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Analysis of maternal–offspring HLA compatibility, parent-of-origin and non-inherited maternal effects for the classical HLA loci in type 1 diabetes

P. G. Bronson[1], **P. P. Ramsay**[1], **G. Thomson**[2], **L. F. Barcellos**[1], and **the Type 1 Diabetes Genetics Consortium**

[1] Division of Epidemiology, School of Public Health, University of California, Berkeley, CA, USA

[2] Department of Integrative Biology, University of California, Berkeley, CA, USA

Abstract

Aim—Type 1 diabetes (T1D) is a complex trait for which variation in the classical human leucocyte antigen (HLA) loci within the Major Histocompatibility Complex (MHC) significantly influences disease risk. To date, HLA class II *DR-DQ* genes confer the strongest known genetic effect in T1D. HLA loci may also influence T1D through additional inherited or non-inherited effects. Evidence for the role of increased maternal–offspring HLA compatibility, and both parent-of-origin (POO) and non-inherited maternal HLA (NIMA) effects in autoimmune disease has been previously established. The current study tested hypotheses that classical HLA loci influence T1D through these mechanisms, in addition to genetic transmission of particular risk alleles.

Methods—The Type 1 Diabetes Genetics Consortium (T1DGC) cohort was of European descent and consisted of 2271 affected sib-pair families (total n = 11 023 individuals). Class I genes *HLA-A, Cw* and *B,* and class II genes *HLA-DRB1*, *DQA1*, *DQB1*, *DPA1* and *DPB1* were studied. The pedigree disequilibrium test was used to examine transmission of HLA alleles to individuals with T1D. Conditional logistic regression was used to model compatibility relationships between mother–offspring and father–offspring for all HLA loci. POO and NIMA effects were investigated by comparing frequencies of maternal and paternal transmitted and non-transmitted HLA alleles for each locus. Analyses were also stratified by gender of T1D-affected offspring.

Results—Strong associations were observed for all classical HLA loci except for *DPA1*, as expected. Compatibility differences between mother–offspring and father–offspring were not observed for any HLA loci. Furthermore, POO and NIMA HLA effects influencing T1D were not present.

Conclusions—Maternal–offspring HLA compatibility, POO and NIMA effects for eight classical HLA loci were investigated. Results suggest that these HLA-related effects are unlikely to play a major role in the development of T1D.

Keywords

HLA; maternal–offspring HLA compatibility; non-inherited maternal; parent-of-origin; T1D

Introduction

Type 1 diabetes (T1D) (MIM 222100) is an autoimmune disease characterized by chronic T cell–mediated destruction of pancreatic insulin-producing β-cells [1]. While age-at-onset peaks in late childhood, adults also develop this disorder, and incidence rates for females and males are similar [2]. Incidence in the USA is estimated to be ~15 in 100 000 children per year; however, it varies widely around the world and has been increasing over the past decade [2]. Although the aetiology of T1D remains unknown, evidence for genetic susceptibility is well established [3,4]. Concordance for T1D in monozygotic twins is 70% compared with just 13% in dizygotic twins; the relative risk for sibs (λ_s) is approximately 15 in the US Caucasian population [5].

The human leucocyte antigen (HLA) class II genes *HLA-DRB1, DQA1* and *DQB1* in the Major Histocompatibility Complex (MHC) region (6p21) are directly involved; the MHC region accounts for 40–50% of the genetic susceptibility in individuals of Northern European Caucasian descent [6]. The majority of Caucasian individuals with T1D carry the *HLA-DR3* (*DRB1*0301-DQA1*0501-DQB1*0201*) or *DR4* (*DRB1*04-DQA1*0301-DQB1*0302*) class II haplotype, and approximately 30–50% of individuals are *DR3/DR4* heterozygotes [7]. *DR3/ DR4* heterozygosity confers the highest diabetes risk [8]. Different class II HLA associations with T1D are present in non-Caucasian populations [9]. Class I *HLA-B* has also been associated with T1D risk, specifically the *B*39* and *B*18* alleles [10,11]. Interestingly, the class II *HLA-DR2 (DRB1*1501-DQB1*0602*) haplotype is protective in all populations studied to date [12]. Additional non-MHC genetic risk factors for T1D include *PTPN22* (1p13), *CTLA4* (2q33) and *IDDM2* (11p15) [13–15]. Environmental factors have also been strongly implicated in both pathogenesis and outcome of T1D [16].

