Lack of evidence for the 1484insG variant at the 3′-UTR of the protein tyrosine phosphatase 1B (PTP1B) gene as a genetic determinant of diabetic nephropathy development in type 1 diabetic patients

Sir,

Insulin resistance (IR) is likely to precede and to play a role in diabetic nephropathy (DN) in both type 1 (T1D) [1] and type 2 diabetes [2]. IR and DN may also share common genetic determinants [3–6]. The gene encoding PTP1B, a tyrosine phosphatase which inhibits insulin signalling, is an excellent candidate for IR and related disorders. We recently have identified a 1484insG variation in the 3′-untranslated region (UTR) of the gene which stabilizes PTP1B mRNA and associates with IR in the general population [7]. Our aim was to verify whether the PTP1B 1484insG variant [as evaluated by polymerase chain reaction (PCR) and SacII enzyme digestion] plays a role in the development of patients in T1D. In a case–control study, 288 European patients with T1D were enrolled. There were 170 patients with microalbuminuria [albumin excretion rate (AER) = 30–300 μg/min] or albumin/creatinine ratio (ACR) = 2.5 mg/mmol, 35 females, 30 mg/mmol on two or more consecutive occasions) or persistent proteinuria (AER >30 mg/mmol) in data not shown). In a subset of 80 patients of the first cohort reported here, we have retrospective information on the rate of decline of the glomerular filtration rate (GFR, as derived by the Cockcroft-Gault formula), whose median value was 4.4 ml/min/year (range –3.8 to 16.6). Also in this case, no statistical difference in GFR decline was observed between patients carrying (n = 8) or not carrying (n = 72) the 1484insG variant (3.2 ml/min/year, range:1.4–11.7 vs 4.7 ml/min/year, range 3.8 to 16.6; P = 0.9). The low number of patients carrying the 1484insG variant does not allow us to draw a firm conclusion about a possible role for this variant in the rate of diabetic nephropathy progression, and indicates the need for a larger study to obtain insight into this specific issue.

Our study clearly indicates, therefore, the lack of association of the 1484insG variation in the PTP1B gene with the risk of developing DN in patients with T1D. Although a negative case–control study may be the consequence of insufficient statistical power, we believe this possibility is unlikely in our case. In fact, the number of patients we have studied is at least comparable with that of other major studies in this field (reviewed in [8]). Given a genotype frequency of the PTP1B 1484insG of 15% in the general population [7] and assuming the same frequency in control patients, the two cohorts pooled and analysed together have a power of 80% (P = 0.05) to detect twice as high a risk of developing DN in patients carrying the gene variant. A similar risk has been reported for other genetic determinants of DN (as indicated in [5,6,8]). In addition, data replication in two different cohorts minimizes the risk of a false-negative result due to population stratification bias. Overall, we believe, therefore, that the possibility of a false-negative result in our study is very unlikely. Our finding adds complexity to the potential relationship between IR genes and DN, indicating that not all functional genetic variations affecting insulin sensitivity play a role in DN development. An additional functional single nucleotide polymorphism (SNP) in the PTP1B gene (a missense SNP, P387L) has been identified recently and associated with type 2 diabetes among Caucasians [9]. However, no association was observed with IR, making the relevance of this observation to DN uncertain. In addition, due its extremely low frequency (i.e. ~1% in the general population), the possibility that it may exert a relevant and detectable population-attributable risk of DN is trivial.

In conclusion, the 1484insG variant of the PTP1B gene, which increases the susceptibility to IR in the general population, is unlikely to play a role in modulating the risk of developing DN in patients with T1D. Whether this variant plays a role in other aspects or stages of DN pathophysiology as reported for other IR genes, including time to development since diabetes onset [10] or rate of disease progression [3,4] once the complication is established, is currently unknown and cannot be answered by our present study design. Further prospective and larger studies may clarify this issue.

Conflict of interest statement. None declared.

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Renal involvement in Cogan’s syndrome

Sir,

Nephrologists are accustomed to managing patients with systemic vasculitis. However, some of the rarer vasculitides may be primarily non-renal in their target organ damage and present with a long prodrome. We would like to briefly discuss one such syndrome that may not be well known to the general nephrological community.

Our patient presented aged 32 when, with no risk factors for coronary atheroma, he sustained a myocardial infarction. Aged 40, he presented with fever, bilateral uveitis and renal impairment (serum creatinine 420 mmol/l). Inflammatory markers and autoimmune profile including ANA, ANCA and anti-GBM antibody were normal. Renal biopsy revealed a diffuse proliferative glomerulonephritis with mesangial hypercellularity, irregular granular deposits of C3 in both the mesangium and capillary loops but no features of vasculitis or crescents. He was treated with a course of antibiotics that coincided with the resolution of his symptoms. His serum creatinine improved to 180 mmol/l and remained stable. Over the next 12 years he developed left hemiparesis; bilateral sensorineural deafness needing a cochlear implant; a second myocardial infarction with ventricular arrhythmia needing coronary stenting and an implantable cardioverter defibrillator.

Aged 52, he presented with bilateral pleural effusion, a widespread scaly erythematous rash and generalized lymphadenopathy. CRP was 64 mg/l (N < 10) and the serum creatinine 270 mmol/l. Pleural fluid was haemorrhagic showing only inflammatory cells. Echocardiography revealed severe left ventricular dysfunction. Skin and lymph node biopsy revealed leucocytoclastic vasculitis and dermatopathic lymphadenopathy, respectively.

This clinical presentation was consistent with a diagnosis of Cogan’s syndrome (CS). He was commenced on intravenous methyl prednisolone (0.5 g for 3 days), followed by oral prednisolone (1 mg/kg/day) and oral cyclophosphamide (2 mg/kg/day). Azathioprine was substituted for the cyclophosphamide at 3 months. There was significant clinical improvement returning to his baseline physical function at 6 months although still restricted by his cardiac disease. His serum creatinine had stabilized at 220 mmol/l after 6 months of treatment.

CS is a rare multisystem disease of unknown cause predominantly affecting young adults. Recent studies suggest an autoimmune process directed against the Cogan’s peptide, which is homologous to autoantigens such as Connexin 26 and DEP-1/CD148 on the sensory epithelia of inner ear and endothelial cells, as well as other antigens such as Ssa/Ro, lamin, ladin1, kinesin and calcineurin [1,2].

CS comprises the association of inflammatory eye disease and audiovestibular dysfunction. However, firm diagnostic criteria have not been established. The audiovestibular disturbance presents with Meniere’s-like illness and progressive sensorineural deafness which is irreversible in ~50–85% of the patients. The eye signs include interstitial keratitis, scleritis, episcleritis and uveitis [3–5].

Systemic manifestations are seen in ~72% of cases and are usually non-specific but may include lymphadenopathy, hepatosplenomegaly, aortitis, coronary arteritis, pleuritis and pulmonary nodules [3,5]. A systemic vasculitis may occur in ~10% of cases usually affecting medium-sized vessels although any sized vessel may be affected [6].

Renal disease is poorly described in the literature. In a review of 78 cases, 14 had abnormal urinalysis, and three had renal impairment. Histopathological findings were available in seven of these patients and were abnormal in five patients. The abnormal findings included glomerulonephritis, renal vasculitis, gross cortical scarring and renal infarction [5].

Corticosteroids are used topically for ocular inflammation and systemically for ear manifestations. Treatment of the