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Microarray analysis of complex traits

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Abstract

The pathways and gene loci involved in causing type 1 diabetes in a murine model (NOD mouse) are being uncovered using microarrays and conventional genetics

Significance and context

Type 1 diabetes is an autoimmune disease leading to the destruction of the insulin-producing cells in the pancreas. Numerous studies have concluded that it is a multigenic disease, but although over 20 loci seem to be associated with it, how they interact with each other to cause disease is not known. The non-obese diabetic (NOD) mouse is a model for type 1 diabetes and is being studied to determine the pathways involved in disease development. The study of diabetes-resistant congenic animals carrying single or multiple *Idd* loci derived from non-diabetic B6/B10 mouse strains allows analysis of the role of each chromosomal region implicated in the development of type 1 diabetes. Eaves *et al*. have profiled tissues from diabetic, non-diabetic and diabetes-resistant animals using microarray analysis, with the aim of establishing a link between genotype and phenotype for type 1 diabetes.

Key results

Eaves *et al*. analyzed NOD mice, four congenic diabetes-resistant mouse strains derived from the NOD strain, and two non-diabetic B10 control strains. The microarray experiments were carried out on tissues rich in T cells - spleen and thymus - as T cells are directly involved in the pathology of type 1 diabetes. Three different comparisons were made using the results of the array experiments. Pairwise comparisons between each of the congenic diabetes-resistant strains (NOD.B6 *Idd3,* NOD.B10 *Idd5*, NOD.B10 *Idd9*, B10.NOD $H2^{g7}$, B10.NOD $H2^{g7}$ *Idd3*, NOD *Idd3+5*) and the NOD strain revealed that none of the genes differentially expressed in NOD *Idd3* and NOD *Idd5* mice mapped to the chromosomal regions previously identified as being potentially involved in diabetes. Six of the genes differentially expressed in the thymus in congenic NOD Idd9 mice compared to NOD mice were, however, deduced to be *cis*-acting variant alleles, which can affect gene activity on the same chromosome.

The second analysis compared all diabetes-resistant strains to the NOD mice. This revealed only seven genes differentially expressed, including that for CD90 (a T-cell surface antigen). Finally, Eaves

et al. compared the non-diabetic B10 mice and NOD mice. They identified 295 genes with altered expression, of which 35 are upregulated in erythrocytes in all NOD strains analyzed, and 23 pancreas-specific genes were increased in all NOD strains. Of the remaining 247 genes, 21 localized to the *Idd* loci and are therefore potential candidate genes for type 1 diabetes. These are the genes for proliferating cell nuclear antigen (*Idd13*), protein kinase C delta (*Idd8*/*12*), vinculin (*Idd8*), CD79a, v-RelB, CEA cell adhesion molecule and paired-immunoglobulin-like receptor A1 (*Idd7*), Kirsten rat sarcoma oncogene 2 (*Idd6*), Scya5 (*Idd4*), MHC (H-2) class I molecules (*Idd1*) and other genes of the H-2 region.

Links

Supplementary data is to be found at the Juvenile Diabetes Research Foundation/Wellcome Trust Diabetes and Inflammation Laboratory website.

Conclusions

The dramatic protection (55-80%) against the disease seen in congenic strains carrying the *Idd* loci cannot be explained by global effects on the non-induced immune system. Comparison of the non-diabetic versus NOD mouse has nevertheless identified a few good candidate genes that might represent some of the *Idd* loci - for example, *Scya5*. The authors conclude that the selection of the right target for analysis is essential for detecting links between genome and phenotype.

Reporter's comments

This is an important breakthrough in the analysis of complex traits, as it shows that such analysis is possible and that there are very few differences in gene expression between the genetically different mouse strains. It also addresses the important issue of linking the genotype of a complex disease with its phenotype. The paper is, however, as complex as the problem addressed, making it demanding reading. It would have been nice if the role and significance of the *cis*-acting polymorphisms in the Idd9 genotype and the seven genes found to be differentially expressed in diabetes-resistant and NOD mice had been discussed further. The authors point out that because of the complexity of the tissues examined they might have missed some of the differences in gene expression. This might also account for the small differences observed between the congenic strains. This paper highlights the problems facing research into human complex traits that aims to use microarray analysis either using human samples or mouse models to analyze the relation of genotype to phenotype.

Table of links

Genome Research

Juvenile Diabetes Research Foundation/Wellcome Trust Diabetes and Inflammation Laboratory

References

1. Eaves IA, Wicker LS, Ghandour G, Lyons PA, Peterson LB, Todd JA, Glynne RJ: Combining mouse congenic strains and microarray gene expression analyses to study a complex trait: the NOD model of type 1 diabetes. Genome Res. 2002, 12: 232-243. 1088-9051