HLA loci may also influence T1D through additional inherited or non-inherited effects. Differences in maternal and paternal transmission rates, or parent-of-origin (POO) effects, have been observed in T1D. One potential mechanism is 'genomic imprinting', an epigenetic modification of the genome that results in unequal transcription of parental alleles and subsequent allele expression, depending on whether alleles were transmitted maternally or paternally.

HLA compatibility between a mother and her offspring may also contribute to susceptibility to autoimmunity, possibly because HLA similarity between the mother and foetus may promote the persistence of foetal cells in the host or perhaps through specific exposure to non-inherited maternal HLA (NIMA) risk or protective alleles. Risk for an autoimmune disease would be potentially increased in either mother or offspring. Maternal–offspring HLA compatibility that increases disease risk in the mother could explain: (i) increased prevalence of autoimmune diseases in women following their child-bearing years and (ii) clinical similarities between scleroderma (systemic sclerosis (SSc)] and graft-vs.-host disease [17]. With regard to T1D, maternal–offspring HLA compatibility could affect risk in the offspring. Maternal–offspring cell trafficking is common and bidirectional; maternal nucleated cell and plasma DNA transfers into foetal circulation in 24 and 30% of offspring, respectively [18]. Maternal–offspring effects can present as excess HLA compatibility between the mother and affected offspring or excess maternal homozygosity. Possible maternal–offspring HLA compatibility relationships are illustrated in figure 1.

Finally, non-host exposure during foetal development and potential long-term persistence of maternal cells in offspring may play a role in T1D pathogenesis [19–22]. The developing immune system of the foetus is exposed to NIMA *in utero* [21,23,24]. Decreased B-cell responses and cytotoxic T-cell activity to HLA class I NIMA have been reported [25–29].

NIMA can have a lifelong influence on the immune system and may tolerize or pre-dispose to autoimmune reactions [30–32].

The current study tested hypotheses that classical HLA loci influence T1D through these additional biological mechanisms in addition to genetic transmission of particular risk alleles.

Methods

Subjects

TheT1DGCcohort (release 2007.02.MHC) was of European descent and consisted of 2271 affected sibling-pair families with 11 023 individuals. This research resource has been previously described [33]. Briefly, the families were derived from multiple cohorts: Asia-Pacific (177), British Diabetes Association (BDA) (422), Danish (147), European (475), Human Biological Data Interchange (HBDI) (421), Joslin (117), North American (321), Sardinian (77) and UK (114). The mean number of individuals per family was 5 and ranged from 3 to 26. The mean number of generations per family was two and ranged from one to four.

A subset of 1780 affected sib pair (ASP) families had at least two-digit classical HLA genotypes available. Analyses were conducted on trio families consisting of two parents and one affected offspring; one affected offspring per family was chosen randomly from all affected offspring with *HLA-DRB1* genotypes. We created two additional trio family samples for gender-stratified analyses. For the male sample, we randomly selected one male affected offspring per family. There were 1376 families with at least one male affected offspring. For the female sample, we randomly selected one female affected offspring per family. There were 1291 families with at least one female affected offspring. Parental genotypes were available to determine transmission for all affected offspring. A total of 6227 individuals were analysed, as presented in table 1.

For the HLA compatibility analyses, we limited the samples described in the previous paragraph to 1213ASP families (5804 individuals) with complete four-digit classical HLA genotypes available. There were 954 families and 876 families in the male and female samples, respectively. A total of 4256 individuals were utilized for the analyses of compatibility patterns, as shown in table 2.

The families were collected for both linkage and association studies; the sample size was designed to be sufficiently large to detect associations as well as secondary gene effects in a region such as HLA. The data were generated as part of a high-density screen of the MHC designed for association and haplotype analysis and to detect genes in the HLA region additional to the well-documented HLADR-DQ effect. The nuclear family study design is advantageous because it precludes potential confounding from ethnic mismatching between patients and randomly ascertained controls because of population stratification, migration or admixture. This design also reduces the potential of misclassification error from genotyping because we can check the data for pedigree inconsistencies.

