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Estimation of Transmission Probabilities in Families Ascertained through a Proband with Variable Age-at-Onset Disease: Application to the HLA A, B and DR Loci in Finnish Families with Type 1 Diabetes

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Key Words
Transmission probability · Ascertainment · Recruitment window · Variable age at onset · HLA · IDDM

Abstract
An open problem of some interest in the study of HLA has been the possible existence of transmission distortion in the human HLA complex. In this paper, transmission probabilities are estimated and tested using data on HLA A, B and DR loci genotypes of parents and offspring ascertained from the entire population of Finland (Childhood Diabetes in Finland Study) through one or more offspring diagnosed with insulin-dependent diabetes mellitus (IDDM) during the recruitment period from September 1986 to July 1989. First, we show how to get unbiased estimates of transmission probabilities from the family data collected in the disease registry of incident cases. This is accomplished by assuming that transmission of HLA genes to children in the general population is conditionally independent given the parents' genotypes, and the birth dates of all offspring. Based on the sampling (ascertainment) process in the study on Childhood Diabetes in Finland, younger siblings of the index child (the oldest proband) are independent of the ascertainment and therefore give rise to unbiased inference regarding allele transmission. The hypothesis of Mendelian transmission of alleles at each locus was tested using the standard χ^2 test. Goodness-of-fit of the Mendelian inheritance model to the individual locus data is calculated by maximizing the likelihood function over allele transmission intensities at each locus. The existence of a strong transmission distortion is not supported by this study at the loci considered.

Introduction

Both genetic and environmental risk factors are thought to contribute to the susceptibility of insulin-dependent diabetes mellitus (IDDM). A major contribution to the genetic susceptibility to IDDM is conferred by the gene(s) at the HLA region in chromosome 6 [1, 2]. Earlier studies have found a strong association between IDDM and both DR3,DQ2 and DR4,DQ8 haplotypes.

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Several hypotheses about the mode of inheritance have been put forward, but the true mechanism remains unclear. It has been claimed that the inheritance of diabetes-associated alleles (mainly DR3 and DR4) might be distorted, being higher than 50% from either the mother or the father or both [3–6], but the results are conflicting [7–9]. In the context of diabetes research and in the study of HLA evolution, these observations are of special interest, as there are several insufficiently understood phenomena affecting the inheritance of the disease as well as its epidemiology: the risk of developing diabetes appears to be higher in the offspring of diabetes fathers than in those of diabetic mothers [10], which suggests that the inheritance of susceptibility to IDDM might be influenced by the sex of the affected parent. Secondly, the incidence of IDDM is increasing worldwide [11, 12], which has been proposed to reflect a change in the genetic pool of populations [13]. Thirdly, despite the obviously deleterious effect of the diabetogenic haplotypes DR3,DQ2 and DR4,DQ8, they are common in many populations, which is yet to be explained.

According to Mendel's first law (law of segregation), every individual receives one of the two parental alleles with equal probability. Deviation from this law, called transmission distortion, has been established in certain organisms [14]. Specifically, in mice some alleles of the T/t complex, which is linked to H-2 (the HLA homologue of mice), cause extreme transmission distortion. Concerning humans, there have recently been several claims of transmission distortion for loci associated with diseases caused by trinucleotide repeats [15–17] as well as a segment of the X chromosome [18].

The evidence concerning transmission distortion in HLA is conflicting. Most studies in this field have been conducted using small samples of subjects ascertained through an HLA-associated disease, like IDDM, which makes the interpretation of the results difficult and is also a potential source of bias. To our knowledge, there are only two studies using random samples from nondiseased populations [6, 7]; however, the data were collected from several populations around the world (International Histocompatibility Workshop data [19]), and thus transmission distortion could be found only if it existed simultaneously in several populations. Neither of the studies mentioned above found evidence of significant transmission distortion.

Results from the studies based on diabetic families are varying and inconclusive. Vadheim et al. [4] reported a statistically significant transmission distortion. They claimed that fathers with a DR4 allele were significantly more likely to transmit this allele to their offspring than were mothers with a DR4 allele, and that DR3 is transmitted significantly more than 50% by either parent. However, they had erroneously included both the affected and unaffected children in their data analysis, and a reanalysis using only unaffected siblings showed significant transmission distortion merely for DR3 – though this most likely is overcorrecting. Tuomilehto-Wolf et al. [5] reported transmission of a high-risk haplotype (A2,B56,DR4,DQ8) from the mothers to the offspring in Finnish families with IDDM to be 62%. In this study, the index children, through whom the families had been ascertained, were excluded in order to obtain less biased estimates of the transmission probabilities. Martin-Villa et al. [8] and Kockum et al. [9], using diabetic families, do not find any support for the non-Mendelian transmission of alleles at the DR and DQ loci.

