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Genome-wide scan for type 1 diabetic nephropathy in the Finnish population reveals suggestive linkage to a single locus on chromosome 3q

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Diabetic nephropathy (DN) is the primary cause of morbidity and mortality in patients with type 1 as well as type 2 diabetes, and accounts for 40% of end-stage renal disease in the Western world. Familial clustering of DN suggests importance of genetic factors in the development of the disease. In the present study, we performed a two-stage genome-wide scan to search for chromosomal loci containing susceptibility genes for nephropathy in patients with type 1 diabetes. In total, 83 discordant sib pairs (DSPs), sibs concordant for type 1 diabetes but discordant for nephropathy, were collected from Finland, a homogeneous population with one of the highest incidences of type 1 diabetes. To map loci for DN, we applied DSP analysis to detect linkage. In the initial scan, 73 DSPs were typed using 900 markers with an average intermarker distance of $\sim$4 cM. Multipoint DSP analysis identified five chromosome regions (3q, 4p, 9q, 16q, and 22p) with maximum logarithm of odds (LOD) score (MLS) $\geqslant$1.0 (corresponding to a nominal *P*-value $\leqslant$0.015). In the second stage, additional 43 markers flanking these five loci were genotyped in all 83 DSPs. Using simulations, we determined the empirical threshold with LOD score of 1.76 and 3.12 for suggestive and significant linkage, respectively. No locus reached the genome-wide significance of 5%. However, one locus on 3q reached suggestive linkage with MLS of 2.67 ($P = 4.4 \times 10^{-4}$). These results, together with data from others, suggest that the locus on 3q most likely has a susceptibility gene for DN.

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Nephropathy is a frequent complication of diabetes mellitus, and the single most common disorder leading to end-stage renal disease (ESRD). Diabetic nephropathy (DN) is the primary cause of morbidity and mortality in patients with type 1 diabetes mellitus (T1DM), and it also affects patients with type 2 diabetes mellitus (T2DM).[1] The changes in kidney structure caused by diabetes are specific, with a pattern not seen in other renal diseases. The kidney complications manifest themselves first as microalbuminuria, which then progresses to overt albuminuria, suggesting that the renal filtration barrier, which consists of the glomerular basement membrane and the podocyte slit diaphragm, is first affected.[1] The glomerular basement membrane gradually becomes thicker and structurally disorganized, leading to severe distortion of glomerular filtration. DN is frequently associated with hypertension and often contributes to the development of cardiovascular disease in type 1 diabetic patients already at a relatively young age.[2] Once overt proteinuria has developed, progression to ESRD can be retarded, but not prevented, by antihypertensive treatment and careful glycemic control.

DN is believed to be a multifactorial disease caused by both environmental and genetic factors. Duration of diabetes and hyperglycemia are two of the strongest determinants of DN.[3] Other risk factors are hypertension, smoking and hyperlipidemia.[4,5] However, there is considerable evidence showing that nephropathy is influenced by genetic factors, particularly in T1DM.[6–8] Although the proportion of ESRD resulting from DN is high in T2DM, the kidney failure may often be caused by non-diabetic factors, such as hypertension or chronic infections. Epidemiologic studies have shown that 35% of patients with diabetes develop nephropathy irrespective of glycemic control,[9,10] suggesting that a subgroup of patients is at a high risk of developing nephropathy. The incidence of nephropathy peaks during the second decade of diabetes in T1DM subjects, and declines thereafter.[10] Familial clustering of nephropathy and ethnical variation have been observed, regardless of the type of diabetes.[3,8,9,11–14] The risk

of developing DN to a second diabetic sibling within a family is 71 or 25%, respectively, depending on whether the first diabetic sibling has DN or not.[14] In a recent Finnish nationwide study, the estimated probability of progression to DN by 20 years after onset of diabetes was 17% for the siblings of the type 1 diabetic probands without DN, 38% for the siblings of the probands with DN, and 41% for the siblings of the probands with ESRD.[7] The prevalence of DN is especially high in Pima Indians, Nauruan, Asian Indians, African-Americans, and Mexican-Americans.[11,12,15,16] It is not clearly known why there is an inter-racial difference in the incidence of DN, but differences in genetic predisposition might be a reason.

In this study, we describe a genome-wide linkage analysis aimed at identifying DN susceptibility loci in Finnish discordant sib pairs (DSPs) that are concordant for diabetes but discordant for nephropathy,[17] instead of the commonly used affected sib pairs analysis. The main idea is to map loci specifically for nephropathy in patients with T1DM, but not for diabetes.

RESULTS

To search unbiased for genetic loci linked with DN, we collected 73 families with type 1 diabetes, containing 83 DSPs from Finland where the population is homogeneous and has the highest incidence (~3%) of type 1 diabetes.[18] The clinical characteristics of the siblings are shown in Table 1. Among 83 DSPs, DNA was available from 20 families with two parents and 20 families with a single parent.