Classical HLA Genotyping

The T1DGC protocol has been previously described [34].

Statistical Analyses

We used PEDCHECK (v1.1) to identify pedigree inconsistencies in our overall sample of 1780 trio families [35]. For any pedigrees with an inconsistency, we "zeroed out" genotypes for the entire family at that specific locus only, assuming a genotyping error. MEGA2 (v3.0 R12) was

used to manipulate data [36]. The pedigree disequilibrium test (PDT 6.0, build 5) was used to perform to examine frequencies of transmitted vs. non-transmitted alleles for each HLA locus [37]. The PDT is a powerful analytical method that uses genetic data from related nuclear families and discordant sibships within extended pedigrees.

We defined maternal–offspring compatibility categorically: (i) unidirectional child-to-mother compatible, (ii) unidirectional mother-to-offspring compatible, (iii) bidirectional and (4) incompatible. We modelled maternal–offspring compatibility in R (v2.6) using conditional logistic regression and for controls the compatibility of the affected child to the father was used [38]. The analysis was restricted to trios from the previously described overall, male and female samples that had complete four-digit genotyping information available.

We pair matched on family in a matched case–control analysis using conditional logistic regression; parent's gender was the outcome [39].

$$\text{logit} P(Y) = \beta_0 + \beta_1 \text{unidirectional} \, p. \\ + \beta_2 \text{unidirectional} \, c. + \beta_3 \text{bidirectional} \\ + \sum_{i=1}^{n} \gamma_i V_i$$

In the above formula, n refers to the number of families in the matched analysis, unidirectional p. is unidirectional parent-to-child compatibility and unidirectional c. is unidirectional child-to-parent compatibility. These analyses were repeated with HLA compatibility as a binary exposure (any compatibility vs. none).

$$\text{logit} P(Y) = \beta_0 + \beta_1 \text{any compatibility} + \sum_{i=1}^{n} \gamma_i V_i$$

For the POO analyses, frequencies of maternal vs. paternal transmitted alleles were compared using a chi-squared contingency table test for heterogeneity in AFBAC (v1.13) [40]. The same test was used in the NIMA analyses to compare frequencies of maternal vs. paternal non-transmitted alleles. Both global and allele-specific analyses (when appropriate) were performed. Based on a Bonferroni correction for the total number of tests performed in this study (n = 24), a criterion of $p < 0.002$ was set for statistical significance.

Results

There were no pedigree inconsistencies for *HLA-DQA1, DPA1* or *DPB1*. There were one, six and five families with pedigree inconsistencies at the *HLA-DRB1*, *DQB1* and *Cw* loci, respectively. None of the families had more than one pedigree inconsistency, indicating genotyping error rather than non-paternity. As expected, the majority of classical HLA loci were strongly associated with T1D in both the overall and gender-stratified analyses. The only exception was the class II gene *HLA-DPA1*, which did not show evidence for association. Table 3 displays global p values. The primary disease genes are *DR-DQ*; we have not investigated whether the associations at the other loci are because of linkage disequilibrium with *DR-DQ*. Table S1 presents observed and expected transmitted and non-transmitted allele frequencies with the test statistic and odds ratio (OR).

Unidirectional offspring-to-mother compatibility at the class I genes *HLA-A*, *Cw* and *B* and the class II genes *HLA-DRB1*, *DQA1*, *DQB1*, *DPA1* and *DPB1* was not associated with T1D. The

corresponding OR, 95% confidence intervals and p values are listed in table 4. Unidirectional mother-to-offspring compatibility, bidirectional compatibility and any compatibility did not demonstrate association with T1D (data not shown). Table S2 provides frequencies of maternal–offspring and paternal–offspring HLA compatibility relationships.

In addition, POO and NIMA effects were also examined for each classical HLA locus; evidence for involvement in T1D was not present (table 5) even when specific T1D risk alleles were examined separately, including *DRB1*0401, DRB1*0301* and *DQB1*0302*. Table S3 shows observed and expected allele-specific transmitted maternal and paternal allele frequencies with ORs. Table S4 shows observed and expected allele-specific non-transmitted maternal and paternal allele frequencies with ORs. Comparison of paternal and maternal transmitted and paternal and maternal non-transmitted T1D risk HLA alleles in the overall data set and for male and female cases analysed separately revealed nearly identical frequencies (figure 2).

