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SCIENTIFIC COMMENTARY

Somatic mosaicism as a basic epileptogenic mechanism?

In this issue of *Brain*, Professor Ingrid Scheffer and colleagues describe four unrelated families with epilepsy in females, in which the disease is transmitted through virtually unaffected obligate carrier males. Based on this segregation pattern and the clinical phenotype, they made the diagnosis of epilepsy and mental retardation limited to females (EFMR), and linkage analysis confirmed a locus on Xq22. The value of this study is the further phenotypic delineation of EFMR and the confirmation of the existence of this peculiar inverse pattern of X-linked inheritance—heterozygous females affected, hemizygous males virtually unaffected. The study also provides challenging new views on pathogenic mechanisms possibly involved in a number of more common forms of epilepsy.

EFMR was initially recognized and described by Juberg and Hellman (1971). Subsequent studies on the same extended family confirmed its unique pattern of inheritance (Fabisiak and Erickson, 1990). X-linkage was supported by mapping of the locus to Xq22 in a 25 cM interval between the markers DXS1222 and DXS6804 (Ryan *et al*., 1997). Linkage analysis in the four newly reported families confirmed the map position of the putative disease gene to Xq22, without further narrowing of the linked region (Scheffer *et al*., 2008). Array comparative genome hybridization (CGH) with an estimated resolution of 150 kb, and sequence analysis of four from about 150 positional candidate genes with known expression in brain failed to identify the genetic defect in these four new families. Importantly, Scheffer *et al*. found X inactivation patterns to be normal, as in the original family (Ryan *et al*., 1997). Thus, the primary genetic defect still waits to be resolved.

The clinical phenotype of EFMR in females is highly variable. This can be explained by random X inactivation, as in many other X-linked diseases with expression in carrier females, and is dependent on the proportion and distribution of cells that have the X chromosome carrying the inactivated normal allele versus the abnormal allele. However, in hemizygous males the single disease allele is apparently not sufficient for clinical expression. A number of hypotheses have been put forward in order to explain this phenomenon:

- A putative functional homologue of the disease gene on the Y chromosome is protective in males, and not affected by random X inactivation (Page *et al*., 1984).
- Regional interference of the mutation with the X inactivation process downstream of *XIST* results in functional disomy of one or more X-linked genes, resembling the lack of inactivation of the small ring X chromosomes next to a normal active X chromosome with 46,XX,r(X) associated with severe handicap or variant Rett syndrome (Migeon *et al*., 1994; Rosenberg *et al*., 2001).
- Dependence of the female brain, and not the male brain, on the presence of an active copy of the EFMR gene (Ryan *et al*., 1997).
- Metabolic interference between the two allelic protein variants or cellular interference between two cell populations expressing one or the other allelic protein (Johnson, 1980; Rollnick *et al*., 1981).

The last hypothesis found recent support in another disorder with a similar pattern of X-linked inheritance, including an inverse expression pattern in heterozygous females and hemizygous males, craniofrontonasal dysplasia (CFNS) (Cohen, 1979). CFNS is caused by mutations in the *EFNB1* gene (Xq12) that encodes for the ligand ephrin-B1 (Wieland *et al*., 2004). Ephrin-B1 plays an important role in cell–cell interactions through regulation of gap junction communication involving connexin-43 (Davy *et al*., 2006). Heterozygosity in a mouse model ($Efnb^{+/-}$) is characterized by mosaic *Efnb1* expression leading to inhibition of gap junction communication between cells and cell sorting. This is supposed to explain the abnormal patterning during embryonic and fetal development observed in this mouse model for human CFNS (Davy *et al*., 2006).

It is noteworthy that, in addition to areas with more normal architecture, a surgical frontal lobe specimen obtained from a female EFMR patient showed microscopically cortical dysplasia, abnormal neurons in the white matter and abnormal morphology of individual cortical neurons (Ryan *et al*., 1997). This suggests that tissue patterning is also affected in EFMR. Whether cellular interference between two populations of cells plays a role in EFMR can only be confirmed or refuted through identification of the gene and characterization of the genetic mechanisms involved. It is tempting to assume that random patchy distribution of two cell populations within the brain, each with a functionally different genetic make-up, may cause maldevelopment and dysfunction leading to epilepsy and a number of other CNS disorders. Furthermore, the

rarity of EFMR does not preclude that this kind of adverse interaction between (epi)genetically different cell populations may explain a number of other epileptic conditions. Somatic mutations occur regularly during the entire development of the organism, and will also affect progenitor cells that populate the CNS. This may lead to two or more functionally different populations of cells in the brain and abnormal functioning of neuronal networks or neuronal–glial interaction. The clinical effect, if any, will depend on the functional role of the gene involved and the location and distribution of the somatically mutated cell population within the brain. This basic mechanism may explain a much larger proportion of common epilepsies and behavioural disorders than previously anticipated. It may also partly explain the difficulties in identifying genes that confer the risk to more common epilepsies (epilepsy as a somatic disease). One approach to test this hypothesis is to screen more systematically surgical or post-mortem brain specimen of patients with well classified epilepsies for somatic mutations of a large number of functional candidate genes. This approach will soon become within reach by means of the new high-throughput deep sequencing technologies that are becoming rapidly available.

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