In the initial scan, 73 DSPs were typed with 900 markers evenly distributed on the 22 autosomal chromosomes and the X-chromosome. Successful typing data were obtained from 868 markers and the information content of the markers was in average ⩾70%. The initial genome scan results are displayed in Figure 1. The most prominent linkage was observed on chromosome 4p with a maximum logarithm of odds (LOD) score (MLS) of 2.25 at 25 cM. The second highest linkage with MLS of 1.71 at 143 cM was found on

Table 1 | Clinical characteristics of 83 DSP included in the study

	DN^+ siblings, *n*=76	DN^- siblings, *n*=79
Female/male (%)	41/59	51/49
Age at diabetes onset (years)	12.44±8.22 (*n*=75)	17.65±13.5 (*n*=76)
Duration of diabetes (years)	29.07±7.84 (*n*=73)	25.49±9.77 (*n*=70)
Blood pressure (mm Hg)		
Mean systolic	139.49 (*n*=59)	132.64 (*n*=45)
Mean diastolic	79.8 (*n*=59)	81.22 (*n*=45)
ESRD (%)	16	—
Macroalbuminuria (%)	84	—

DN, diabetic nephropathy; DSP, discordant sib pairs; ESRD, end-stage renal disease; *n*, number.
Data are means±s.d., % or *n*.

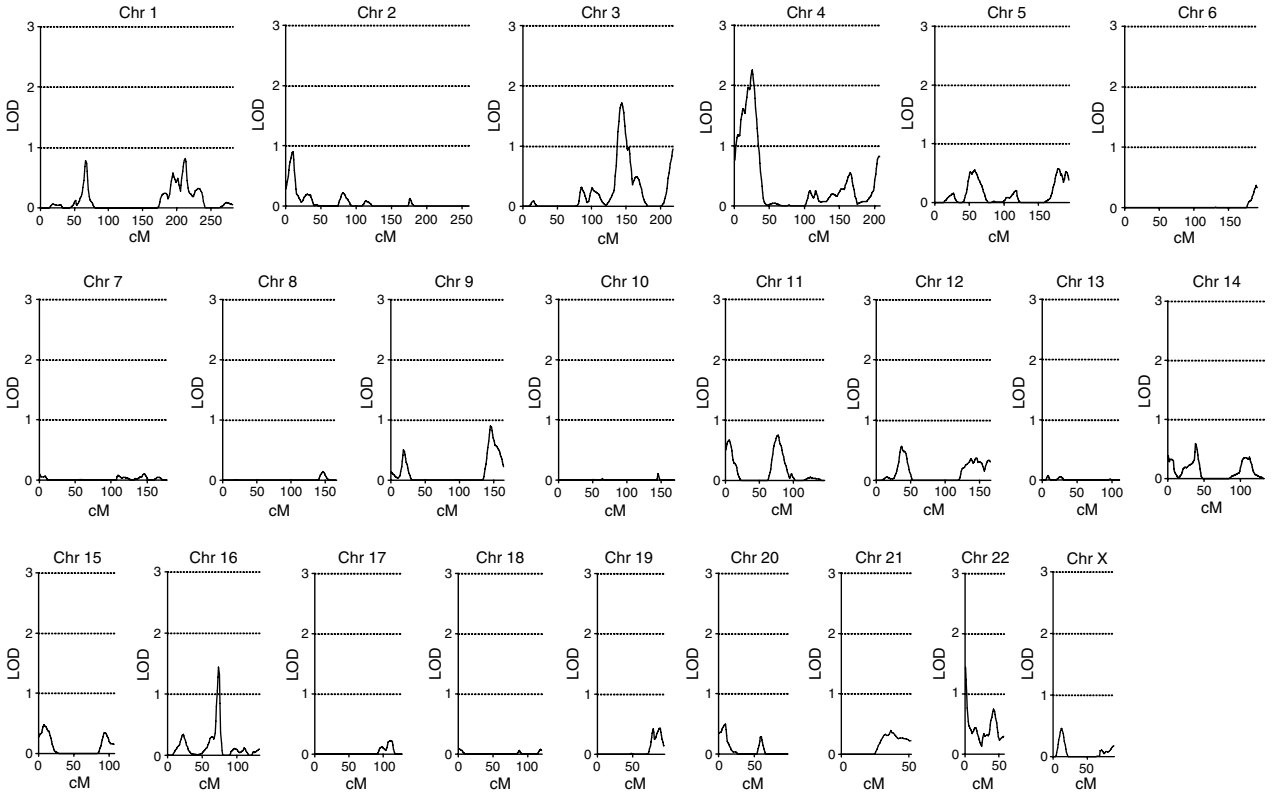

Figure 1 | Results of the initial genome-wide scan of 73 Finnish DSPs. LOD scores on the *y* axis are plotted against the genetic distance (cM) on the *x* axis. Chromosome numbers are listed in each graph.