Discussion

To date, the MHC confers the strongest known genetic effect in T1D; associations are well established for class I and class II loci, particularly for the class II *HLA-DRB1* 0301-* and **04*-associated haplotypes. HLA loci may also influence T1D through additional inherited or non-inherited effects. Evidence for increased maternal–offspring HLA class II compatibility has been reported for systemic lupus erythematosus (SLE) and SSc. Compared with controls, male SLE patients were more likely to have *HLA* class II genotypes identical to their mothers [41]. In addition, compared with controls, SSc patients exhibited increased *HLA* class II compatibility with their offspring or with their offspring or mother [42,43]. Taken together, these results suggest that *HLA* class II loci may be involved in the aetiology of both SLE and SSc through undefined mechanism(s) that are dependent on maternal–offspring compatibility. Several biological hypotheses have been proposed where increased compatibility could result in a small number of non-host cells that could ultimately (i) cause dysregulation among host cells, (ii) lead to presentation of non-host peptides by host cells to other host cells, (iii) inactivate T lymphocytes upon interaction or (iv) undergo differentiation and become targets of a later immune response [20,44–46].

The current study is the first to examine maternal–offspring HLA compatibility in T1D. Our results indicate that maternal–offspring compatibility at the MHC class I genes *HLA-A*, *Cw* and *B* and class II genes *HLA-DRB1*, *DQA1*, *DQB1*, *DPA1* and *DPB1* does not influence T1D. Our study used paternal–offspring HLA compatibility as controls in an analysis matched on family. Future studies would ideally test for differences in patterns of compatibility using an independent controls sample of mother–offspring pairs without T1D.

POO effects, potentially operating through the phenomenon of imprinting, have been observed previously in T1D and multiple sclerosis (MS) with respect to the inheritance of HLA class II alleles but results have been inconsistent. Excess paternal inheritance of the *DR3* risk haplotype has been reported in female Sardinian MS patients [47]. More recently, excess maternal inheritance of *HLA-DRB1*15* was observed in a larger study of 1515 MS families (p = 0.005) [48]. An early study of 107 T1D families reported increased paternal transmission of *DR4* to affected and unaffected offspring (72.1%) compared with maternal transmission (55.6%) [49]. A study of 28 Japanese T1D families reported that the *DQA1*0301-DQB1*0302* haplotype exhibited preferential maternal transmission and strong transmission disequilibrium with T1D positive for antibodies to glutamic acid decarboxylase [50]. Others have reported no POO effects in HLA class II alleles [51–53]; these studies examined 61, 108 and 282 T1D families, respectively. Many of these studies suffered from relatively small sample sizes and did not account for multiple testing when reporting statistical significance. In contrast, this study is the largest (table 2) to date to examine POO effects in the classical HLA loci and

account for multiple statistical tests. Results do not support a role for HLA-associated POO effects in T1D, even for T1D risk alleles *DRB1*0401*, *DQB1*0302* and *DRB1*0301*, and indeed are in agreement with others [51–53].

Interestingly, POO effects have also been examined in T1D for non-MHC genetic risk factors. There were no POO effects observed for *PTPN22* in a study of 341 T1D families [54]. A study of the *CTLA4* exon 1 polymorphism (49 A/G) in 70 T1D families showed increased maternal allele transmission of the G allele to T1D-affected offspring: 71% vs. the random 50% observed in unaffected offspring (p < 0.03). This distortion was stronger in T1D offspring with maternal inheritance of *HLA-DRB1*03* (80%, p < 0.01) or variable number tandem repeats at the *IDDM2* locus (80%, p < 0.02) [55]. A paternal origin effect has been observed for *IDDM8* (6q27) and a maternal origin effect has been observed in 404 parent–offspring T1D trios for the *IGF2R* locus (6q26) [3,56]. Further research is needed to confirm these findings.

