NON-TRADITIONAL INHERITANCE

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In the last few years a number of non-traditional forms of inheritance has been recognized. These include mosaicism, cytoplasmic inheritance, uniparental disomy, imprinting, amplification/anticipation and somatic recombination. Many of these present mechanisms whereby mutations may manifest in unusual ways which have not been predicted by traditional forms of inheritance. In addition, the possibility of transgenerational affects seems likely.

Genomic imprinting is the observation that phenotype depends on the sex of the transmitting parent. It has been recognized on many different lines of research:

(1) pronuclear transplantation;

(2) triploid phenotypes;

(3) chromosomal deletions;

(4) uniparental disomy;

(5) transgenic mouse work;

(6) childhood cancers; and

(7) single gene disorders.

The mechanism involved in parent of origin affects is likely to have some major affect during meiosis. Observations with parent of origin affects include:

(1) mutation rates;

(2) recombination rates;

(3) chromosome condensation;

(4) imprinting;

(5) late replication; and

(6) chromosome pairing.

It seems possible that each of these processes involve particular areas of chromosomes which are more or less susceptible.

The genomic imprinting phenomenon in humans seems to involve growth, behaviour and, *in utero*, survival. The only human gene which has been demonstrated to have parent of origin affects thus far is insulin-like growth factor type II in which only the paternal protein is expressed while only the maternal receptor is expressed. Parent of origin affects are also seen in childhood cancers, suggesting that all the growth factor genes which have the potential to become oncogenes must be examined for this type of affect. Further, there appear to be tissue-specific parent of origin affect such that, for instance, the retinoblastoma gene has a parent of origin affect in bone but not in the eye while the mutation rate does have a parent of origin affect in the eye.

The mechanism of genomic imprinting is now known. However, it appears that some process is involved in functionally turning a gene off. It would appear that there may be two genes involved therefore in the process; one which produces the product that turns the gene off (the imprinting gene) and the gene itself which is turned off (the imprintable gene). The process of imprinting (functionally turning the gene off) may be associated with methylation, although the initiating event is not known. It is quite clear, however, that erasure of imprinting can occur and this seems most likely to in some way be associated with meiosis.

Imprinting affects can be manifested in a pedigree in such a way as to look like dominantly inheritance, recessively inheritance or multifactorial inheritance. Thus they allude the usual type of genetic analysis of pedigrees.

Interactions between mosaicism and imprinting are thought to occur and in particular have been observed in monozygous twins. In addition, somatic recombination may lead to uncovering imprinting or producing functional hemizygosity.

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