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Values and limits of the genome-wide association studies in type 2 diabetes

Genome-wide association studies (GWAS) represent a major tool in the understanding of the genetics of complex diseases including type 2 diabetes (T2D). More than 120 loci have been identified for T2D. Surprisingly, most of the known loci act through an effect on insulin secretion rather than insulin resistance. Details will be given. However, these variants explain only a small fraction of the estimated heritability of T2D. Possible explanations may be that:

- 1. the phenotypes of interest are not precise enough
- 2. several independent variants in a given gene or pathway, each of them having a small effect size, contribute synergistically to increase the susceptibility to the disease
- 3. the functional variants responsible for the GWAS signals, with stronger effect sizes, have not been deciphered
- 4. rare variants with stronger effect sizes exist and will need deep sequencing on large studies
- 5. gene-gene and gene-environment interactions are not covered by classical GWAS as their studies need extremely large sample sizes
- 6. epigenetic changes in critical genes during intra-uterine life may play a major role in altering the risk of T2D
- 7. parent-of-origin effects should be dissected as the paternal and maternal alleles may have effects in opposite directions, leading to the impossibility to detect such an association in traditional case-control studies.

Also, molecular post-GWAS data are necessary to elucidate the function of the proteins encoded by the disease-associated genes if one wants to obtain a complete picture of how genetic variation leads to T2D. Examples will be provided.

Biography

Aline Meirhaeghe has completed her PhD from University of Lille (France) and Post-doctoral studies from Cambridge University (UK). She is leading a group, in Inserm UMR1167 Laboratory, investigating the molecular genetics of metabolic diseases at the Institut Pasteur de Lille (France). She has published more than 85 papers in reputed international journals.

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