**TITLE: ASSESSMENT OF A GENETIC RISK SCORE FOR CELIAC DISEASE IN DOWN SYNDROME**

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**OBJECTIVES**:

Celiac disease (CD) is considered an HLA-restricted autoimmune disease of which individuals with Down syndrome (DS) are at increased risk. This study aims to examine the HLA genotypes involved in CD risk, and to test a previously developed genetic risk score (GRS) for CD in our DS cohort.

**METHODS**:

HLA genotypes were available for 201 individuals with DS from the Human Trisome Project, of whom 19 (9%) had CD. We compared HLA genotype frequencies observed in DS individuals with and without CD against published genotype frequencies observed in euploid cases and controls. Permissive HLA haplotypes explored were DQ2.5, DQ2.2, DQ8.1, and DQ7.5. These were combined with 38 available non-HLA-DQ SNPs to generate the CD GRS.

**RESULTS**:

Permissive HLA genotypes were carried by 55% of DS participants without CD (n=135) and 90% with CD (Table 1). Surprisingly, there was no observed DQ2.5 homozygosity in our DS cohort. Furthermore, we observed a higher prevalence of DQ7.5/X and X/X among those with CD and DS than reported in the typical population\*\*. Among individuals with DS, mean GRS was significantly higher in those with celiac disease (OR 1.62, 95% CI 1.22-2.22; P<0.0013). The GRS predicted celiac disease in DS with an AUC of 0.73.

**CONCLUSIONS**:

The HLA genetic risk profile of those with DS and CD in this cohort differs from the published risk profile of those without DS. The published CD GRS performed well, but was not as predictive in this DS cohort. Further study is needed to understand the contribution of non-traditional HLA haplotypes and non-HLA variants to the markedly increased risk for celiac disease in DS.

**Table 1: HLA genotype frequency by celiac status and karyotype**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Observed frequencies\* in those with Down syndrome** | | **Published frequencies\*\* in those without Down syndrome** | |
| **HLA\_DQ\_Genotype** | **Freq Controls** | **Freq Cases** | **Freq Controls** | **Freq Cases** |
| **(DS without celiac)** | **(DS with celiac)** | **(Without celiac)** | **(With**  **celiac)** |
| DQ2.5/DQ2.5 | 0 (n=0) | 0 (n=0) | 0.019 | 0.16 |
| DQ2.5/DQ2.2 | 0.017 (n=3) | 0.053 (n=1) | 0.029 | 0.24 |
| DQ7.5/DQ2.5 | 0.088 (n=16) | 0.053 (n=1) | 0.032 | 0.048 |
| DQ2.5/DQ8 | 0.011 (n=2) | 0.053 (n=1) | 0.025 | 0.06 |
| DQ7.5/DQ2.2 | 0.044 (n=8) | 0.053 (n=1) | 0.025 | 0.076 |
| DQ2.5/X | 0.11 (n=20) | 0.263 (n=5) | 0.148 | 0.309 |
| DQ8/DQ8 | 0 (n=0) | 0 (n=0) | 0.008 | 0.009 |
| DQ2.2/DQ8 | 0.033 (n=6) | 0.158 (n=3) | 0.02 | 0.016 |
| DQ7.5/DQ8 | 0.039 (n=7) | 0.053 (n=1) | 0.023 | 0.006 |
| DQ8/X | 0.11 (n=20) | 0 (n=0) | 0.106 | 0.023 |
| DQ2.2/X | 0.104 (n=19) | 0.211 (n=4) | 0.113 | 0.018 |
| DQ2.2/DQ2.2 | 0 (n=0) | 0 (n=0) | 0.011 | 0.005 |
| DQ7.5/DQ7.5 | 0 (n=0) | 0 (n=0) | 0.021 | 0.002 |
| DQ7.5/X | 0.154 (n=28) | 0.053 (n=1) | 0.127 | 0.012 |
| X/X | 0.291 (n=53) | 0.053 (n=1) | 0.292 | 0.017 |
| **Total (n=201)** | **(n=182)** | **(n=19)** |  |  |

**DQ2.5=** DQA1\*05:01–DQB1\*02:01

**DQ2.2**= DQA1\*02:01–DQB1\*02:02

**DQ8** = DQA1\*03–DQB1\*03:02

**DQ7.5** = DQA1\*05-DQB1\*03

**X**= None of the above annotated HLA haplotypes

\* The Crnic Institute Human Trisome ProjectÔ (HTP).

\*\*Sharp, Seth A., et al. “A Single Nucleotide Polymorphism Genetic Risk Score to Aid Diagnosis of Coeliac Disease: A Pilot Study in Clinical Care.” Alimentary Pharmacology & Therapeutics, vol. 52, no. 7, 2020, pp. 1165–73.