There is evidence that HLA alleles may also act as environmental risk factors. This current study tested the hypothesis that cells and antigens of the mother may modulate the antigen-specific reactivity of the foetal immune system. Exposure to NIMA via several different mechanisms may therefore shape the immune repertoire of the offspring and either predispose to or protect against future immune reactions. A tolerogenic effect may explain the longer survival of renal transplants from sibling donors expressing NIMA vs. non-inherited paternal antigens (NIPA) [57]. In the pre-cyclosporine era, breastfeeding exposure was associated with improved graft survival in recipients of maternal kidney transplants [58,59]. The role of breast milk in this observation was confirmed using a highly immunogenic heart allograft mouse model in which both *in utero* exposure and milk feeding were required for the NIMA effect [60].

In addition to maternal–offspring cell trafficking and oral exposure through breast milk, another potential mechanism for NIMA is maternal microchimerism, when a small population of cells or DNA in an individual is derived from their mother. Maternal cells have been detected in offspring several decades following birth [61]. Compared with healthy women, female SSc patients have increased frequencies of maternal cells in their peripheral blood cells [62].

An NIMA effect on risk for rheumatoid arthritis (RA) has been explored in several studies. An early study reported association between NIMA and RA for *HLA-DR4* alleles [63]. Negative findings were later reported by a study of familial RA: frequencies of *HLA-DRB1*04*, *0401/ *0404*, and shared epitope (SE)-positive NIMA compared with NIPA were not increased in RA patients lacking these susceptibility alleles [64]. A later study reported an excess of *DRB1*04* and SE NIMA (p = 0.05) compared with NIPA; a combined analysis with previous studies showed that mothers were more likely to carry a non-inherited *DRB1*04* and SE alleles [65]. Recently, in the largest study of NIMA to date, the first evidence for a protective NIMA effect was reported: a mother carrying the protective amino acid sequence DERAA (*HLA-DRB1*0103, *0402, *1103, *1301* and **1304*) at the SE may transfer protection against RA to her DERAA-negative offspring [66].

To date, only one study of NIMA effects in T1D has been reported. T1D patients who did not carry any high-risk HLA alleles presented *HLA DR3-DQ2* and *DR4-DQ8* risk haplotypes more frequently as NIMA compared with NIPA [67]. The results from the current study, however, do not support a NIMA effect in T1D. A global test for NIMA effects, and a specific examination of the known T1D risk alleles *DRB1*0401*, *DQB1*0302* and *DRB1*0301* revealed negative results.