A major complication in interpreting and comparing the results from studies of diabetic or other HLA-associated diseases is in the various procedures of data collection. Failure to take into account how the data were collected (the ascertainment process) will often lead to biased results. This was noted e.g. by Falk et al. [20] in a letter to the editor concerning the results of Vadheim et al. [4]. Concerning the study on Childhood Diabetes in Finland (DiMe Study), ascertainment bias has been investigated on the issue of rate ratio estimation by Langholz et al. [unpubl. data].

This paper has two purposes. First, we show how unbiased estimates of the transmission probabilities, i.e. probabilities that a heterozygote parent transmits a particular allele, can be obtained from data ascertained through a proband with variable age-at-onset disease. Then we estimate transmission probabilities of alleles at HLA A, B or DR loci to offspring, using families with IDDM and taking into account the ascertainment. The data (DiMe Study) consist of nuclear families ascertained through at least 1 child (under the age of 15) diagnosed with IDDM during the recruitment period.

Subjects and Methods

The DiMe Study is the largest population-based genetic-epidemiological family study of IDDM [21]. Nationwide, all cases under the age of 15 in Finland were identified during the recruitment period from September 1986 to April 1989. The data set consists of 801 participating families with at least 1 IDDM child. Affected children as well as their parents and siblings were HLA genotyped at A, B and DR loci using conventional serology. HLA genotyping was done on 757 families. Details of the study procedure are described elsewhere [21]. Only parent-child sets with complete HLA genotypes were eligi-

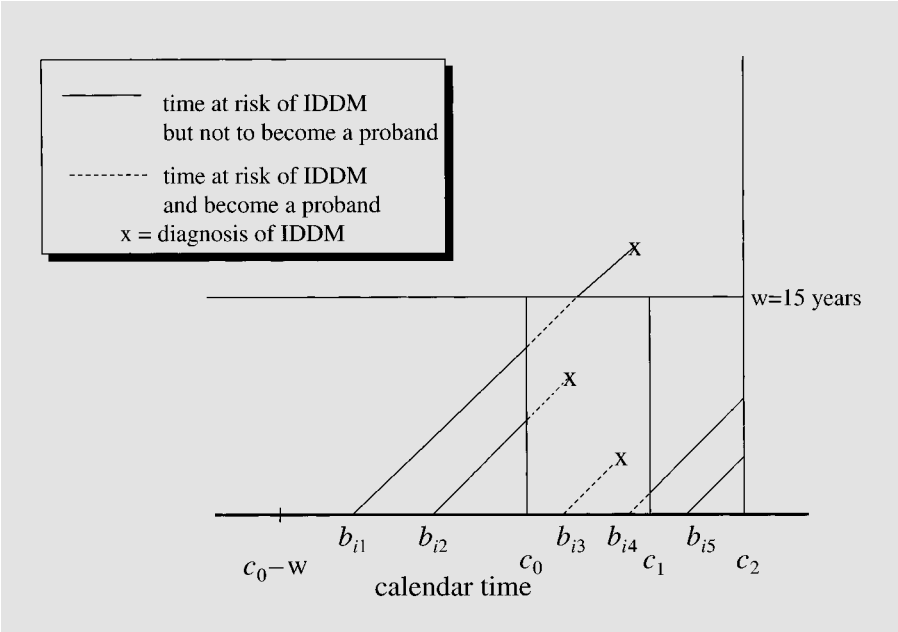

Fig. 1. Lexis diagram of the ascertainment of sibship *i* in the DiMe Study
$b_{i1,...,}$ b_{i5} birth dates of child in sibship *i*,
c_o date of the beginning of the recruitment period,
c_1 date of the end of the recruitment period,
c_2 end of the follow-up.

Table 1. Number of families and transmissions according to the parental source of allele at the A, B and DR loci in the DiMe Study, where both parents and younger children than the index child are HLA genotyped

	Locus A		Locus B		Locus DR	
	paternal	maternal	paternal	maternal	paternal	maternal
Number of families[1]	217	231	257	261	221	234
Number of transmissions	293	310	332	346	284	303

[1] Both parents and at least one younger child than the index child are HLA genotyped.

ble for this study. In the DiMe data there were altogether 718 siblings in 471 families who were born after the oldest child in a family to be diagnosed with IDDM during the enrollment period. The numbers of families, individuals and transmissions eligible for the analysis are given in table 1.

The estimation and testing of transmission probabilities at a multiallelic locus can be done, in the case of a random sample, by applying the methods described by Jin et al. [6]. However, since the participating nuclear families in the DiMe Study were collected through an affected offspring, naive use of standard estimation techniques could easily lead to spurious results. Therefore the method of ascertainment had to be taken into account in the estimation. In the following, we show how a natural conditional independence assumption can be applied for drawing unbiased inferences on the transmission probabilities.

