Genome Biology

RESEARCH HIGHLIGHT

The role of imprinted genes in humans

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Abstract

Detailed comprehensive molecular analysis using families and multiple matched tissues is essential to determine whether imprinted genes have a functional role in humans.

Imprinted or parent-of-origin-dependent gene expression has over the past 25 years developed into an exciting and dynamic research field. Its functional or even evolutionary importance is considered most relevant in mammals and in flowering plants [1]. In mammals the link to the existence of the placenta and the differences between the two parental sexes in terms of resources and evolutionary drive through imprinting has been the focus of much debate. One fundamental question remains: has parent-of-origin gene expression evolved and been maintained because of the different needs of the mother and father in producing viable, strong offspring? The mother needs to survive the pregnancy but the father's drive is focused on the offspring being the fittest. Much of the functional relevance of the research in the imprinting field, particularly with its application to the human, has grown out of this 'resources for fittest' debate. A study in this issue of *Genome Biology* [2] starts to analyze more thoroughly which genes are truly imprinted in humans using genome-wide assessment.

Imprinting in the mouse is well understood. It was discovered separately by the Surani [3] and McGrath [4] groups in the early 1980s, who found that gynogenetic embryos (which contain only maternal genomes) developed differently *in utero* and with emphasis on different tissues to the androgenotes (only paternal genomes). Interestingly, the androgenotes had a more developed placenta and the gynogenotes had a better developed embryo. Links were soon made between imprinted gene models in the mouse and human diseases, imprinted genes were implicated in many fetal growth syndromes, and they were shown to regulate maternal-fetal interactions, postnatal feeding behaviors and neurological development. Disturbance of the apparently rigorous mono-allelic imprinted gene expression was also linked to cancer, and alterations in imprinting methylation patterns or expression in peripheral blood leukocytes were considered as biomarkers for cancer [5].

The study by Morcos *et al.* [2] extends this human analysis comparison further. Here the authors [2] make a genome-wide assessment of imprinted expression in paired sets of samples of adult human tissue, comparing lymphoblastoid cell lines with primary fibroblasts. These two cell lines are both relatively easy to obtain from humans with ethical approval. Using families they could track parental-allele-specific expression, and using paired tissue samples they could study tissue-specific variation between lymphoblastoid cells and fibroblasts. To truly confirm whether a gene is imprinted, differential methylation, tissue-specific expression and parental allele origin must all be tracked in the same family. Observing differentiated methylated patterns in isolation, however, does not always totally reflect monoallelic expression [6]. These all-inclusive experiments can be done relatively easily in mouse but are ethically impossible to copy in humans. These authors [2] have achieved the best compromise by using matched tissues and by studying families. Their results are both interesting and intriguing.

Previous careful comparative analysis between the imprinted genes in mouse and humans showed that roughly half of the mouse imprinted genes are either not or never have been imprinted in humans. Of the about 140 imprinted genes identified so far in the mouse, only 60 are imprinted in humans and several are specific to humans. In addition, some have different tissue-specific expression profiles; for example, growth factor receptor binding protein 10 (*GRB10*) in humans is imprinted only in invasive trophoblasts (maternally expressed) and brain (paternally expressed) [7], whereas in mouse it is maternally expressed in most embryonic tissues and predominantly paternally expressed in brain [8]. If the regulation of gene dosage is so important, why is there not greater conservation of imprinted expression? Or maybe the genes still imprinted in humans have been selected and/

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or maintained for important reasons. Epigenetics provides the mechanisms through which imprinting influences gene expression. These mechanisms affect the processes of cell differentiation and embryonic growth, although they are as yet not completely understood. When epigenetic mechanisms go awry, transcriptional activity may be perturbed and result in disorders and syndromes. This underscores the rationale for studies such as these [2], particularly on a genome-wide scale, for identifying imprinted genes and classifying their conservation across mammalian species.

In the study by Morcos *et al.* [2], of the 44 informative imprinted genes from the literature that were analyzed, 19 were validated as imprinted using this rigorous assessment. More importantly, only 1 in 13 candidate imprinted genes were confirmed. This demonstrates again that only over 50% of mouse imprinted genes are truly imprinted in humans in the adult tissues assayed and only 10% of candidates can be verified.

One caveat of this approach stems from the fact that human embryonic tissues are extremely difficult to access and thus the authors [2] used lymphoblastoid cells and fibroblasts instead; this has some limitations. It is known that imprinting is important in the developing embryo and fetus and typically occurs in a tissue-specific manner. So the use of transformed lymphoblastoid cells as a human tissue resource does not necessarily reflect the *in situ* state. It could be argued that the true role of imprinted genes is in fetal development but, even so, analysis of fetal tissues and placenta has also revealed much lower numbers of imprinted genes in humans than in mouse [9]. In humans there are fewer imprinted genes and these may be the ones that are most relevant for the 'resources for fittest' needs that are most important in human fetal growth.

This study [2] plus other work on human tissues in this dynamic field are all helping to clarify the numbers of imprinted genes in humans and lead towards an understanding of the role of imprinting in humans. There remains no doubt that gene dosage control in the developmental period is exquisitely sensitive and needs accurate control mechanisms. The future focus in humans needs to be on careful dissection of the function of those genes that are confirmed to be imprinted using methods similar to those in this study [2].

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