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Familial risks in understanding type 1 diabetes genetics

Kari Hemminki

There have been impressive advances in the genetics of type 1 diabetes (T1D) that are increasingly being translated into a greater understanding of the disease mechanisms, as reviewed in this journal by Polychronakos and Li (Understanding type 1 diabetes through genetics: advances and prospects. *Nature Reviews Genetics* **12**, 781–792)[1]. Each susceptibility gene confers a familial relative risk (λ), and multiple susceptibility genes can be modelled to give a joint λ. The derived λ can be compared to the empirical familial clustering of the disease as measured in epidemiological family studies that consider different family members: for example, parents and offspring or siblings. Sibling familial risk (λ_s) is often used in genetic studies. Polychronakos and Li gave λ_s values for 34 loci that are reliably associated with T1D (Figure 1 of Polychronakos and Li[1]), and the authors concluded that the joint contribution of the identified loci was ~60% of the empirical λ_s of 15. We would like to raise concerns about the use of an empirical λ_s of 15 for T1D and to highlight the wider need for empirical λ_s values to be regularly re-evaluated for other complex diseases.

The λ_s of 15 for T1D has been used in other prominent studies and reviews without discussion of where it has come from[1–3]. In 2003, Hirschhorn[4] cited a paper by Spielman and co-workers[5] from 1980 as the origin of this value; this paper based λ_s on a literature review. As the incidence of T1D has increased rapidly, it is likely that a pre-1980 value for λ_s is no longer accurate. In 2009, we published a family study of T1D and other autoimmune diseases based on nationwide hospitalizations in Sweden between the years 1964 and 2007 (REF. 6). Practically all childhood patients with T1D are hospitalized in Sweden[7]. These data suggested that λ_s for T1D is about 12 for Swedes who were diagnosed in the mid-1990s. Using a λ_s of 12 instead of 15 suggests that the joint gene effects actually account for a larger proportion of the familial clustering than was previously believed.

In summary, we recommend for T1D and other diseases that the effects of temporal changes in the empirical λ_s need to be monitored synchronously with genetic λ_s.

The author is at the Division of Molecular Genetic Epidemiology, German Cancer Research Centre (DKFZ), 69120 Heidelberg, Germany; and the Center for Primary Health Care Research, Lund University, Malmö, Sweden.

e-mail: k.hemminki@dkfz.de

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Competing interests statement
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