Let $i = 1, ..., I$ index the families and $j = 1, ..., J_i$, the children in the ith family born during the calendar time interval $(c_0–w,c_1)$, where c_0 is the beginning and c_1 is the end of the recruitment period. A Lexis diagram (fig. 1) is used to illustrate the ascertainment of a hypothetical family with 5 children. Children born at dates b_2 and b_3 are probands, and the former is the index child whose diagnosis led to the ascertainment of the family. Let b_{ij} be the date of birth of the jth child in family i and let the children be arranged in their birth order: $b_{i1} < b_{i2} < ... < b_{iJ_i}$. In order for a child to be ascertained into the study set,

his/her age at the time of the diagnosis must be less than $w = 15$ years. Let T_{ij} be the calendar time of diagnosis of IDDM of the jth child in family i. We follow the convention that if there is no such diagnosis $T_{ij} = \infty$. Let $Y_{ij} = \min(T_{ij}, c_1)$, and let $\delta_{ij} = 1$ if $c_0 \le Y_{ij} < c_1$, $c_0 - w \le b_{ij} \le c_1$ and $Y_{ij} - b_{ij} < w$. Here Y_{ij} is the onset time of IDDM of child j in family i if $\delta_{ij} = 1$ (in which case this child is a proband).

Consider a particular HLA locus of interest, and let $g_{ij} = (g_{ijm}, g_{ijf})$ be the observed HLA genotype of the jth child in the ith family, where g_{ijp} is the allele inherited from parent p (where m indicates mother and f father). Let $G_i^p = \{G_i^{p1}, G_i^{p2}\}$ be the observed genotype at that locus of parent p of the ith sibship, where superscripts 1 and 2 indicate the two alleles, because grandparental origin is not known. The data we consider can be represented by $\{Y_{ij}, \delta_{ij}, \{g_{ijp}, G_i^{p1}, G_i^{p2}; p = m,f\}, b_{ij}; i = 1, ..., I, j = 1, ..., J_i\}$.

Using index r for the alleles of a locus (the total number of different alleles being A), a random variable Z_{ijp} is created, which gets value r, $r = 1, ..., A$, if child j in family i got allele r from parent p, writing then $Z_{ij} = (Z_{ijm}, Z_{ijf})$. Let K_i be the index (in birth order) of the index child, that is

$$K_i = \min(j : Y_{ij} \in [c_0, c_1], b_{ij} \in [c_0 - w, c_1], Y_{ij} - b_{ij} < w).$$

the following assumptions: (1) the values of $\{b_{ij}; j = 1, ..., J_i\}$, $G_i^m G_i^f$ are known (observed); (2) for each sibship i in the general population, the variables $\{Z_{ij}, Y_{ij}, \delta_{ij}; j = 1, ..., J_i\}$ are conditionally mutually independent given $\{b_{ij}; j = 1, ..., J_i\}$ and G_i^m, G_i^f; (3) sibships are ascertained independently.

Assumption (2) implies that the conditional independence $\{Z_{ij}, Y_{ij}, \delta_{ij}; j \le k\} \perp \{Z_{ij}, Y_{ij}, \delta_{ij}; j > k\} \mid \{b_{ij}; j = 1, ..., J_i\}, G_i^m, G_i^f$ holds for all $k \ge 1$. In particular, since the truth of the ascertainment event $\{K_i = k\}$ can always be decided from $\{Z_{ij}, Y_{ij}, \delta_{ij}; j \le k\}$ it will also be true that $\{Z_{ij}, Y_{ij}, \delta_{ij}; j \le K_i\} \perp \{Z_{ij}, Y_{ij}, \delta_{ij}; j > K_i\} \mid \{b_{ij}; j = 1, ..., J_i\}, G_i^m G_i^f$. But this shows that, given $\{b_{ij}; j = 1, ..., J_i\}$ and G_i^m, G_i^f, the genotypes Z_{ij} of all siblings younger than the index child K_i are always sampled independently of the events that led to the ascertainment of the family.

Thus, there are three possible subsets of children in each sibship: (1) children who were older than 15 at the beginning of the recruitment period (obviously, the same conditional independence applies to all older siblings, in case there were any), (2) children who were eligible to become a proband and older than the index child, or the index child himself/herself, and (3) children younger than the index child. Genotypes, i.e. the transmission of alleles from parents to offspring, are independent of the ascertainment in sets 1 and 3, but not in set 2 through which the ascertainment of the family has taken place. Children in set 2 who were not diagnosed with IDDM during the recruitment period are less likely to have inherited diabetic genes than a random child of the same parents. Excluding set 2 from analysis allows one to make unbiased inference without need to model the probability of the ascertainment event.

