

Reference

1. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med* 2005; 353: 2643–53.

Type 1 diabetes susceptibility loci from genome scans in multiplex families

Original article:

Type 1 diabetes: evidence for susceptibility loci from four genome-wide linkage scans in 1,435 multiplex families. Concannon P, Erlich HA, Julier C, Morahan G, Nerup J, Pociot F, Todd JA, Rich SS, for the Type 1 Diabetes Genetics Consortium. *Diabetes* 2005; 54: 2995–3001.

Summary and Comment:
Vincent Geenen, Liège, Belgium

Key words:

Genetics, type 1 diabetes, genome-wide analysis, multiplex families, HLA locus, non-HLA loci

Summary

A combined linkage analysis was performed in 1435 multiplex families with 1636 affected sib-pairs. In addition to the HLA region (*IDDM1*, on chromosome 6p21), nine non-HLA-linked regions showed evidence of linkage to type 1 diabetes, including three at (or very close to) genome-wide significance (2q31–q33, 10p14–q11, 16q22–q24), as well as evidence supporting linkage for the 6q21 region. As one of the largest studies ever performed, this work provides significant information in favour of susceptibility loci on these chromosome regions but fails to support some previously suggested locations. It clearly illustrates the importance of such large multicase family genome scans for delineating the precise loci to be further explored.

Comment

Since type 1 diabetes is strongly clustered in certain families, application of genome-wide analyses to multiplex families is logically expected to provide important insights into the identification (or refutation) of genetic loci conferring significant susceptibility (or protection) to this disease. Such a large analysis was performed in this study, under the auspices of the Type 1 Diabetes

Genetics Consortium (www.t1dgc.org), after combining four datasets: three previously published genome scans (UK, USA and Scandinavia) and one set of 254 families newly assembled for this objective. Such merging and joint analyses of existing families are required to clarify the role of non-HLA-linked loci in type 1 diabetes. In the present study, the locus-specific risk ratio and statistical significance ($p = 10^{-4}$) were very high, since each genome scan included around 400 polymorphic microsatellite markers.

The strongest evidence of linkage to type 1 diabetes was on chromosome 6p21 in the HLA region, in agreement with the knowledge that approximately 40% of the familial risk of type 1 diabetes is due to allelic variation of HLA loci in the major histocompatibility complex (MHC) region. The same analysis also identified non-HLA regions with evidence supporting linkage to type 1 diabetes, including 2q31–q33 (*IDDM7* and *IDDM12*), 10p14–q11 (*IDDM10*) and 16q22–q24. Chromosomes 7, 8, 18, 20, 21 and 22 did not harbour any loci conferring susceptibility to type 1 diabetes, nor did the majority of chromosome 6 outside the 6p21/MHC region. Interestingly, extensive areas (>50%) on chromosomes 16, 19 and X could not be excluded and should be explored by further genotyping. Thus the increased sample size of families enabled the exclusion of more than 80% of the human genome for locus-specific and population-independent susceptibility regions.

Using *t*-statistic and taking into account genetic distance, an HLA-independent effect was also strongly supported for the *IDDM15* (6q21) region. A linkage to this *IDDM15* locus has been previously reported [1], but both the identification of the responsible gene(s) and further definition of the effects exerted by this locus require further study.

The *IDDM12* locus in the 2q31–q33 region partially corresponds to single nucleotide polymorphisms in the 3'-untranslated region of the T-cell regulator *CTLA4* gene [2]. However, the presence of other loci in this region is suggested by the study to fully account for the magnitude of the observed evidence of linkage.

The study confirms linkage of type 1 diabetes to 10p14–q13 (*IDDM10*). Since previous association studies have suggested that *GAD2* is not a susceptibility locus, further studies are needed to identify the functional gene(s).

The evidence for a type 1 diabetes susceptibility locus on chromosome 6p12–q11.1 should be considered with the reported linkage to chromosome 16p in UK families with early-onset rheumatoid arthritis [3]. The overlap of loci with

susceptibility to different autoimmune diseases is certainly not coincidental.

