EDITORIAL

What Means Familial?

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The paper by Shirani et al[1] illustrates some of the problems involved in interpreting the pedigrees of "familial" disorders. Most patients with complex regional pain syndrome (CRPS) report no affected relatives. A substantial minority reports one or more affected relatives. Does this mean that there is a "sporadic", i.e. non-recurrent type, and a "familial", presumably genetic, recurrent, type? Well some clearly genetic disorders often occur only once in the family (viz. autosomal recessive disorders), so maybe the "sporadic" group comprises just those "familial" families in which, for one reason or another, no affected relatives have occurred, and there is no sporadic non-recurrent group. If there are indeed two groups – sporadic (non-recurrent) and familial - trying to separate them is complicated by the fact that the "sporadic" group will include some recurrent families with only one affected member. This leads to nomenclatural confusion, some using "sporadic" to mean non-recurrent, and others to mean simply "only one affected".

Shirani et al[1] report four families with more than one affected member, and have suggested several explanations, of varying degrees of plausibility, for the familial patterns they show – recurrence in sibs in two families, and in parent and child in the other two. To a geneticist, a "familial" condition is one that occurs in relatives more often than in the general population. Others, including Shirani et al[1], appear to use the term more loosely, simply to mean occurring more than once in a particular family. Nevertheless, they seem to assume that there are, indeed two types, "familial" and "sporadic".

Disorders can be familial for various reasons, including:

- A familial environmental factor, such as a parasite, or a nutritional deficiency. The rarity of CRPS, and its occurrence both intergenerationally and in sibships, makes this a highly unlikely explanation.
- A single gene disorder, i.e. one following a Mendelian pattern of inheritance. In this case one could evoke an autosomal dominant gene, albeit with considerably reduced penetrance, considering the proportion of obligate carriers. Families 1 and 3 could also result from an autosomal recessive gene, but the existence of two different mutant genes for this rare condition seems very unlikely.
- Mitochondrial inheritance. There is nothing in the reported families to suggest mitochondrial inheritance, though the numbers are too small to rule it out.
- Multifactorial threshold (MFT) inheritance: the disorder is caused by several genes, interacting with each other and with environmental factors. There are many genes, of small effect, that increase liability. Each predisposing gene contributes a small amount to the liability, and persons who inherit enough of them reach the threshold and develop the disorder[2].

Anyone who has worked with such conditions, e.g. pyloric stenosis, cleft lip, neural tube defects, will have seen families where the condition occurs in sibs, or in parent and child, or even in three generations, without conforming to a Mendelian pattern. And most patients will not have any affected relatives, just as in the case of CRPS. By Occam's razor one concludes that the MFT model is by far the best explanation for the familial occurrences reported by Shirani et al[1].

The MFT model has several statistical properties that may help to identify it[2,3]. There may be enough families in the literature to provide material in which to look for such properties.

For example:

- The sib recurrence rate is roughly the square root of the population frequency. But one would need a reasonably accurate estimate of the population frequency.
- The recurrence rate is higher in sibs of probands with more severe disease. Shirani et al[1] point to some evidence for this if early onset and multiple affected sites are a manifestation of severity.
- The sex ratio is closer to 1 in multiplex (more than one affected) than in simplex families.

If CRPS families show these properties there would be less reason to try to distinguish a familial from a sporadic form, or to do a DNA search since, in a multifactorial model, the predisposing genes would be of small effect, and hard to map.

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References

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