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Epigenetic variation in twins: heritability and the role of body fatness

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Diseases such as CVD and cancer, and associated risk factors such as obesity, have a significant heritable component but the precise genetic basis for this is yet to be identified. There is an increasing interest in the role of epigenetics in health and disease. Certain types of epigenetic mark (e.g. imprinting) can be passed across generations and could contribute to disease heritability. Our aim was to investigate the heritability of epigenetic marking in imprinted and non-imprinted genes and to determine how this varies with body fatness in a study of healthy identical and non-identical twins.

The study was passed by Grampian Research Ethics Committee and all participants gave informed written consent. The average of multiple methylation sites within H19, IGF2, SNRPN, LINE1 and p16 was determined in blood DNA from 56 monozygotic and 67 dizygotic twin pairs. Methylation was determined by pyrosequencing (PyroMark MD Qiagen, Crawley, UK) after bisulphite conversion of DNA using Epitect Bisulfite kits (Qiagen, Crawley, UK). Weight, height, abdominal circumference and percent body fat (by bioelectrical impedance using the Bodystat[®] 1500; Bodystat Ltd, Isle of Man) were measured in each twin. Statistical analysis was carried out using STATA 11MP (Stata Corp, College Station, TX, USA). The additive genetic effect on epigenetic status was calculated in an ACE twin model using an implementation of Mx⁽¹⁾ for twin data. Methylation associations with phenotype were assessed by fitting mixed effects models.

There were significant but weak within pair correlations for LINE1 ($P = 0.004$, $r^2 = 6.4$), P16 ($P = 0.009$, $r^2 = 4.7$) and SNRPN ($P = 0.005$, $r^2 = 5.5$). The association was stronger for H19 ($P < 0.001$, $r^2 = 30.3$). There was no significant association for IGF2. Significant heritability was detected for H19 (67% of the variation attributed to additive genetic factors in the ACE model; $P < 0.05$). Methylation status of P16 and IGF2 were significantly related to weight (P16: $P = 0.001$; IGF2: $P = 0.039$), waist circumference (P16: $P = 0.001$; IGF2: $P = 0.022$) and body fatness measured by impedance (P16: $P = 0.003$; IGF2: $P = 0.004$), but not to height (all adjusted for age and sex).

Altered imprinting has been implicated in a number of human diseases. The heritability of variation in the epigenetic status of imprinted genes and the correlation of imprinting methylation between family members could contribute to disease heritability. It is important to identify the factors that give rise to this variability. Body fatness is related to a number of cancers, but the causal connection is yet to be established. Epigenetic change is a hallmark of tumours and the methylation status of P16, in particular, is thought to be important in a number of cancers. The link between P16 methylation and body fatness merits further study.

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1. Neale MC, Boker SM, Xie G *et al.* (2003) *Mx: Statistical Modeling*, 6th ed. Richmond, VA: Department of Psychiatry.