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Background

The incidences of autoimmune disorders, such as rheumatoid arthritis and hypothyroidism, were found to be higher among parents, especially mothers, of autistic children than various control groups (e.g., families of typical children or children with autoimmune disorder) (Comi et al., 1999; Sweeten et al., 2003). Some specific antigens/alleles of the HLA (Human Leukocyte Antigens) system are often associated with autoimmunity.

For example, Class II HLA-DR4 has been identified as a susceptibility marker for rheumatoid arthritis in Caucasians. A number of previous studies have reported that DR4 alleles occur in individuals with autism more often than in controls (Torres et al., 2002). This study examined incidences of types and sub-types of HLA-DR4 in single-birth and multiplex families with autism.

Methods

HLA-DR4 in the following three groups was typed and sub-typed:

- Single-birth families with autism:** a geographically defined sample, including 17 families with one autistic child from East Tennessee.
- Multiplex families with autism:** a genetically loaded sample from all areas of the USA, which included 33 families with multiple autistic children from AGRE (Autism Genetic Resource Exchange).
- Control:** 475 healthy, unrelated Caucasians

Table 1. Frequencies of DR4 types and DR4 subtypes

	Single-Birth			Multiplex			Control n = 475
	Mother (n = 17)	Father (n = 14)	Child (n = 17)	Mother (n = 34)	Father (n = 33)	Child (n = 41)	
DR4	11 (64.7%)	5 (35.7%)	10 (58.8%)	12 (35.3%)	12 (36.4%)	18 (43.9%)	135 (28.4%)
<i>Allele Frequencies of DR4 subtypes</i>							
Allele #	n = 34	n = 28	n = 34	n = 68	n = 66	n = 82	n = 950
0401/04011	8 (23.53%)	6 (17.65%)	6 (17.65%)	6 (8.82%)	3 (4.55%)	6 (7.32%)	70 (7.37%)
0402	1 (2.94%)	2 (7.14%)	1 (2.94%)	2 (2.94%)	2 (3.03%)	5 (5.53%)	15 (1.58%)
04031				1 (1.47%)			5 (0.53%)
0404	2 (5.88%)	2 (7.14%)	3 (8.82%)	1 (1.47%)	3 (4.55%)	3 (3.66%)	32 (3.37%)
04051	1 (2.94%)			1 (1.47%)		1 (1.22%)	5 (0.53%)
0407/04071		1 (3.57%)		1 (1.47%)	1 (1.52%)	5 (6.10%)	9 (0.95%)

Table 2. Bivariate statistics of DR4 frequency¹

	DR4 frequency	OR ²	95% CI ³
Single Birth: Mother (n=17)	11 (64.7%)	4.62	1.54, 14.34
Single Birth: Father (n=14)	5 (35.7%)	1.40	0.40, 4.67
Single Birth: Child (n=17)	10 (58.8%)	3.60	1.23, 10.72
Multiplex: Mother (n=34)	12 (35.3%)	1.37	0.62, 3.00
Multiplex: Father (n=33)	12 (36.4%)	1.44	0.65, 3.17
Multiplex: Child (n=41)	18 (43.9%)	1.97	0.98, 3.94

¹ As compared to 475 Caucasian controls, of which 135 have DR4 (28.4%)

² OR: Unadjusted Odds Ratio

³ 95% CI: 95% Confidence Interval

Figure 1. Low Resolution typing – Frequency of HLA-DR4

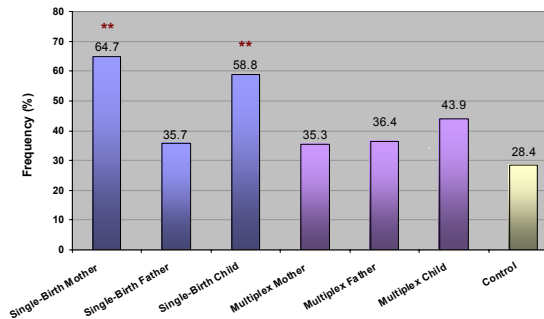
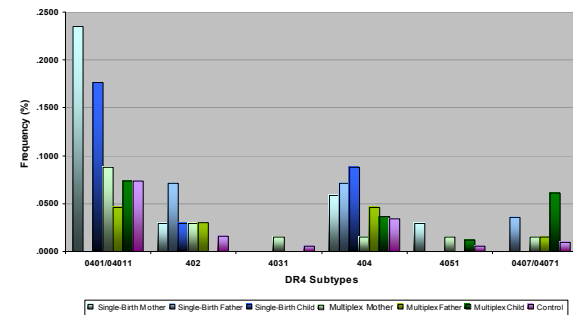


Figure 2. High Resolution – Frequency of HLA-DR4 subtypes



Results

Low resolution HLA typing:

As compared to the control group, single-birth children with autism and their mothers had significantly higher frequency of DR4 than controls (Figure 1 and Table 1).

High resolution HLA typing:

Results from HLA-DR4 high resolution typing suggested no sharing of alleles, and no significant change in the distribution of DR4 alleles among those with DR4. No distortion in the segregation of the maternal DR4-bearing haplotype was seen among the autistic children. There was a normal distribution of HLA homozygotes and heterozygotes and no evidence of antigen sharing between parents.

Discussion

Increased HLA-DR4 in single-birth children and their mothers is consistent with a hypothesis that prenatal maternal-fetal immune interaction can affect fetal brain development in autism. There is no evidence of increased DR4 frequency in the families with multiplex autistic children. This suggests that different etiologies or combinations of pathological mechanisms are involved in single-birth and multiplex families. Regional differences in maternal HLA types may reflect genetic clustering or susceptibility to environmental factors. Future studies need larger samples to confirm whether certain DR4 subtypes are related to autism.