The role of genetic and epigenetic factors in the development of type 2 diabetes.

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The incidence of diabetes mellitus is on the rise globally. Insulin resistance in peripheral tissues i.e. skeletal muscle and adipose tissue together with impaired insulin-secretion from pancreatic β-cells and increased glucose-output from liver represent hallmarks of type 2 diabetes. Obesity, reduced physical activity and aging are non-genetic risk factors well known to increase susceptibility to the disease. However, all individuals do not respond to an affluent diabetogenic environment in the same way. Multiple studies provide evidence that genetic factors are important contributors to the large inter-individual variation in diabetes susceptibility. Among genetic factors common variants in i.e. the *PPAR-γ, calpain 10*, *PGC-1α* and *TCF7L2* genes have been associated with increased risk of the disease. The interaction between genes and environment may be even more complex and involve epigenetic factors such as DNA methylation and histone acetylation to promote type 2 diabetes. However, the influence of epigenetic factors on the pathogenesis of the disease remains unknown.

Cytosine residues occurring in CG dinucleotides are targets for DNA methylation and gene expression is usually reduced when DNA methylation takes place at a promoter. Monozygotic twins who are discordant for a given phenotype are excellent for the study of effect of environmental and epigenetic factors on the phenotype as the genotype is shared. We were recently involved in a study investigating if epigenetic differences may be an important part of this puzzle. We found that, although twins are epigenetically indistinguishable during early years of life, older monozygotic twins exhibited remarkable differences in their content of DNA methylation and histone acetylation, affecting their gene-expression portrait. These findings indicate that environmental factors and age can influence the genotype through epigenetic changes and thereby possibly susceptibility to disease, e.g. type 2 diabetes. The present study will investigate if epigenetic factors influence the pathogenesis of type 2 diabetes, by collecting muscle and fat from monozygotic twins discordant or concordant for the disease as well as healthy twins.