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Editorial

Genomic imprinting for pathologists

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The epigenetic process of genomic imprinting plays an important role in development, allowing some homologous alleles to function differently in the conceptus depending on whether they come from the mother or father.

The mechanism of imprinting is not understood in man but it is possible to speculate about the occurrence of the phenomenon. Imprinting apparently involves some form of tagging of chromatin that will survive mitosis but not meiosis (Hall 1990a). The process must occur during the chromosome pairing stage of the first meiosis. During meiosis crossing over usually occurs in each arm of a chromosome (at least once) and there are differences in recombination rates in male and females. Imprinting sites, recombination sites and initiation of replication sites may have specific structural properties where various failures could give rise to mismatching, malalignment or failure of normal pairing in crossing over, leading to increased mutation rates, failure of recombination or abberant imprinting.

There is a clear functional difference between the activity of paternal and maternal chromosomes at several levels in development. This difference is manifest in haploid and diploid genomes, in single chromosome effects, at the level of part of a chromosome and at the single locus. A conceptus composed entirely of paternal chromosomes will form a complete hydatidiform mole, which usually arises as the result of duplication of a haploid chromosome set but sometimes occurs following dispermy with elimination of the maternal genomic contribution. Maternally derived diploid development gives rise to teratomata in the ovary; these are frequently homozygous for centromeric chromosomal polymorphisms for which their host is heterozygous, suggesting that they are derived following the first meiotic division. The (mal)development of extraembryonic tissues in the paternally derived mole without evidence of fetal development, and of embryonic development in the teratoma without evidence of extraembyonic tissue formation, is evidence that the two genomes have different parts to play in early embryogenesis (Fox 1989).

At the chromosome level, uniparental disomy (UD) – the inheritance of two copies of one chromosome type from one parent – may be clinically relevant if the duplicated chromosome carries a recessive gene defect or if one or more loci on the chromosome is imprinted. In the mouse UD will produce embryonic lethality, marked differences in growth or body size, or alteration in activity. In man, two children with cystic fibrosis have been described with maternal isodisomy (two identical copies of the same chromosome from one parent) for chromosome 7 (see Clarke 1990). A considerable body of data suggest that the difference between the phenotypes in the Prader-Willi and Angelman syndromes, both of which are associated with cytogenetically indistinguishable deletions of chromosome 15q 11–13, are due to differing contributions from maternal and paternal genomes (Hall 1990b). Deletions in the Angleman syndrome appear always to involve the maternally inherited chromosome 15.

The rarity of this type of effect at the whole chromosome level on any set of assumptions about frequency make the most likely explanation of the causation of such defects in man to be the early loss of one chromosome from a trisomic zygote or embryo. Trisomy is almost always lethal (see Berry 1989 for data) and there is thus a high selection pressure for chromosome loss acting during intrauterine life, in order to ensure fetal survival. This process has been demonstrated (for trisomy 13 and 18) by Kalousek et al. (1989). Imprinting may also be recognised by chromosomal translocations in which the phenotype of the unbalanced offspring differs in a way which depends on which parent transmitted the anomaly.

Single gene imprinting has been shown to be tissue specific in the mouse, and is sometimes related to differing methylation (* see footnote) patterns in inserted transgenes. Though this degree of specificity of effect has not yet been found in man, the best examples of single gene level imprinting are seen in the familial neoplastic disorders. Benign familial glomus tumours are transmitted as an autosomal dominant trait, but are only

manifest in those who inherit the gene from their father (van der May et al. 1989). It appears that the maternal locus is inactivated in oogenesis and can only be reactivated during spermatogenesis. The excess of non-familial cases seen in females is accounted for by the lack of risk in the proband's offspring. Imprinting in nephroblastoma and retinoblastoma is considered in a later editorial, but it is worth noting here that while glomus tumours are an example of imprinting at a single locus, the genetics of retinoblastoma/osteogenic sarcoma suggest that the susceptibility to somatic mutation at the RB1 locus varies with the parental origin of the gene and the type of tissue.