We use the notation introduced by Jin et al. [6]. Considering alleles r and s,

$$n_{rs} = \sum_{i=1}^{I} \sum_{p=m,f} \sum_{j=K_i+1}^{J_i} 1\{Z_{ijp} = r, G_i^p = \{r,s\}\}$$

denotes the number of r alleles inherited from parental genotype $\{r,s\}$, where the first character in the subscript indicates the transmitted allele and the second the nontransmitted. Obviously, $w_{rs} = n_{rs} + n_{sr}$ is the total number of transmissions seen from parental genotype $\{r,s\}$ in the data. The shorthand notation $\tau_{rs} = P(Z_{ijp} = r \mid G_i^p = \{r,s\})$ is used for transmission probabilities, noting that $\tau_{rr} = P(Z_{ijp} = r \mid G_i^p = \{r,r\}) = 1$. These probabilities obviously satisfy $\tau_{rs} + \tau_{sr} = 1, \forall\, r \ne s$. Our statistical inference is now based on the likelihood function

$$L(\{n_{rs}; r < s\} \mid \{w_{rs}; r < s\}, \{\tau_{rs}, r \ne s\}) = \prod_{r,s} \binom{w_{rs}}{n_{rs}} \tau_{rs}^{n_{rs}} \tau_{sr}^{n_{sr}},$$

where the product is over all pairs of r and s such that $r < s$ and $w_{rs} > 0$. Following Jin et al. [6], we then assume that the transmission probabilities τ_{rs} can be written as $\alpha_r/(\alpha_r + \alpha_s)$, where $\alpha_s > 0$, $r = 1, ..., A$. Parameters α_r and α_s can be interpreted as transmission intensities of alleles r and s that are competing with each other in meioses. For the purpose of identifiability, we constrain their values by the requirement $\sum_{r=1}^{A} \alpha_r = A$.

An overall test statistic (global test) for Mendelian transmission (H_0: $\tau_{rs} = 0.5, \forall\, r,s\, r \ne s$) is based on the sum of squared standardized normally distributed random variables

$$\sum_{r,s} \left[\frac{n_{rs} - 0.5 w_{rs}}{\sqrt{0.25 w_{rs}}} \right]^2,$$

where the sum is over all possible pairs of r and s such that $r < s$. Under the null hypothesis, this is approximately χ^2-distributed with $A(A-1)/2 - A_0$ degrees of freedom. Here A_0 is the number of total pairs for which $w_{rs} = 0$.

To assess the possible contribution of multiple alleles to transmission distortion at a particular locus, genotype-specific transmission probabilities are written as functions of allele-specific transmission intensities. First, we estimated the single allele transmission probabilities and their variances [6] (formulas 11 and 12). These probabilities were tested, with test statistic $Z = (\hat{\alpha}_r - 1)/\sqrt{V(\hat{\alpha}_r)}$, ($V(\hat{\alpha}_r)$ being the variance of the transmission intensity) which, under the null hypothesis, follows the standard normal distribution. Next, we calculated a goodness-of-fit for this model using the statistic

$$\sum_{r,s} \frac{(n_{rs} - \hat{\tau}_{rs} w_{rs})^2}{\hat{\tau}_{rs} w_{rs}},$$

where $\hat{\tau}_{rs}$ is calculated from the transformation $\tau_{rs} = \alpha_r/(\alpha_r + \alpha_s)$, after having maximized the likelihood function above with respect to the transmission intensity vector $\alpha = (\alpha_1, ..., \alpha_A)$.

Results

A Locus

According to the global test, there was some evidence of transmission distortion in both maternal ($\chi^2 = 40.12$, 26 d.f., $p = 0.04$) and paternal alleles transmitted ($\chi^2 = 37.39$, 24 d.f., $p = 0.04$). Estimated transmission probabilities with 95% confidence intervals are shown in figure 2 for fathers and in figure 3 for mothers. Paternal A26 ($Z = -3.65$, $p < 0.01$) and maternal A32 alleles ($Z = -2.73$, $p < 0.01$) were transmitted less often than expected under the hypothesis of Mendelian transmission probabilities. There is also some indication that segregation of alleles of

