ferences in the age at onset of diabetes in the two populations. In our study the median age at onset was young at 10.5 years and we find a high rate of transmission of high-risk haplotypes from both parents. For example, of 223 *DRB1*0401-DQB1*0302* haplotypes present in mothers, 194 (87%) were transmitted to the affected child, and of 210 in fathers, 170 (81%) were transmitted. The low overall frequency of high-risk haplotypes among those that are not transmitted mask their effect, and this might be more clearly seen in populations with an older age of onset in which a higher proportion of high-risk haplotypes could remain untransmitted.

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Authors' reply

To the Editor: Hermann et al. question the influence of non-transmitted maternal *HLA DQ* risk alleles in Type 1 diabetes as shown in our recent study [1] and as earlier shown in mothers of *HLA DR4*-negative patients with rheumatoid arthritis [2]. Although this observation in rheumatoid arthritis could not be confirmed in a study from the United Kingdom [3], a more recent analysis of rheumatoid arthritis families clearly confirms the association of maternal non-inherited *HLA DR4* and rheumatoid arthritis susceptibility in two independent populations [4].

Herman et al. report their findings of 622 nuclear families with Type 1 diabetic children from Finland without significant differences between non-transmitted maternal and paternal *HLA DR-DQ* risk haplotypes. Although their data outline is similar to ours there are different frequencies of *HLA DQ* allele risk constellations: *HLA* genotypes *DQ2/x* and *DQ8/x* (51.93% in the Finnish and 39.64% in our population), *DQ2/DQ2* and *DQ8/DQ8* (10.77% vs 14.35%) and *DQ2/DQ8* (23.47% vs 32.57%). This could reflect a different background of genetic susceptibility. Nevertheless, more mothers are carrying a non-transmitted *HLA DQ2* or *DQ8* (18.6% vs 12.8% in fathers) in the group of patients with genotype *DQx/x*, similar to our observations, although not significant in the Finnish population.

In addition there are differences in the genotyping strategy between the two studies that could explain differences in their and our observations: If parent-child transmissions are screened for selective *DQB1* alleles or certain *DQA1-B1* combinations without including all possible variants, those alleles could be underdetected that are not transmitted. The full *DQA1-B1* typing enhances this resolution [5].

Lambert et al. analysed the *HLA DQA1-DQB1* genotypes in patients with Type 1 diabetes onset before age 21 and find no excess of non-transmitted maternal *DQ* risk haplotypes. However they observe a higher frequency of maternal non-transmit-

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ted *DQB1*0602* (16.3%) in comparison to this paternal non-transmitted allele (10.6%). This is of interest since the *DQB1*0602*'s frequency in the general population (19% [5]) is higher. This finding, if confirmed, suggests that mothers could confer more protection from Type 1 diabetes in offspring than fathers.

To test for data consistency we examined 26 additional families including patients with Type 1 diabetes thereby expanding our combined Belgian-German study population to 465 families (Table 1): More mothers carry *HLA DQ* risk alleles as non-transmitted in families with *DQ2/x* and *DQ8/x* patients and in *DQx/x* patients ($p=0.006$ and $p=0.048$), whereas the difference in *DQ2/DQ2* and *DQ8/DQ8* offspring shows merely a trend ($p=0.0747$). Mothers of all patients (except the *DQ2/DQ8* heterozygous ones) carry more often a non-transmitted *DQ* risk allele (35.9%) than fathers (21.6%, $p=8.5 \times 10^{-4}$). Thus we confirm our earlier findings and we are confident in the consistency of our data.

The inherited form of Type 1 diabetes susceptibility conferred by *HLA DQ* remains the single most important risk factor. Only 18 patients out of 465 (3.9%) who have the genotype *HLA DQx/DQx* have a mother with a non-transmitted risk allele, whereas 86% of patients have at least one inherited susceptible *HLA DQ*. Therefore the contribution of non-transmitted alleles to disease susceptibility is small. However, it shows a potential of *HLA DQ* to act in a non-genetic, but "environmental" fashion. Whether this mode of action is due to maternal microchimerism or caused by an in utero acquired infection or antigen presentation remains to be examined. We believe the main reason for the discrepancy between Hermann's et al. and our findings is due to the different populations studied. There are major differences between the Finnish, Belgian and German populations, most of which are reflected by a different incidence of the disease but also by particular predisposing haplotypes unique to the Finnish population [6, 7]. Also, disease heterogeneity between and within the two populations could result in a different selection of families [8].

The discrepancy of our to the United Kingdom or Finnish findings could result from such heterogeneous variables as age of onset (median of 7 years in the Belgian and 6 years in those German families with an age at manifestation recorded) but

Table 1. Maternal and paternal non-transmitted diabetogenic *HLA DR-DQ* haplotypes (*DQ2* or *DQ8*) in 465 families with a Type 1 diabetic patient (*DQ2* is *DQA1*05-DQB1*02*; *DQ8* is *DQA1*03-DQB1*0302*)

<i>HLA DQ</i> genotype of affected offspring	Number of patients	Number of <i>DQ2</i> or <i>DQ8</i> as not transmitted parental haplotype	$p(\chi^2)$
a) <i>DQ2/DQ8</i>	145	Mothers: 33 (22.8%) Fathers: 41 (28.3%)	0.3457
b) <i>DQ2/DQ2</i> and <i>DQ8/DQ8</i>	68	Mothers: 22 (32.4%) Fathers: 12 (17.6%)	0.0747
c) <i>DQ2/x</i> and <i>DQ8/x</i>	187	Mothers: 75 (40.1%) Fathers: 49 (26.2%)	0.0060
d) <i>DQx/DQx</i>	65	Mothers: 18 (27.7%) Fathers: 8 (12.3%)	0.0484
e) All except <i>DQ2/DQ8</i> hetero-zygous offspring	320*	Mothers: 115 (35.9%) Fathers: 69 (21.6%)	8.5×10^{-4}

*Equals the sum of subsets b, c and d

also from differences in the ascertainment methods and thus possibly an influence of hitherto poorly understood factors. These issues need to be addressed further.

Despite the conflicting results between our and the two other studies there is a uniform finding of more maternal non-transmitted *DQ* risk haplotypes in patients carrying the *DQx/DQx* constellation: Pooling the data of Hermann et al. and Lambert et al. as shown in their tables with our new results yields 221 families with *DQx/DQx* offspring. In these families there are more mothers with non-transmitted *HLA DQ2* or *DQ8* (50, 22.62%) than fathers (31, 14.03%, $p=0.0269$) which confirms our original observation.

Since the influence of non-transmitted *HLA DR-DQ* risk alleles is now shown in two autoimmune diseases from two independent populations, we expect that it can be found in other populations and possibly other autoimmune diseases. The better understanding of a non-genetic action of *HLA DQ* risk alleles will help to clarify the pathogenesis of Type 1 diabetes and other autoimmune disorders.

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