Heterogeneity in Genetic Conditions

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The use of the term genetic heterogeneity in connection with type 2 neurofibromatosis in this edition [1] reflects the increasing clinical importance of precise genetic diagnosis. At its simplest genetic heterogeneity implies clinical similarity produced by different genes. In practice a number of different genetic mechanisms may underlie this potent source of diagnostic and counselling confusion.

LOCUS HETEROGENEITY

This term is applied when an apparently single clinical disease is caused by either of two or more separately located genes. Perhaps the best example is tuberous sclerosis, which may result from mutation in at least two different genes. In 1987 Fryer et al. [2] showed linkage to the long arm of chromosome 9 in several families. However, many subsequent reports were contradictory, although linkage to 9q was confirmed in some families [3]. Other families show linkage to 11q [4]. A third possible locus for tuberous sclerosis on chromosome 12 has been proposed [5].

Predisposition to a common cancer may also demonstrate locus heterogeneity. Breast cancer may be part of several different syndromes including the Li Fraumeni syndrome involving the p53 gene on 17p [6], Lynch type II syndrome [7] and breast/ovarian cancer predisposition [8]. However, as the linkage of site specific breast cancer predisposition to 17q [8] makes up only about 40 per cent of familial breast cancers, it is likely several other loci exist.

INTRA-LOCUS HETEROGENEITY

Different mutations or deletions within a single gene may cause very different phenotypes. An example of this is the dystrophin gene on the X chromosome, different mutations of which cause Becker and Duchenne muscular dystrophy [10]. In this case the disease breeds true in the family, the age at onset and disease course being characteristic for the specific mutation involved. A more recent discovery has been that different mutations of the neurofibromatosis type 1 NF1 gene cause clinically distinctive variations of NF1 such as Watson syndrome and Noonan NF1 phenotype [11-13]. Although café-au-lait patches are present in Watson syndrome, skin neurofibromas are usually absent and there is often right ventricular outflow obstruction. Noonan NF1 phenotype describes individuals and families with the typical dysmorphic features of Noonan syndrome, such as short stature, hypertelorism, down-slanting palpebral fissures and cardiac defects along with the full range of complications of neurofibromatosis type 1.
INTRA-FAMILY HETEROGENEITY

This refers to the situation where the disease manifestations and course are very variable even within a family with the same inherited gene defect. Although there is relatively good correlation between identical twins with neurofibromatosis type 1, this concordance diminishes sharply in siblings and there is virtually no correlation between the number of café-au-lait spots and cutaneous neurofibromas in second-degree relatives, who none the less share the same NF1 mutation [14]. It has been proposed that this variability is due to the action of two or more modifying genes; these will be identical in monozygotic twins, but each of these modifying genes would have only a 25 per cent chance of being present in second-degree relatives [14].

ANTICIPATION

This refers to the severity of the disease increasing with successive generations. Until recently it was believed that anticipation resulted from bias in reporting and earlier diagnosis in more recent generations. However, in myotonic dystrophy, the clinical impression of anticipation [15] is reflected at the molecular level by progressive alteration of the gene between generations [16].

GENOMIC IMPRINTING

Perhaps the best example of this is the finding of two completely separate clinical conditions, Angelman and Prader-Willi syndromes, depending on whether a deletion on chromosome 15 is inherited from the mother or the father. If the deletion is maternally inherited Angelman syndrome results and if paternally inherited Prader-Willi syndrome results [17, 18]. There is widespread clinical and molecular evidence of the validity of imprinting [19] and it is likely that some mechanism, such as differential methylation, which is sex-specific at the gamete level, causes this variation in gene expression.

INTER-FAMILY HETEROGENEITY

This term applies to the situation reported in this issue in type 2 neurofibromatosis [1]. Between families there is great variation in the disease phenotype, but the disease within families is remarkably constant. A similar dominantly inherited disorder, von Hippel Lindau disease, has been noted to show similar inter-family heterogeneity. Several authors have noted clustering of features within families [20, 21]. As there is tight linkage of von Hippel Lindau to chromosome 3 [22] and of neurofibromatosis to type 2 chromosome 22 [23] it is likely the heterogeneity in these diseases is due to intra-locus differences rather than their being due to two separate but closely linked genes.

CONCLUSION

There is a need for clinical diagnostic precision in both counselling and molecular studies. Counselling in families with a history of neurofibromatosis type 2, for example, should not necessarily reflect the disease variation observed in all patients, but should be influenced mainly by that already observed in the family. Accurate clinical observation will also allow meaningful phenotype/genotype studies once the gene is cloned and specific molecular pathology is identified. The aim is to be able to predict the disease course and response to
treatment by appropriate molecular studies in both patients and their relatives and perhaps even to design new and specific genetic treatments.

REFERENCES