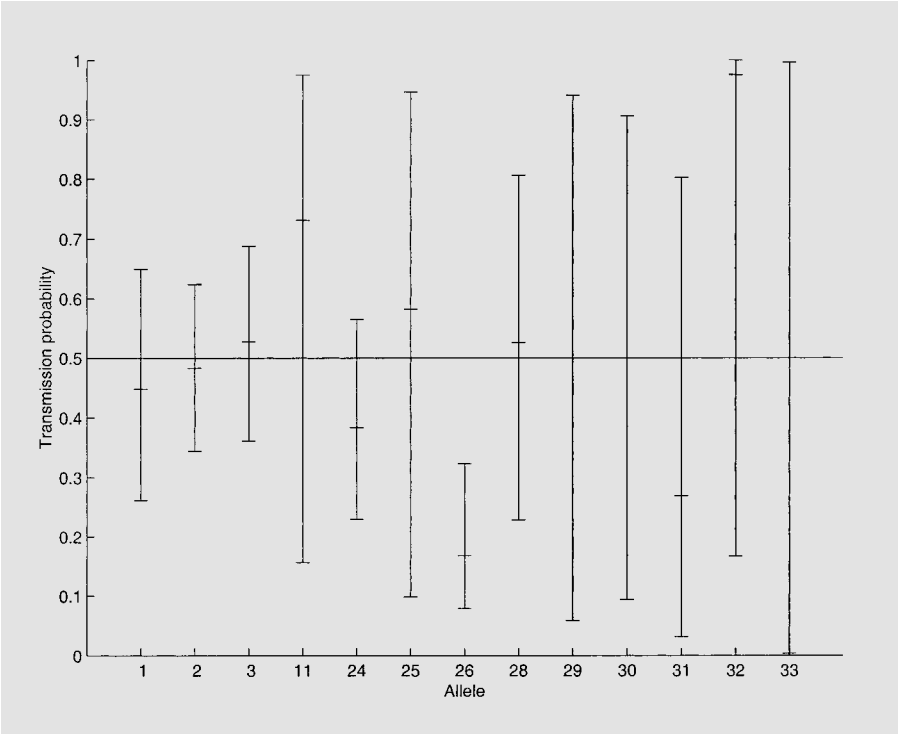

Fig. 2. Single allele transmission probabilities and 95% confidence intervals of paternal alleles at the A locus.

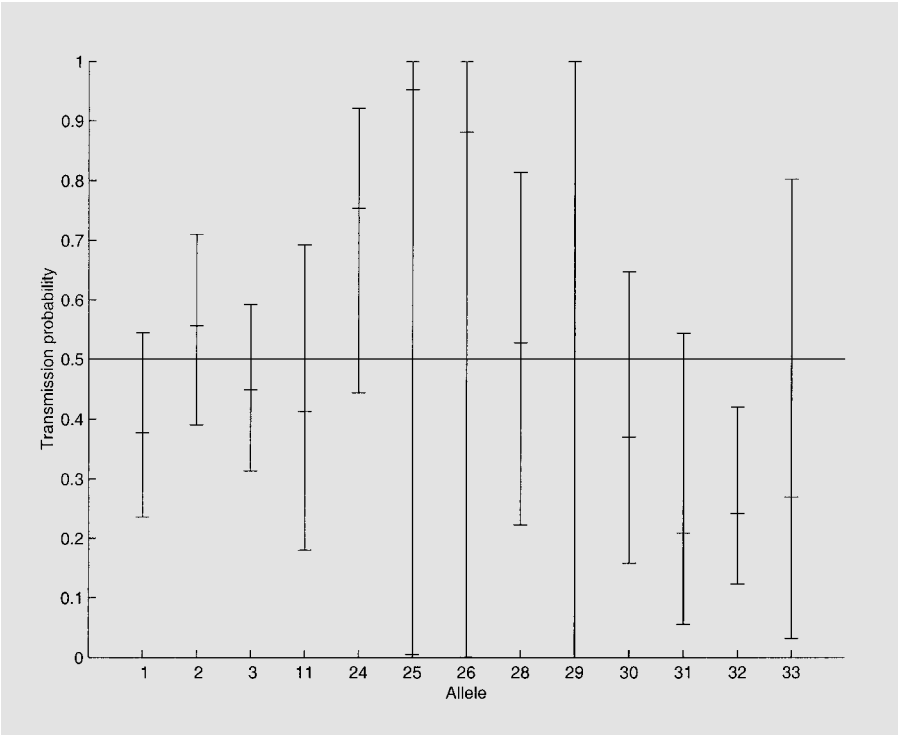

Fig. 3. Single allele transmission probabilities and 95% confidence intervals of maternal alleles at the A locus.

