Review

UHN Microarray Centre

Explaining phenotypic differences in identical twins

Review of: Kaminsky ZA, Tang T, Wang S-C, Ptak C, Oh GHT, Wong AHC, Feldcamp LA, Virtanen C, Halfvarson J, Tysk C, McRae AF, Visscher PM, Montgomery GW, Gottesman II, Martin NG, Petronis A. DNA methylation profiles in monozygotic and dizygotic twins. Nature Genetics 2009, 41(2):240-245

The greater phenotypic similarity among monozygotic (MZ) twin pairs compared with dizygotic (DZ) twin pairs can be attributed to the fact that MZ twins have virtually identical DNA sequence. Despite their similar appearance, MZ twins are often discordant for important phenotypes, including complex diseases, and such discordance has mostly been attributed to environmental effects (1). Recently, there is mounting evidence that DNA methylation and other epigenetic mechanisms may explain the phenotypic differences between MZ twins (2). DNA methylation shows only partial stability due to environment, hormonal factors, and stochastic events (3), and such metastability may result in significant epigenetic differences across genetically identical organisms (1). One study has revealed that the patterns of epigenetic modifications in MZ twins diverge as they become older (4). Such "epigenetic drift" is also thought to be involved in diseases such as late-onset Alzheimer's disease (5). By mapping the methylation profiles of MZ and DZ twins using UHNMAC 12K CpG island arrays, this study investigated the epigenetic variation among MZ twins and the epigenetic similarities between MZ and DZ twins.

By mapping DNA methylation differences, Kaminsky *et al*. were able to annotate the epigenetic metastability of 6000 genomic loci in MZ twins. The methylation profiles of MZ twins were assessed in white blood cells, buccal epithelial cells, and gut biopsies and the results show a large degree of MZ co-twin DNA methylation variation in all three tissues. Interestingly, the DNA methylation profile data of buccal epithelial cells showed that the variation within monochorionic MZ twin pairs was significantly greater than the variation among dichorionic MZ twins. It is postulated that this result may reflect differences in epigenetic divergence among embryonic cells at the time the twin blastomeres separated (6). The methylation profile data also found that the epigenetic similarity in MZ twins was more highly conserved in regulatory regions of the genome, suggesting a functional stratification of the epigenome. Kaminsky *et al*. speculate that stochastic events in epigenetically determined phenotypic differences in MZ twins are more important than environment as MZ twins tend to be quite similar (based on an array of traits including electroencephalogram, IQ, personality, and social attitudes) whether they are raised together or apart (7).

The second part of the study focused on comparisons of epigenetic similarities between MZ and DZ co-twins, the same design used in heritability studies. Such comparisons found that DZ twins had significantly more epigenetic variation than MZ co-twins, as one might expect. The authors were careful to consider the effect that DNA sequence may have played in the enrichment of differentially methylated sequences prior to methylation profiling, thus *in silico* SNP analyses and animal studies were also performed. These studies support the theory of "zygotic epigenetic effects" which explains that DZ twins have more epigenetic differences because they originated from two zygotes, each having its own epigenome.

This publication also illustrates the diverse capabilities of the UHNMAC Bioinformatics team. In particular, Carl Virtanen and his group were instrumental in helping with the analysis of the methylation data and assembling figures presented in this paper. This study suggests that molecular mechanisms of heritability may not be limited to DNA sequences. Future studies may include a more detailed annotation of epigenetic differences in MZ co-twins, a search for disease-specific epigenetic changes in discordant MZ twins, and a dissection of environment-induced versus stochastic epigenetic differences (6).

References

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