In conclusion, the largest study of T1D families, to date, does not support a major role for the classical HLA loci in disease susceptibility mediated through maternal–offspring compatibility, POO or NIMA effects.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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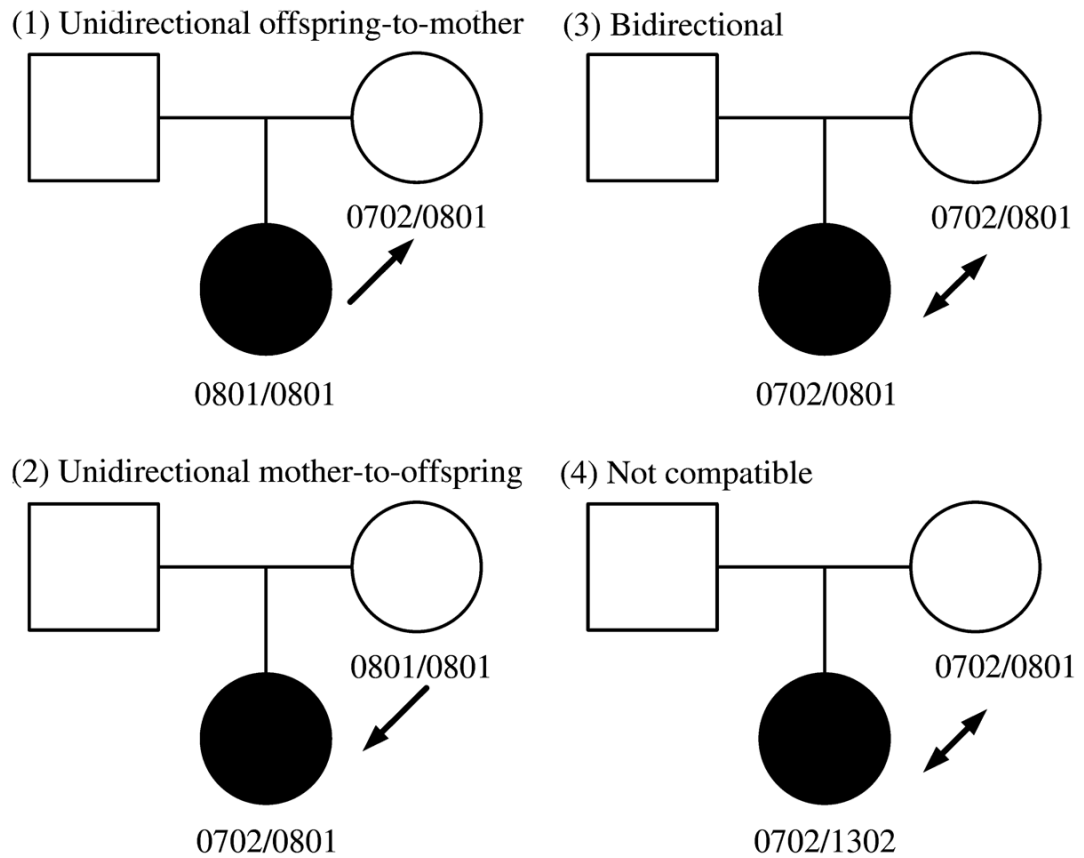
Fig. 1.
Illustration of possible maternal–offspring human leucocyte antigen (*HLA*) compatibility relationships using the *HLA-B* locus as an example.
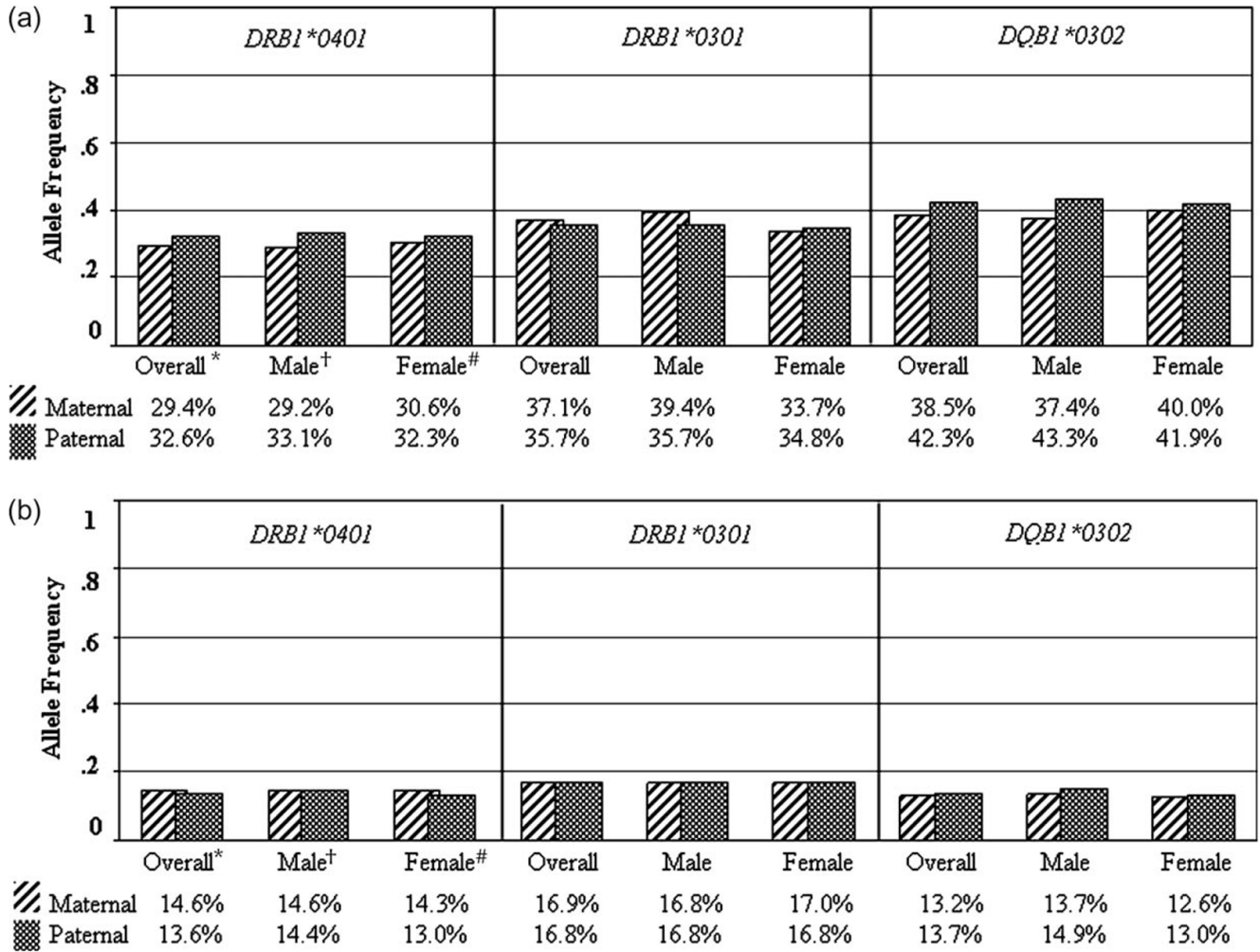
Fig. 2.
(A) Transmitted paternal and maternal allele frequencies for type 1 diabetes (T1D)
susceptibility alleles from analyses of parent-of-origin (POO) effects in T1D families; (B) non-
transmitted paternal and maternal allele frequencies for T1D susceptibility alleles from
analyses of non-inherited maternal HLA (NIMA) effects in T1D families. *The overall sample
(n = 1780) compares maternal vs. paternal non-transmitted alleles using one affected child per
family. †The male sample (n = 1376) compares maternal vs. paternal non-transmitted alleles
using one affected male offspring per family. ‡The female sample (n = 1291) compares
maternal vs. paternal non-transmitted alleles using one affected female offspring per family.
HLA, human leucocyte antigen.