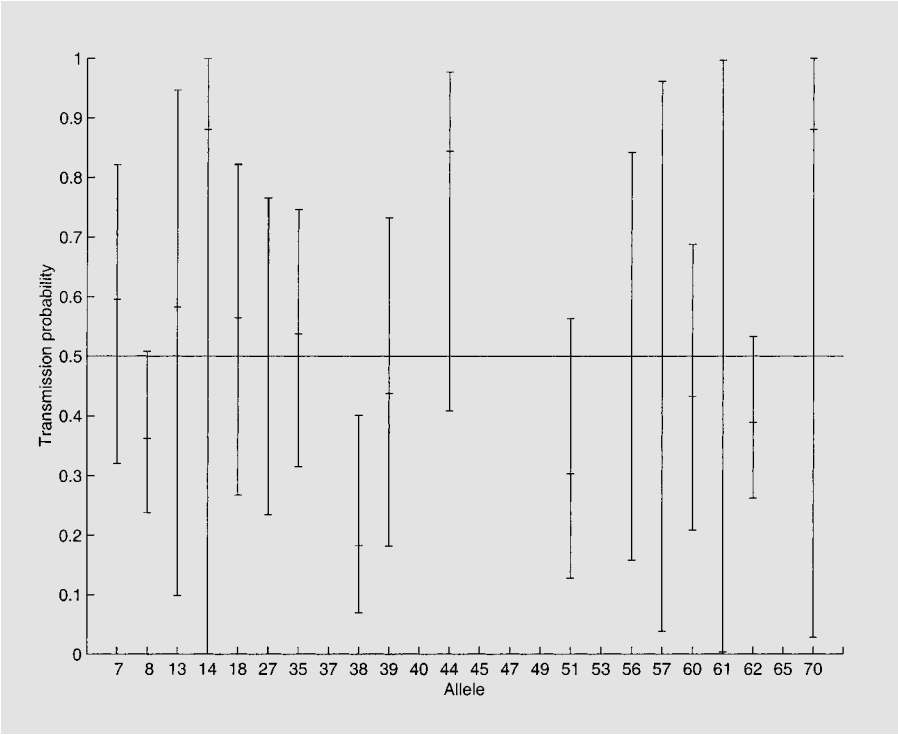

Fig. 4. Single allele transmission probabilities and 95% confidence intervals of paternal alleles at the B locus.

paternal genotypes A28,A32 (χ^2 = 5.48, 1 d.f., p = 0.02) and A2,A3 (χ^2 = 4.62, 1 d.f., p = 0.03) may not happen according to Mendel's law. However, the goodness-of-fit test of neither maternal alleles (χ^2 = 13.7, 13 d.f., p = 0.40), nor paternal alleles (χ^2 = 17.06, 12 d.f., p = 0.15) was not statistically significant.

B Locus

There was statistically significant distortion in the maternal alleles transmitted according to the global test (χ^2 = 97.58, 63 d.f., $p < 0.01$), but only borderline significance of the paternal alleles (χ^2 = 71.88, 54 d.f., p = 0.05). Estimated transmission probabilities of individual alleles with their 95% confidence intervals alleles are shown in figure 4 for fathers and in figure 5 for mothers. Both paternal B38 (Z = −2.68, $p < 0.01$) and maternal B62 (Z = −2.67, $p < 0.01$) alleles were transmitted at a lower frequency than expected. The goodness-of-fit tests of maternal alleles (χ^2 = 39.59, 35 d.f., p = 0.27) and paternal alleles (χ^2 = 24.84, 31 d.f., p = 0.78) were not statistically significant.

DR Locus

Considering the locus as a whole, there was no evidence of transmission distortion of either maternal alleles (χ^2 = 42.01, 39 d.f., p = 0.34) or paternal alleles (χ^2 = 43.79, 29 d.f., p = 0.25). Estimated transmission probabilities of alleles at the DR locus with their 95% confidence intervals are shown in figure 6 for fathers and in figure 7 for mothers. Only the transmission of maternal DR2 alleles differed significantly (Z = −2.60, $p < 0.01$) from the pattern expected under the hypothesis of Mendelian transmission. The goodness-of-fit tests of the transmission of maternal (χ^2 = 17.4, 27 d.f., p = 0.92) and paternal (χ^2 = 13.3, 17 d.f., p = 0.72) alleles were not statistically significant.

Discussion

Our data do not provide direct support to the hypothesis of non-Mendelian inheritance of alleles at the HLA A, B and DR loci. To make this conclusion, we rely on the goodness-of-fit test where single allele transmissions are estimated simultaneously and there are less parameters to be estimated than in the global test. Single allele transmission probabilities were calculated to reveal individually the alleles inherited in a non-Mendelian fashion. Even though some single allele transmission frequencies were statistically significantly different from 50%, these find-

