Nature Reviews Genetics | AOP, published online 12 January 2010; doi:10.1038/nrg2741

COMPLEX DISEASE

Adding epigenetics to the mix

Three recent papers highlight the importance of considering epigenetics in the study of both heritable and non-heritable influences on complex human disease.

Because of the genetic near-identity between monozygotic twins, cases of discordance provide opportunities to explore non-genetic factors that influence phenotypic differences. By DNA methylation profiling of DNA from white blood cells, Javierre and colleagues uncovered epigenetic differences that might contribute to discordance among monozygotic twins for the autoimmune disease systemic lupus erythematosus (SLE). They identified a set of genes that differ in promoter methylation and expression between affected and unaffected twins. These genes are enriched for immune-related functions, which suggests that epigenetic differences arising from, for example, different diets or environmental exposures might influence the development of SLE. However, as the authors point out, further studies in specific types of immune cells will be needed to confirm effects that are relevant to SLE.

FANCY

Another recent study indicates that epigenetic effects also need to be taken into account to understand the heritability of complex diseases. Genome-wide association studies have generally identified variants that account for only a fraction of the heritability of a particular disease. Some of the 'missing heritability' might be explained by variants that have different phenotypic effects depending on whether they have been inherited maternally or paternally. Kong and colleagues extensively genotyped 38,167 Icelanders and used the detailed genealogical information that is available in Iceland, together with long-range phasing of haplotypes, to determine the parent of origin for the vast majority of genotyped SNPs. Genomic imprinting — in which differences in epigenetic status cause differential expression between the two parental alleles — is a likely cause of parental origin effects. The authors identified 5 SNPs that lie within 500 kb of imprinted genes and that show associations with disease that depend on the parent of origin — 1 SNP is associated with breast cancer, 1 with basal cell carcinoma and 3 with type 2 diabetes. They showed that failing to take the parent of origin into account can lead to underestimates of the size of the effect of a SNP on the phenotype and that some associations can be missed altogether: for example, they identified a parent-of-origin-specific association with type 2 diabetes that had been overlooked by previous large genome-wide association studies.

In a third study, Feinberg and Irizarry suggest a previously unexplored way in which epigenetics can influence complex traits, including human disease. They propose that some genetic variants can lead to stochastic variation in epigenetic status that in turn causes increased variability for a phenotype, which can be selected for in certain conditions. To test their hypothesis, they investigated DNA methylation patterns in mouse and human tissues and showed that regions that are highly variable for DNA methylation exist both within and between species. They also showed that loss or gain of CpG dinucleotides provides a heritable basis for changes in this variability, which might therefore provide material for evolution. Using a modelling approach, the authors provided theoretical evidence that increased phenotypic variability can lead to increased fitness in fluctuating environments. Furthermore, such genetically encoded stochastic epigenetic variation might contribute to the low heritability of some phenotypic effects — another potential explanation for the missing heritability tackled by Kong and colleagues.

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ORIGINAL RESEARCH PAPERS

Javierre, B. M. *et al.* Changes in the pattern of DNA methylation associate with twin discordance in systemic lupus erythematosus. *Genome Res.* 22 Dec 2009 (doi:10.1101/gr.100289.109) | Kong, A. *et al.* Parental origin of sequence variants associated with complex diseases. *Nature* **462**, 868–874 (2009) | Feinberg, A. P. & Irizarry, R. A. Stochastic epigenetic variation as a driving force of development, evolutionary adaptation, and disease. *Proc. Natl Acad. Sci. USA* 22 Dec 2009 (doi:10.1073/pnas.0906183107)