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 250 mutations have been described (CF Analysis Genetic Consortium, 1992). The most common disease causing mutation, ΔF508, occurs in approximately 70% of CF chromosomes and causes moderate to severe disease,2 with variable prevalence in populations of different ethnic origin.3 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 ΔF508 occurring in the other CFTR gene; the compound heterozygotes are mildly affected.4

We have studied a 30 year old French male with sterility owing to congenital bilateral absence of the vas deferens (CBAVD). 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 CBAVD or CF in his family.

Based on the primary finding of a higher rate of AF508 heterozygosity in infertile males,1 it has recently been suggested that isolated CBAVD might represent a primary genetic form of CF.5 Several males presenting with infertility have been found to be heterozygotes for AF508 and 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. It results in a clinical presentation of CBAVD cystic fibrosis completely devoid of the classical 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 CBAVD, as it may represent a common CF mutation causing very mild, if not infertility as the only clinical presentation.

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Limb/pelvis/uterus-hypoplasia/aplasia syndrome

I read with great interest the recent papers of Garag et al.1 from Kuwait and Camera et al.2 from Italy reporting additional patients similar to those we described in 1985 as a new autosomal recessive syndrome.3 This brings the number of cases of limb/pelvis-hypoplasia/aplasia syndrome (LPHAS) to nine (five female and four male).

This total includes one case from Brazil1 and the three sibs from Israel.2 Among these five sibships, the three sets of parents were first cousins or double first cousins.1,2 I was delighted to see these reports because they provided further evidence (T. R. Garag, personal communication) that the 'private' syndrome does not exist. Often many 'new' syndromes are referred to as 'private' particularly if they are first described in the third world. So called 'private' syndromes may in fact be previously unrecognised or unreported and yet be 'relatively common' in certain populations. The absence of known parental consanguinity in two families with LPHAS could imply that the gene frequency in the relevant population may not be very low.

I wish to report further data on one of the original patients who were re- evaluated at the age of 18 (in 1990) because of absent menarche. Her further secondary sexual characteristics had developed by the age of 15 years. She and her parents were not particularly anxious about her fertility because of her severe handicap. They wanted to be sure that there were no life threatening consequences of the disease. Her FSH, LH, and prolactin levels were normal. Ultrasonography showed apparently normal ovaries and absent uterus. This was confirmed by another ultrasonographer. It was not possible to perform pelvic examinations because of virginity. Laparoscopic examination was declined.

These data indicate normal gonadal development in a female and support the finding of Garag et al of uterus hypoplasia/aplasia. Such findings in two out of five reported females suggest that it is not fortuitous and is probably a variable manifestation of LPHAS that should be considered in future cases.

From a nosological perspective, LPHAS is an appropriate nosological designation for these cases. However, in the light of the müllerian hypoplasia/aplasia, the term limb/pelvis/uterus-hypoplasia/aplasia may be a more precise name. Three of the eight reports have used the respective authors' names for syndrome identification.1,3 To avoid confusion, I suggest the use of the name of the first reporting author followed by a brief description of the disorder. To avoid the expansion in the number of new reported syndromes, this policy would make for easier cataloguing of genetic disorders.

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The frequencies of four different β thalassaemia alleles in a Brazilian population.

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Type</th>
<th>No of chromosomes</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) CD 39 (C-T)</td>
<td>β</td>
<td>45</td>
<td>64.3</td>
</tr>
<tr>
<td>(2) IVS-110 (G-A)</td>
<td>β′</td>
<td>14</td>
<td>20.0</td>
</tr>
<tr>
<td>(3) IVS-1 6 (T-C)</td>
<td>β</td>
<td>5</td>
<td>7.1</td>
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<tr>
<td>(4) IVS-1 1 (G-A)</td>
<td>β′</td>
<td>4</td>
<td>5.7</td>
</tr>
<tr>
<td>(5) Unknown</td>
<td></td>
<td>2</td>
<td>2.9</td>
</tr>
</tbody>
</table>

The effect of variation in the disease allele frequency (q), the marker allele frequency (r) and disease allele frequency q = 0.02.

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 or 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 homozygosity 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 Smith2 and more recently by Lander and Botstein3. 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 consanguineous pedigrees for a single affected offspring can be derived by the use of the formula:

\[ \text{Eld} = \log \left[ \frac{qF^2 + (1 - q)^2}{(qF + (1-q)F)^2} \right] \]

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.

Figure 2 Effect of various prior inbreeding coefficients of the population (Fp) at q=0.02 on the lod score for a single affected offspring of first cousins for marker allele frequency (r) and disease allele frequency q = 0.02.