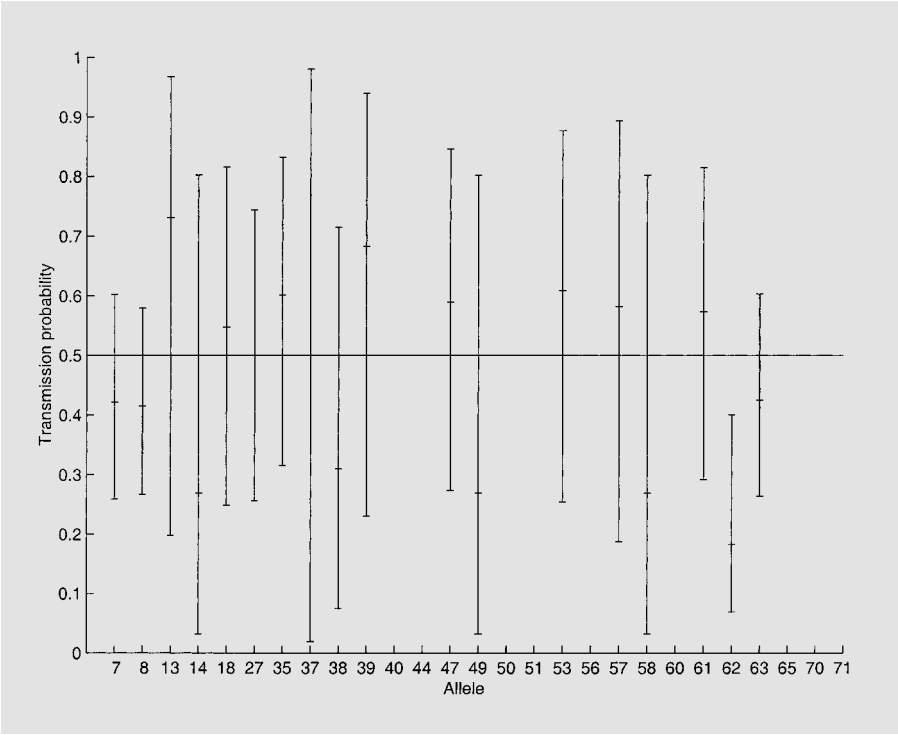

Fig. 5. Single allele transmission probabilities and 95% confidence intervals of maternal alleles at the B locus.

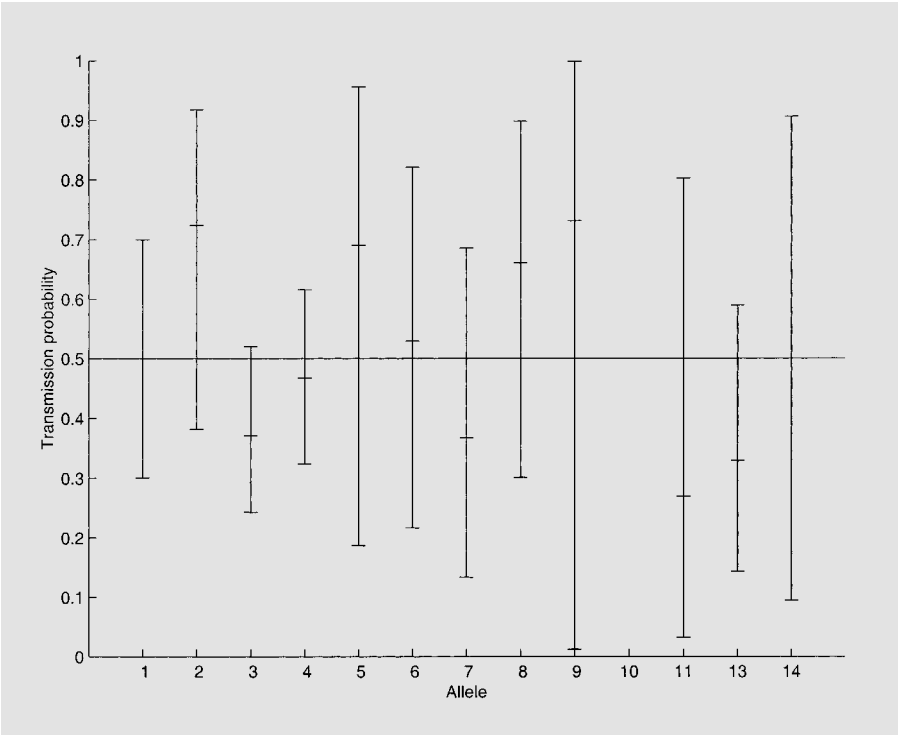

Fig. 6. Single allele transmission probabilities and 95% confidence intervals of paternal alleles at the DR locus.