Table 1

Type 1 diabetes families with two-digit genotyping available for the classical human leucocyte antigen (HLA) loci used in analyses of parent-of-origin and non-inherited maternal HLA effects

Sample	Families	Families with affected offspring of one gender only	Families with affected offspring of both genders	Affected offspring in analysis	Individuals in analysis
Overall	1780	893	887	1780	5340
Male	1376	489	887	1376	4128
Female	1291	404	887	1291	3873

Table 2

Subset of type 1 diabetes families with four-digit genotyping available for the classical human leucocyte antigen (HLA) loci used in the HLA compatibility analyses

Sample	Families	Families with affected offspring of one gender only	Families with affected offspring of both genders	Affected offspring in analysis	Individuals in analysis
Overall	1213	596	617	1213	3639
Male	954	337	617	954	2862
Female	876	259	617	876	2628

Table 3

Results from pedigree disequilibrium test analyses of transmission of HLA alleles to individuals with type 1 diabetes

HLA locus	Global p values		
	Overall[*] (n = 1780)	Male[†] (n = 1376)	Female[‡] (n = 1291)
A	7.2×10^{-9}	2.3×10^{-8}	1.4×10^{-5}
Cw	7.2×10^{-11}	8.7×10^{-11}	4.8×10^{-11}
B	8.2×10^{-11}	8.9×10^{-11}	9.1×10^{-11}
DRB1	8.4×10^{-11}	9.2×10^{-11}	8.7×10^{-11}
DQA1	7.6×10^{-11}	8×10^{-11}	7.4×10^{-11}
DQB1	6.6×10^{-11}	8.4×10^{-11}	9.5×10^{-11}
DPA1	0.03	0.14	0.36
HLA-DPB1	4.9×10^{-11}	1.3×10^{-8}	6.6×10^{-11}

HLA, human leucocyte antigen.

[*] The overall sample (n = 1213) compares transmitted vs. non-transmitted HLA alleles using one affected offspring per family.

[†] The male sample (n = 954) compares transmitted vs. non-transmitted HLA alleles using one affected offspring per family.

[‡] The female sample (n = 876) compares transmitted vs. non-transmitted HLA alleles using one affected offspring per family.

