Male infertility as the only presenting sign of cystic fibrosis when homozygous for the mild mutation R117H

Since the identification of the cystic fibrosis gene (CFTR),1 more than 265 mutations have been described (CF Genetic Analysis Consortium, 1992). The most common disease causing mutation, ∆F508, occurs in approximately 70% of CF chromosomes and causes moderate to severe disease,2 with variable prevalence in populations of different ethnicities. Among the numerous rare mutations, R117H (a G to A transition at nucleotide 482) produces a missense amino acid substitution (arginine to histidine) in the first transmembrane domain of CFTR. It has only been reported in the heterozygous state, usually with ∆F508 occurring in the other CFTR gene; the compound heterozygotes are mildly affected.3

We have studied a 30 year old French male with sterility owing to congenital bilateral absence of the vas deferens (CBVAD). He is homozygous for the R117H CFTR mutation, which was detected by DGGE screening and characterised by direct sequencing of PCR amplified DNA from 4 using the Sequenase USB kit. The subject has no respiratory or pancreatic involvement and has a normal sweat electrolyte value. His parents are not consanguineous and there are no other cases of CBVAD or CF in his family.

Based on the primary finding of a higher rate of AF508 heterozygosity in infertile males,4 it has recently been suggested that isolated CBVAD may represent a primary genitourinary syndrome.5 Attempts to detect other known mutations and on investigation have mild CF with normal or raised sweat electrolytes and subclinical lung disease. However, this is the first report of homozygosity for R117H in a patient presenting with CBVAD.6 It results in a clinical presentation of CBVAD cystic fibrosis completely devoid of the classic symptoms of CF.

Among the reported cases of rare alleles of CFTR found in compound heterozygotes, the R117H mutation seems to be highly represented. It should be systematically screened for in all patients with CBVAD, as it may represent a common CF mutation causing very mild disease, with infertility as the only clinical presentation.


Autozygosity mapping, complex consanguinity, and autosomal recessive disorders

Mapping of autosomal recessive disorders is more problematical than for autosomal dominant or X-linked disorders. Many autosomal recessive disorders are individually rare, making it difficult to collect sufficient numbers unless this is done on an international collaborative basis. In addition, in most parts of the world family sizes are limited, with it being uncommon for families to have more than three to four children and therefore making it unusual for there to be more than two affected sibs within a sibship.

Mathematical analysis of the power of nuclear families with autosomal recessive disorders has shown that in order to have a high likelihood of showing linkage in gene mapping studies, inordinate numbers of families, preferably with multiple affected sibs, are required as described by Wong et al.1

Use of homogeneity mapping with affected offspring of first cousins has been advocated as far fewer families are needed to have the same likelihood of showing linkage, an approach originally suggested by Smith and more recently by Lander and Botstein.6 Morton1 has reminded us that this approach is more correctly called autozygosity mapping.

An estimate of the lod score under complete linkage to determine rapidly the potential usefulness of various consanguinous pedigrees for a single affected offspring can be derived by the use of the formula:

\[ \text{Eld} = \log_{10} \left[ \frac{q^2 f_r (1 - 4 f_s a^2)}{4 f_s (1 - f_s) (1 + 4 f_s a^2)} \right] \]

![Figure 1](http://example.com/figure1.png)

**Figure 1** Effect on the lod score under complete linkage (0-0) of the disease allele (q) and marker allele (r) for an affected offspring of first cousins.

The effect of variation in the disease allele frequency (q), the marker allele frequency (r) will affect the power of this approach in individual pedigrees (fig 1).

Detailed enquiry into the family history of affected offspring of ostensibly first cousin matings from ethnic groups in which consanguineous marriage is common usually shows the consanguinity to be much more complex than at first enquiry. In addition, ostensibly unrelated affected subjects from that population are often found to be related but in different sibships within the same pedigrees.7 Efficient use of linkage information from such complex consanguineous families requires conventional linkage analysis.8

When pooling linkage information from different complex consanguineous families, the possibility of genetic heterogeneity must be considered. It is likely, however, that a limited number of genes will be responsible for a particular autosomal recessive disorder in an individually isolated population in which complex consanguinity is common.9

In populations in which consanguineous marriage is common, it has often been the usual pattern of marriage for a number of generations. It has been argued that long term inbreeding will reduce the power of this approach.10 Two factors will affect the usefulness of this approach in this situation. Prior or remote long term inbreeding (FP) combines with the ‘bottleneck’ of close inbreeding (Ff) for a particular pedigree as PF + (1 - FF), which essentially reduces to FP + Ff. The effect of substituting this in the above formula is to increase the apparent power of this approach.

Another consequence of long term prior inbreeding is to ‘redistribute’ the disease and marker alleles with a reduction in the proportion of heterozygotes and increase the proportion of the two homozygotes in the population.11 The effect of this can be...
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