In Huntingdon's chorea (HC) differences in severity and age of onset may depend on the gender of the affected parent – in general the age of onset of HC is lower where the gene is of paternal origin. These data could be explained by imprinting, but few data exist. The phenomenon of anticipation – the tendancy for the age of onset of an autosomal dominant disease to be younger in the proband than the parent – occurs in HC and less certainly, in myotonic dystrophy. In both diseases the phenomenon could be explained by imprinting.

A fascinating series of reports (see Little et al. 1991 for bibliography) describe a further example of imprinting in the relationship between inheritance of two copies of an homologus genetic region in Man and the mouse, leading to syndromes of fetal overgrowth. In a significant proportion of those with the Beckwith-Wiedemann syndrome (BWS) both copies of part of the short arm of chromosome 11 (11p15.5) come from the parental genome. Chimaeric mouse embryos containing cells partially disomic for the distal part of chromosome 7 have features which resemble BWS and are abnormally large. It is important to note that the gene for insulin-like growth-factor 2 (Igf-2) lies in this region in the mouse and that mouse chromosome 7 is homologus to human chromosome 11p15.5. These data have important implications for neoplastic change which will be considered in a further Editorial but here a puzzling somatic finding can apparently be explained by imprinting.

The following characteristics of a phenotype produced by imprinting are evident:

1. Equal numbers of affected or non-manifesting males and females are seen in each generation in both maternal and paternal imprinting.

2. Non-manifesting but transmitting individuals are a clue to whether a trait is maternally or paternally imprinted. In maternal imprinting a male is the non-manifesting or less manifesting carrier who transmits to manifesting offspring and in paternal imprinting, females are the non-manifesting carriers who transmit the trait.

3. The pedigree of a gene that is imprinted can look like autosomal dominant or recessive inheritance, or multifactorial inheritance, depending on which part of the family tree is being observed.

4. The pedigree observed is quite different from that which is seen in mitochondrial or cytoplasmic inheritance.

Pathologists will recognise a number of characteristics of well defined syndromes which are difficult to explain by conventional genetics. Imprinting is a phenomenon with which they need to become familiar.

* Vertebrate DNA contains much 5-methyl cytosine. This has the same relation to cytosine that thymidine has to uracil and thus methylation has no effect on base pairing. 5-methyl cytosine is found in the CG sequence and is base-paired to exactly the same sequence in the opposite strand. There is thus a mechanism which makes certain that the pre-existing pattern of DNA methylation will be inherited; the enzyme maintenance methylase acts only on those sequences CG that are base paired with a CG which is already methylated. In general inactive genes are more heavily methylated than active ones and activity is often associated with loss of methylation, but this level of control of DNA expression appears to be subsidiary to the role of Growth Regulating proteins; in certain circumstances it appears to be a consequence rather than a cause of active expression and relates more closely to levels of expression rather than an "on/off" situation.

References

Berry CL, Keeling JW (1989) Embryonic Tumours of Childhood. In: Berry CL (ed) Paediatric Pathology. Springer Verlag, London, Berlin, Heidelberg, New York, pp 764–796

Clarke A (1990) Genetic imprinting in clinical genetics. Development 1990 Supplement 131–139

Fox H (1989) Hydatidiform moles. Editorial. Virchows Arch [A] 415:387–389

Hall JG (1990b) Angelman's syndrome, abnormality of 15q11–13 and imprinting. J Med Genet 27:141–144

Hall JG (1990a) How imprinting is relevant to human disease. Development Supplement 141–148

Kalousek DK, Barrett IJ, McGillivray BC (1989) Placental mosaicism and intrauterine survival of trisomies 13 and 18. Ann Hum Genet 44:338–343

Little M, van Heyyningen V, Hastie N (1991) Dads and disomy and disease. Nature 351:609–610

Mey AGL van der, Maaswinkel-Mooy PD, Cornelisse CJ, Schmidt PH, Kamp JJP van der (1989) Genomic imprinting in hereditary glomus tumours: evidence for new genetic theory. Lancet ii:1291–1294