere, however. In contrast, nearly all BRCA1 mutations in Italian families are unique. A total of 20-25% of high risk families in Britain, France, Scandinavia, and Hungary have BRCA1 mutations, and everywhere BRCA1 mutations are more common than BRCA2 mutations. Inherited BRCA1 mutations explain <20% of high risk families in Holland, Belgium, Germany, Norway, and Japan. Recent data confirm that BRCA2 mutations are more common than BRCA1 mutations in families with male breast cancer, and they account for 19% of familial male breast cancer in the USA. The difference in frequency of BRCA1 and BRCA2 mutations is examined, and the former appear to be 1.5-2 times more common than the latter (except in Iceland). The lower prevalence of BRCA2 mutations could be accounted for by the existence of fewer mutations, lower penetrance, or later age of onset of BRCA2 breast cancer. The lifetime risks of breast cancer associated with the two genes are approximately equal, but the age of onset is later in BRCA2 mutation carriers. The presence of specific mutations in such varying proportions in different populations reflects founder effects, population drifts and specific waves of migration (the British and the French populations share the most alleles). The age of some of the mutations can now be estimated. For example, the 185delAG mutation is likely to be >2000 years old, and data collected about the 5382insC mutation suggest that it has a Baltic origin, during the Medieval period, about 38 generations ago. The 185delAG BRCA1 mutation occurs with a similar frequency in Iraqi/Iranian and Ashkenazi Jewish families, yet breast and ovarian cancer ratios are considerably higher in the Jewish group. Further studies of these two groups could indicate other genetic, environmental, and possibly even cultural contributors to the development of malignancy.

FRANCES FLINTER

Phenotypic variability in Friedrich ataxia: role of the associated GAA triplet repeat expansion

In the short period since cloning of the Friedrich ataxia (FA) gene frataxin, many questions have been answered about FA and related conditions. Other intriguing questions remain. This paper reports genotype-phenotype correlations in 100 patients with strictly defined FA, 44 patients with Acadian FA (an FA variant characterised by a milder clinical course and rarity of cardiac involvement), eight cases with late onset FA (LOFA), and six cases with FA and retained reflexes (FARR). All patients, except three with typical FA, had two copies of the FA associated GAA triplet repeat expansion, indicating that the clinical spectrum of FA is wider than has been previously defined. Larger expansion size was relatively weakly correlated with an earlier age of onset, faster disease course, and the presence of FA associated complications such as cardiomyopathy, optic atrophy, and hearing loss. The authors showed mitotic instability of expansion size, giving rise to somatic mosaicism. This might explain the weakness of the observed correlation, since expansion size was routinely measured in lymphocytes. Surprisingly, mean GAA expansion size did not differ between patients with typical FA, Acadian FA, and FARR, although patients with LOFA had significantly smaller expansion sizes than the other three groups. How can the distinct clinical differences between the three groups with similar mean expansion size be explained? Modifying gene effects are unlikely and the authors exclude the hypothesis that polymorphic variation in the frataxin gene might be responsible. Alternative possibilities include differences in as yet unknown frataxin motor/regulatory regions, or differences in the expanded repeat sequence, such as the interrupted repeats which have been described in some other conditions. The answer to this particular question may elucidate some of the basic molecular pathological mechanisms of the disease.

EVAN REID

Mutations in the myosin VI A gene cause non-syndromic recessive deafness

The autosomal recessive isolated deafness, DFNB1, and the Usher 1B syndrome are allelic defects of the myosin-VI A gene

The human Usher syndrome type 1B and the mouse shaker 1 phenotypes are forms of syndromic deafness resulting from mutations in the myosin VI A (MYO7A) gene on human chromosome 11q13. Further to this, a family with non-syndromic deafness, DFNB2, linked to chromosome 11q13 has been reported prompting Liu et al and Weil et al to analyse the MYO7A gene for mutations in non-syndromic deafness patients. Liu et al found three mutations in exons 4, 7, and 28 in two out of eight patients of Sichuan Chinese origin, one exhibiting compound heterozygosity. Weil et al describe a Tunisian family with an exon 15 mutation causing an amino acid change and also affecting splicing. The mutations are distinct from those found in Usher syndrome patients, thus presenting another example of different mutations in a single gene causing different phenotypes. Hereditary deafness affects about 1 in 2000 births, about 70% being autosomal recessive and non-syndromic. Estimates of the number of genes involved range from 30 to 100, but none had been cloned until connexin 26 was reported earlier this year. The identification of a second gene responsible for non-syndromic deafness is therefore of significance. Interestingly an autosomal dominant form of deafness (DFNA11) has recently also been assigned to chromosome 11q13 and Usher syndrome (USH1D) has been assigned to the same region on chromosome 10q as non-syndromic deafness (DFNB12).

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J Med Genet 1997 34: 957
doi: 10.1136/jmg.34.11.957-a

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