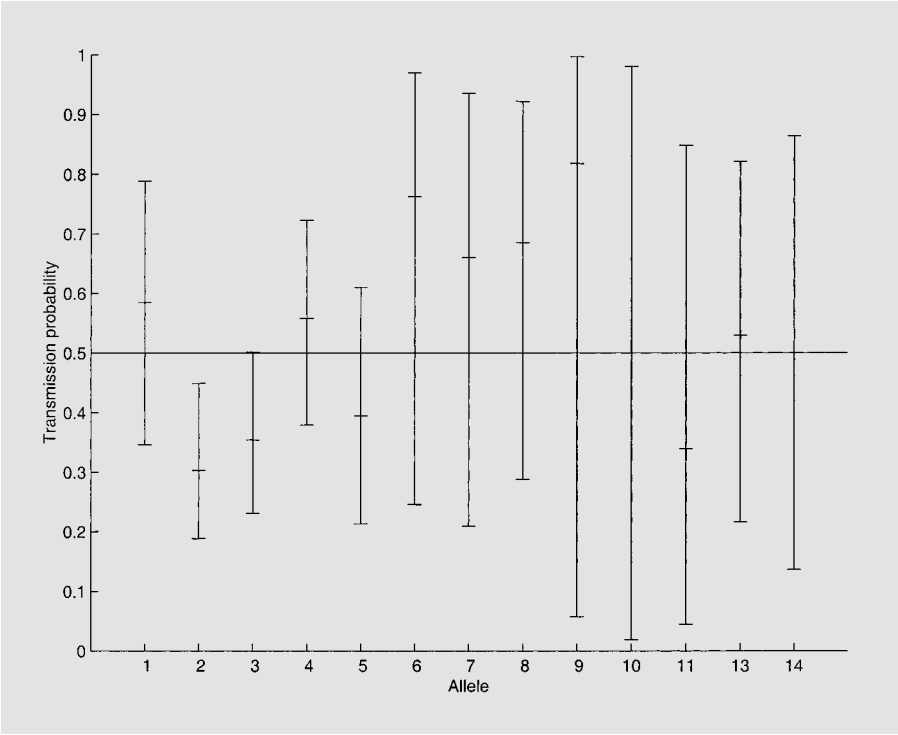

Fig. 7. Single allele transmission probabilities and 95% confidence intervals of maternal alleles at the DR locus.

ings cannot be considered to be conclusive as the significance levels have not been corrected for multiple comparisons. However, we can conclude that the existence of strong transmission distortion in the considered loci is excluded by our study.

Comparison to the results of other studies, like Klitz et al. [7] and Jin et al. [6], does not reveal consistent patterns of HLA allele transmission. In our data set, paternal A26 was transmitted less often than expected, whereas in the Caucasian population sample of Klitz et al. [7] it was transmitted at a higher than 50% frequency. There were no other common alleles detected in these studies which would have deviated from Mendelian transmission ratios in either locus A, B or DR. This inconsistency of the results is not surprising: first, because sparse data on highly polymorphic loci will generally lead to low significance in statistical tests; secondly, there is no inherent reason for alleles to deviate from Mendelian ratios in a systematic way in different populations: the International Histocompatibility Workshop data were collected from several different populations, whereas ours represents the Finnish population. Even if significant transmission distortion existed, it is quite possible that it would affect different alleles in different populations. The other studies on transmission probabilities referred to in this paper [2, 4, 5, 8, 9] showed non-Mendelian transmission for DR3 and DR4, which was not found in this study. Some of the groups had observed such transmission to affected children [4, 8, 9, 22]; however, this may only indicate association between the genes and the disease (penetrance). Still, these considerations are justified if one is interested specifically in the possible differential transmission of diabetic alleles from healthy or affected parents to diabetic offspring. In this study, we did not want to go into these questions because this would have required taking into account the issue of penetrance, which is not a straightforward matter.

This study provides only weak support for the hypothesis of increasing genetic susceptibility in populations and, thereby increasing incidence, due to non-Mendelian transmission of diabetic alleles. This is because the alleles which were now suggested to be inherited in a distorting fashion are not diabetes-associated, except for B62, or are even negatively associated (e.g. DR2, which is called protective). They are all found to be transmitted less often than expected under Mendelian segregation. If the prevalences of these non-diabetes-associated alleles decrease in the population, then the net impact on the frequency of other alleles should be a slight increase. If the genetic pool is changing, this change does not directly influence dia-

betes-associated genes and has a minor effect on the proportion of genetically susceptible individuals. Only if one assumes some degree of transmission distortion of susceptibility alleles and reasonable penetrances for these alleles, could an increase in the incidence of diabetes result. This possibility has been explored by Onkamo et al. [unpubl. data] in a study where the theoretical rate of change was compared to the real increase in incidence seen in Finland during the past few decades.

Finally, we remark that when using analysis methods which are based on the assumption of Mendelian transmission, like TDT [23] or linkage methods, transmission distortion will generally influence the probability of finding a significant association. It is easy to reason that, given that there is transmission distortion in a genome region which contains a candidate gene for disease, ignoring positive transmission distortion would lead to false-positive findings.

Apparently, the possibility of biased transmission should be carefully explored in genetic studies. The method proposed in this paper provides unbiased estimates of transmission probability from data ascertained through an affected individual during the recruitment period. Unfortunately, direct unbiased estimation is only possible by ignoring some of the data (the index child and his/her older siblings). In spite of the resulting loss of power to detect transmission distortion, we find that avoiding bias is more important. To incorporate transmission data from elder siblings, modeling of the ascertainment (disease) process is required. This will be studied in a future work.

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