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Response to 'Familial risks in understanding type 1 diabetes genetics'

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Relating to our Review article published in this journal (Understanding type 1 diabetes through genetics: advances and prospects. *Nature Reviews Genetics* **12**, 781–792)[1], we thank Kari Hemminki (Familial risks in understanding type 1 diabetes genetics. *Nature Reviews Genetics* 17 Jan 2012 (doi:10.1038/nrg3069-c1))[2] for bringing up an important point. The value of the sibling relative risk (λ_s) is not an immutable constant but depends on the population and, in the same population, it may change over time as evolving environmental exposures alter trait heritability. Sweden and other Scandinavian countries offer a good example. There, the incidence of type 1 diabetes (T1D) is substantially higher than that in the United Kingdom[3,4] and North America[4,5], which are geographic regions that are the origin of most population samples used to estimate allele frequencies and odds ratios. Given the dramatic and variable T1D incidence increases in recent decades[3,4], a large portion of these geographic differences can be assumed to be environmental. Consequently, high-incidence regions will be expected to show lower heritability.

A precise estimate of the 'missing heritability' requires solid documentation of incidence and familial relationships that can be assured only by population-based disease registries with pedigree information in the same region or regions from which the genotyped case–control samples originate. A second-best approach might be the use of hospital discharge records that are linked to family relationship databases, as done by Hemminki *et al.*[6]. That study found a λ_s of 12, suggesting that the widely quoted (and decades-old) value of 15 may be an overestimate. One limitation of that study, and a potential source of underestimate, was that it was constrained to T1D onset under the age of 20 and would have missed affected siblings that were discordant for age of onset. Approximately 20% of T1D cases are diagnosed after the age of 20 and, even in monozygotic twins, ages of onset can differ by many years[7].

In our Review, we used the value of 15 for illustrative purposes only, and we allowed for the possibility that it may be an overestimate. However, for all we know and in the absence of reliable λ_s estimates for the lower-incidence populations sampled to calculate the contribution of genetic loci, the value of 15 is just as likely to be an underestimate as it is to be an overestimate.

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Competing interests statement
The authors declare no competing financial interests.