The accelerator hypothesis cannot be tested using the type 2 diabetes gene, *TCF7L2*

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To the Editor: Field and colleagues were unable to find an association between the type 2 diabetes gene transcription factor 7-like 2 (*TCF7L2*) and type 1 diabetes, and concluded that their data did not support the accelerator hypothesis [1].

To a metabolist, this seems an unduly “genocentric” view of disease causation. Furthermore, the accelerator hypothesis is wrongly quoted. The hypothesis does not suggest that ‘type 1 diabetes and type 2 diabetes share a common genetic aetiology’. On the contrary, it proposes a common environmental aetiology (insulin resistance) to which different genotypes respond with different rates of beta cell loss [2]. The hypothesis states that ‘type 1 and type 2 diabetes are the same disorder of insulin resistance set against different genetic backgrounds.’

Apart from rare monogenic forms, genes do not cause diabetes. They fix the level of susceptibility to a given environmental risk. The beta cells of those carrying the *TCF7L2* gene are more susceptible than others to the metabolic demands of insulin resistance [3], but not as susceptible as those carrying the HLA *DR3/DR4* combination. Type 2 diabetes is not so much ‘adult diabetes’ as diabetes in adulthood, and type 1 not ‘childhood diabetes’ but diabetes in childhood. The only difference between the two is the tempo of beta cell loss, which is modulated by the genotype.

The genotypes encoding susceptibility to diabetes respond variably to the rising environmental pressure of insulin resistance imposed by the obesogenic environment in which

we live, and there is no reason to suppose, as Field and colleagues do, that children with type 1 diabetes, in whom the tempo of beta cell loss is the fastest because they carry the most susceptible genotype, would necessarily carry genes associated with a slower tempo as well. It is important that this point be clear. Where there are different degrees of susceptibility and a given risk, those with the highest susceptibility will be selected first (diabetes in childhood). Once that particular genotype (HLA *DR3/DR4*) has succumbed, progressively lower orders of accelerator genotype will follow—diabetes in adolescence (other HLA genotypes), diabetes in adulthood (*TCF7L2*), etc., each independently regulating the tempo of beta cell loss. Of course, differences in risk (insulin resistance) will also vary the tempo among individuals, and the current rise in population risk will inevitably reduce the overall contribution of genes to the probability of diabetes [4, 5].

The analysis by Field et al. is impressive in its numbers, but it does not address the accelerator hypothesis.

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