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EVIDENCE OF SEX DIMORPHISM WITHIN THE HLA REGION IN A COHORT OF JIA PATIENTS.

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Introduction: Juvenile idiopathic arthritis (JIA) encompasses a group of heterogenous diseases characterised by joint pain and swelling where symptom onset is before the age of 16. The disease occurs unequally in female and male patients with a ratio of 2:1 but incidence differs between JIA subtypes. The *HLA* region is reported to have a role within the immune response and has been associated with several autoimmune conditions, including JIA.
Objectives: To investigate the role of variants within the *HLA* region for JIA onset in females and males, using sex dimorphism analysis.
Methods: Genotyping data was available on 2052 females and 961 males with JIA, excluding systemic JIA patients, and 9196 controls (female = 5137, males = 4059). Amino acids, alleles and SNPs within the *HLA* region were imputed using SNP2HLA with a total of 7773 *HLA* markers available for analysis. The *HLA* sex dimorphism analysis combined sex-specific GWAS summary statistics using the GWAMA software package. Sex-specific summary statistics for this analysis were calculated using a logistic regression with three principal components as covariates within PLINK. This analysis provided a sex-heterogeneity p-value (p_{het}), which provides evidence to support the heterogeneity between effect estimates of females and males.
Results: In total, 139 variants within the *HLA* region passed the threshold ($5x10^{-8}$) for significant sex dimorphism. A large proportion of markers that were significant for sex dimorphism were located within *HLA-B*, including *HLA-B27* (p_{het} = $9.7x10^{-15}$), which is a well-established risk locus for enthesitis related arthritis (ERA). ERA is reported to occur more frequently in male patients and effect sizes at *HLA-B27* suggest a male specific effect in this cohort (OR_{female} = 1.6, OR_{male} = 4.1). Amino acids within the YST motif of the *HLA-DRB1* binding groove were also significantly sex dimorphic. Tyrosine at position 10 (p_{het} = $4.7x10^{-19}$, OR_{female} = 1.9, OR_{male} = 1.2), serine at position 11 (p_{het} = $2.3x10^{-11}$, OR_{female} = 1.9, OR_{male} = 1.2) and threonine at position 12 (p_{het} = $2.3x10^{-11}$, OR_{female} = 1.9, OR_{male} = 1.2), make up the YST motif of *DRB1.* The effect sizes of the YST motif markers suggest that these markers contribute to JIA onset only in females. *HLA-DRB1* at position 11 has been previously associated with JIA onset in a cohort of oligoarthritis and rheumatoid factor negative polyarthritis; these subtypes are more common in females.
Conclusion: In conclusion, this is the first fine-mapping of the *HLA* region in a sex dimorphism analysis for JIA susceptibility. This research has provided evidence of differing genetic risk factors for female and male JIA onset that align with clinical observations. However, further research is now required to understand the mechanism behind these findings. Defining the genetic architecture to JIA will aid disease classification and diagnosis of patients in the future.
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