The overlap of loci with susceptibility to different autoimmune diseases is certainly not coincidental

Several studies [4–6] have reported an association of type 1 diabetes with alleles in the *PTPN22* locus (chromosome 1p13), which encodes a lymphoid-specific tyrosine phosphatase (LYP) and is also associated with autoimmune thyroiditis, rheumatoid arthritis and systemic lupus erythematosus [7]. The absence of linkage of type 1 diabetes to chromosome 1p13 in the present study is not surprising given the magnitude of the *PTPN22* association with type 1 diabetes, in particular the low locus-specific genetic risk ratio. This means that the 1p13 region should not be excluded in future larger studies and the same applies to the 1q42 region.

In addition, the current study reported the absence or very little support for linkage to type 1 diabetes of previously reported loci including chromosome 8q, *IDDM4* (11q13), *IDDM6* (18q12–q21), *IDDM9* (3q22–q25), *IDDM11* (14q24–q31), *IDDM16* (14q32), *IDDM17* (10q25) and *IDDM18* (5q33). As suggested by Concannon et al., these putative type 1 diabetes susceptibility loci may represent either false-positive results or have very small effects that may be more easily detected in certain populations (because of variation in allele frequencies or other factors such as the possibility of population-specific genetic or environmental effects).

References

1. Delepine M, Pociot F, Habita C et al. Evidence of a non-MHC susceptibility locus in type 1 diabetes linked to HLA on chromosome 6. *Am J Hum Genet* 1997; 60: 174–87.
2. Ueda H, Howson JM, Esposito L et al. Association of the T-cell regulatory gene *CTLA4* with susceptibility to autoimmune disease. *Nature* 2003; 423: 506–11.
3. Tait KF, Marshall T, Berman J et al. Clustering of autoimmune disease in parents of siblings from Type 1 diabetes Warren repository. *Diabetic Med* 2004; 21: 358–62.
4. Bottini N, Musumeci L, Alonso A et al. A functional variant of lymphoid tyrosine phosphatase is associated with type 1 diabetes. *Nat Genet* 2004; 36: 337–8.
5. Smyth DJ, Cooper JD, Collins JE et al. Replication of an association between the lymphoid tyrosine phosphatase locus *LYP/PTPN22* with type 1 diabetes, and evidence for its role as a general autoimmunity locus. *Diabetes* 2004; 53: 3020–3.

6. Onengut-Gumuscu S, Ewens KG, Spielman RS, Concannon P. A functional polymorphism (1858C/T) in the *PTPN22* gene is linked and associated with type 1 diabetes in multiplex families. *Genes Immun* 2004; 5: 678–80.
7. Jawaheer D, Seldin MF, Amos CI et al., for the North American Rheumatoid Arthritis Consortium. Screening the genome for rheumatoid arthritis susceptibility genes: a replication study and combined analysis of 512 multicase families. *Arthritis Rheum* 2003; 48: 906–16.

Does diabetic retinopathy predict mortality and CVD?

Original article:

Diabetic retinopathy is associated with mortality and cardiovascular disease incidence. The EURODIAB Prospective Complications Study. van Hecke MV, Dekker JM, Stehouwer CDA, Polak BCP, Fuller JH, Sjolie AK, Kofinis A, Rottiers R, Porta M, Chaturvedi N. *Diabetes Care* 2005; 28(6): 1383–9.

Summary and Comment:

Knut Borch-Johnsen, Gentofte, Denmark

Key words:

Retinopathy, microalbuminuria, nephropathy, prognosis, mortality, cardiovascular disease

Summary

The EURODIAB study is a clinic-based study comprising 31 centres in 16 European countries. A random sample of subjects stratified by age and diabetes duration was drawn from patients attending each participating clinic. The primary aim of the study was to examine the prevalence of late diabetic complications in Europe and to establish a cohort that could be used for future identification of risk factors/prognostic markers in relation to the subsequent development of late diabetic complications.

The baseline examination in the EURODIAB study also included fundus photography (two-field 45° photography) and the photographs were sent to a central reading center (Hammer-smith Hospital, London) for independent and blinded reading. The patients were classified into three groups at baseline: no retinopathy, non-proliferative diabetic retinopathy and proliferative diabetic retinopathy.

The aim of the study was to analyse whether retinopathy predicts subsequent development of cardiovascular disease (CVD) and predicts all-cause mortality independently of established risk factors for CVD. This was done by a 6- to 8-year follow-up examination of all surviving members of the cohort, combined with a careful and stan-