Is it all in the genes? HLA risk for celiac disease in a Down syndrome cohort

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BACKGROUND

- Individuals with Down syndrome (T21) have a six-fold greater risk of celiac disease (CD).[1]
- Although not alone sufficient, CD development requires most commonly, human leukocyte antigen (HLA) DQ2.5 or DQ8.1 and less commonly DQ2.2 or DQ7.5 in the typical population.[2]
- While the mechanism of increased risk for celiac in T21 remains to be elucidated, some studies suggest those with T21 may have differing HLA risks than the typical population.[3,4]

OBJECTIVES/AIMS

- To examine and compare the genetic risk profiles of those with T21 in the Human Trisome Project (HTP) with and without a diagnosis of CD.
- To compare the genetic risk profiles of those with T21 and CD to published genetic risk profiles for CD in the typical population.
- To examine whether a published genetic risk score for CD in the typical population[2] can predict CD in individuals with T21.

DESIGN/METHODS

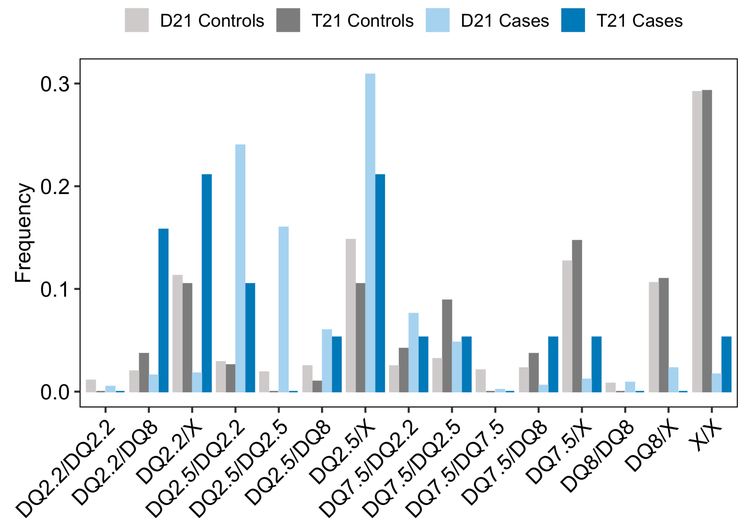
- Genomic data and celiac status were available for 210 individuals with T21 from the Human Trisome Project (HTP).
- Celiac diagnosis was ascertained from participant surveys and medical records.
- Genotyping was performed using the Illumina Multi-Ethnic Global Array (MEGA).
- HLA genotype imputation was performed using the HIBAG algorithm.[5]
- Celiac-permissive HLA genotype frequencies were compared in celiac cases and controls with T21.
- HLA genotype frequencies among CD cases and controls with T21 were compared against published frequencies in the typical population.[2]
- Imputed HLA genotypes and 32 of 38 available non-HLA SNPs were used to approximate a celiac GRS developed for the typical population. [2]
- The modified GRS was evaluated for its ability to predict CD in HTP participants with T21.

RESULTS

Table 1 Demographic data

	Non-Hispanic white %	Female %	Age Mean (SD)
T21 without celiac (N = 191)	77	46.6	24.6 (12.1)
T21 with celiac (N = 19)	84.2	36.8	25.3 (9.5)

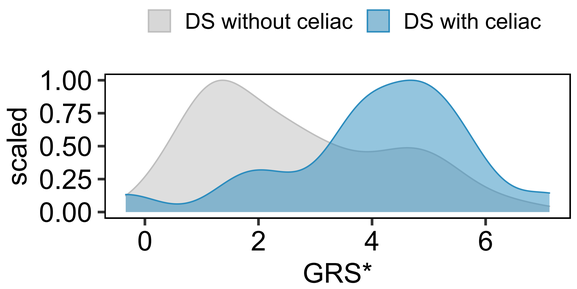
Figure 1 HLA-DQ genotype frequencies among Celiac cases and controls with Down syndrome (T21) and without (D21)



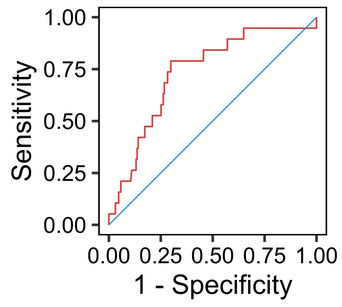
- 95% of T21 participants with CD vs. 71% of T21 participants without CD had permissive HLA genotypes.
- 5% of T21 participants with CD did not carry a traditionally celiac-permissive HLA genotype.
- No T21 participants with CD were DQ2.5 homozygous.
- Participants with T21 and CD most frequently had the following genotypes DQ2.5/X (21.1%) and DQ2.2/X (21.1%).
- Traditionally non-permissive genotypes including DQX/X and DQ7.5/X were observed with higher frequency in the T21 population with celiac disease compared to the typical population.

Figure 2 Performance of celiac GRS in individuals with T21

Distribution of GRS* in T21 cases and controls
OR=1.61 (1.22, 2.17), P<0.0012



Predictive accuracy of GRS* in T21
Area under the curve: 0.7731



SCAN ME

- Celiac GRS[2] significantly predicts celiac in T21 with an area under the curve of 0.7731.

CONCLUSIONS

While a majority of the participants with Down syndrome and celiac disease had the typical high-risk HLA genotypes, the other genotypes typically considered to be low risk (yet still permissive) appear to contribute more to celiac disease in those with T21 compared to the general population.

In clinical practice, this means that HLA testing may not be as useful to rule out celiac disease in the T21 population.

Further multicenter genomic studies are being planned to look at the HLA risk in a larger sample size and the non-HLA contributions.

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