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Imprinting makes its mark

Work published over the past month provides insight into the mechanism of genomic imprinting in mice and the possible phenotypic consequences of imprinting in humans.

THE phenomenon of imprinting — the preferential expression of the maternally or paternally inherited allele — is in itself fascinating. But as several studies[1–6], including two in the latest issue of *Nature Genetics*[1,2], now make abundantly clear, findings on imprinting will have considerable bearing on areas as diverse as gene expression, development, cancer and evolution. These new discoveries further our understanding in two ways: first, by extending part of what is known about murine imprinted genes to their homologous loci in humans; and second, by offering encouraging clues as to the precise molecular mechanisms responsible for the imprint itself.

Four genes in mice are known to be imprinted (see table), the most recently discovered being one that encodes a small nuclear ribonucleoprotein (*Snrpn*) whose human homologue may play a part in the aetiology of the imprinting disorder called Prader–Willi syndrome (reviewed in ref. 7). Much attention has also been paid to the insulin growth factor 2 (*Igf2*) and *H19* genes, which are a pair of physically linked[8], reciprocally imprinted loci on mouse chromosome 7. In humans, these two genes map to chromosome 11p15, a region that is frequently inherited as two paternal copies in patients with Beckwith–Wiedemann syndrome (BWS), a fetal overgrowth disorder characterized by predisposition to tumours including Wilms' tumour[9]. It had been speculated that human *IGF2* is synonymous with the BWS gene, because of its effects on growth and its paternal-specific expression[10]. But there had been no direct evidence that any of the imprinted genes in mice were similarly modified in humans.

Writing in *Nature Genetics*, two groups show definitively that *IGF2* is indeed paternally expressed in human fetuses. Ohlsson *et al.*[1] and Giannoukakis *et al.*[2] examined polymorphisms in the coding sequence and the 3′ untranslated region, respectively, of *IGF2* in a total of 19 fetal tissue samples. Six of these cases proved to be fully informative, allowing the investigators to distinguish between the parental alleles, and then show that only the paternally derived allele was being expressed.

IMPRINTED GENES IN THE MOUSE

Gene	Expressed allele	Mouse chromosome	Human chromosome
H19	Maternal	7	11p15
Insulin growth factor 2 *(Igf2)*	Paternal	7	11p15
Insulin growth factor 2 receptor *(Igf2r)*	Maternal	17	6q25–q27
Small nuclear ribonucleoprotein N *(Snrpn)*	Paternal	7	15q12

Although in many respects this result was to be expected, it is important to clarify the imprinting status of this and other genes in humans, and indeed in other species apart from mouse, if sensible predictions about the evolutionary role of imprinting are to be made.

Given the position of *IGF2* at 11p15.5 and its possible involvement in BWS, Ohlsson *et al.* also examined the parental imprinting of *IGF2* in a perinatal BWS patient, and found that it was imprinted as well. But, as shown a fortnight ago in *Nature*[3,4], the imprinting of *IGF2* and also *H19* may be relaxed in tumours associated with BWS.

Rainier *et al.*[3] and Ogawa *et al.*[4] examined a total of 72 patients with Wilms' tumour, based on the association of the tumour with BWS and the known expression of *IGF2* and *H19* in the kidney. After discounting those cases caused by loss of one allele, and those in which the alleles could not be distinguished, they found that a total of 14 out of 19 Wilms' tumours exhibited expression of both *IGF2* alleles. In addition, Rainier *et al.* found that *H19* is expressed biallelically in two out of seven tumours. In one example, both genes could be demonstrated to be expressed biallelically, suggesting a possible disturbance in a hypothetical switch between the two genes which directs their contrasting allele-specific pattern of expression[8]. More generally, given the frequency of the 'loss of imprinting', both groups propose that this relaxation may be a common contributory factor to the onset of carcinogenesis.

One mechanism that might explain the relaxation of imprinting would be an effect of methylation, which has been correlated with the repression of transcription of many genes. Indeed, work from Ferguson-Smith and colleagues[5] on the mouse *H19* gene is consistent with this view. Using methylation-sensitive restriction enzymes, they found that methylation at specific sites within the *H19* promoter is confined to the repressed paternal allele. Moreover, this allele is less sensitive to nucleases, indicative of a more condensed and less-accessible chromatin structure. A similar pattern of methylation was seen by Stoger *et al.*[6] at the 5′ end of the non-expressed paternal allele of the murine insulin-like growth factor 2 receptor (*Igf2r*). But in this case, an even more striking methylation event occurs within a 5′ intron of the expressed, maternal allele. Methylation at a CpG island in this intron was found only on the maternal allele. This is significant because unlike the promoter, which is methylated after fertilization, the intron is already methylated in the female gamete, consistent with the idea of an imprinting signal. So for *Igf2r*, the 'imprinted' allele and the expressed allele are one and the same — something of a surprise. Further studies of *Igf2r*, in particular in mice that lack the enzyme for DNA methylation, should help to resolve the tantalizing link between methylation and imprinting, which may have evolved from the host defence system employed by bacteria to destroy foreign DNA[11].

Kevin Davies

Kevin Davies is Editor of Nature Genetics.

Also in this month's *Nature Genetics*: a gene for familial glaucoma mapped to chromosome 1; determining chromosomal regions of identity by 'genomic mismatch scanning'; a role for angiotensinogen in pregnancy-induced hypertension; and a full report of the first international *Nature Genetics* conference in Washington, DC.

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