Table 4

Results from analyses of maternal vs. paternal unidirectional offspring-to-parent HLA compatibility in type 1 diabetes families

HLA locus	Sample	OR (95% CI)	Global p value
A	Overall[*]	0.74 (0.42–1.30)	0.31
	Male[†]	0.78 (0.41–1.46)	0.44
	Female[‡]	1.20 (0.61–2.34)	0.59
Cw	Overall	0.87 (0.42–1.82)	0.71
	Male	0.60 (0.25–1.43)	0.25
	Female	0.76 (0.30–1.90)	0.57
B	Overall	0.41 (0.14–1.22)	0.11
	Male	0.18 (0.04–0.84)	0.03
	Female	0.38 (0.11–1.26)	0.11
DRB	Overall	0.77 (0.37–1.58)	0.48
	Male	0.64 (0.29–1.42)	0.28
	Female	0.60 (0.26–1.39)	0.22
DQA	Overall	0.99 (0.61–1.61)	0.96
	Male	0.85 (0.50–1.46)	0.56
	Female	0.83 (0.47–1.47)	0.53
DQB	Overall	0.78 (0.46–1.33)	0.35
	Male	0.70 (0.38–1.28)	0.25
	Female	0.63 (0.33–1.19)	0.15
DPA	Overall	0.97 (0.50–1.90)	0.93
	Male	0.66 (0.28–1.57)	0.36
	Female	2.30 (0.97–5.45)	0.05
DPB	Overall	1.04 (0.68–1.58)	0.86
	Male	0.89 (0.55–1.43)	0.63
	Female	0.83 (0.51–1.30)	0.46

HLA, human leucocyte antigen.

[*] The overall sample (n = 1213) compares maternal vs. paternal HLA compatibility using one affected offspring per family.

[†] The male sample (n = 954) compares maternal vs. paternal HLA compatibility using one affected male offspring per family.

[‡] The female sample (n = 876) compares maternal vs. paternal HLA compatibility using one affected female offspr1ing per family.

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Table 5

Results from analyses of parent-of-origin (POO) HLA effects and non-inherited maternal HLA (NIMA) effects (non-transmitted maternal vs. paternal alleles) in type 1 diabetes families

		Maternal vs. paternal					
		Transmitted			Non-transmitted		
HLA locus	Sample	χ^2	d.f.	p	χ^2	d.f.	p
A	Overall*	7.9	18	0.98	18.3	18	0.44
	Male†	12.4	17	0.77	17.8	17	0.40
	Female‡	15.1	18	0.66	17.0	18	0.53
Cw	Overall	23.4	21	0.32	22.1	21	0.39
	Male	41.2	21	0.01	20.1	21	0.51
	Female	7.1	20	1.00	15.7	20	0.73
B	Overall	30.8	36	0.71	42.1	36	0.23
	Male	46.6	36	0.11	41.9	36	0.23
	Female	29.8	33	0.63	36.2	33	0.32
DRB	Overall	39.6	32	0.17	36.4	32	0.27
	Male	33.9	31	0.33	19.6	31	0.94
	Female	29.3	32	0.60	45.9	32	0.05
DQA	Overall	14.7	8	0.07	5.8	8	0.66
	Male	13.2	7	0.07	2.2	7	0.95
	Female	5.9	8	0.66	9.8	8	0.28
DQB	Overall	20.3	11	0.04	6.9	11	0.81
	Male	18.1	11	0.08	2.7	11	0.99
	Female	14.8	11	0.19	11.6	11	0.39
DPA	Overall	14.9	7	0.04	6.2	7	0.52
	Male	7.5	7	0.38	7.1	7	0.42
	Female	12.1	6	0.06	4.7	6	0.58
DPB	Overall	26.3	31	0.71	24.7	31	0.78
	Male	15.4	27	0.96	18.5	27	0.89
	Female	25.3	31	0.75	23.1	31	0.85

HLA, human leucocyte antigen.

*
The overall sample (n = 1780) compares maternal vs. paternal transmitted or non-transmitted alleles using one affected offspring per family.

†
The male sample (n = 1376) compares maternal vs. paternal transmitted or non-transmitted alleles using one affected male offspring per family.

‡
The female sample (n = 1291) compares maternal vs. paternal transmitted or non-transmitted alleles using one affected female offspring per family.