Somatic Mutations Within the Epitope-Binding Groove DNA sequence of At-Risk HLA DQA1 and DQB1 Genes Are the Cause of Celiac Disease

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Background

- Celiac disease (**CD**) is an inherited autoimmune disease (**AID**) that occurs after exposure to gluten, is associated with other AIDs, and nearly always presents with anti-gliadin and anti-tissue transglutaminase antibodies.
- Previously (DDW 2022) we proposed that the key mechanism of AID consists of a constant rate of somatic mutations within the epitope-binding groove of at-risk HLA genes, that are amplified by mutations in other genes identified by GWAS.

Aim

- To investigate whether existing epidemiological and genetic data are compatible with somatic DNA mutations causing CD assuming that one gene causes CD and any additional autoimmune diseases (**AAID**) in at-risk persons.

Methods (1)

- Published data were reviewed for patterns compatible with a constant rate of DNA mutations.
- HLA haplotypes DQA1*05:01/DQB1*02:01 (DQ2.5) and DQA1*03:01/DQB1*03:02 (DQ8) were evaluated for DNA sites prone to mutation.

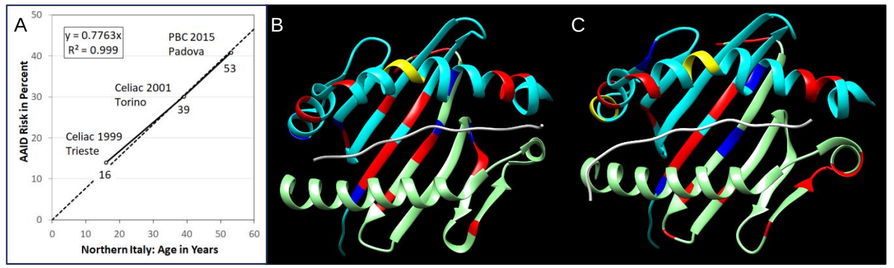
Methods (2)

- GWAS studies were analyzed for (1) HLA; (2) likely autoimmune target; (3) signal amplification factors.

Results (1)

- Three studies from northern Italy showed that the number of AID per person adhered to an exponential distribution supporting a constant rate of mutations (data not shown).
- The chance for an AAID in northern Italy was 0.8% per year per person (**Fig A**).
- Analysis of the DQ2.5 and DQ8 haplotypes shows presence of mutation-prone DNA: somatic diversification hypermutation hotspots (**HH**) and GC-rich DNA (**Fig B-C**), many involving amino acids at the base of the epitope-binding groove.
- GWAS studies show a strong signal for HLA and lesser signal for amplification factors, but do not show a likely autoimmune target as seen in type 1 diabetes (insulin), Graves' disease (TSHR), and vitiligo (MC1R, OCA2).
- The **Table** shows a comparison of GWAS findings for Type 1 diabetes, Graves' disease and CD. GWAS does not show a likely autoantigen for CD.

Results (2)



A. Using Omnipresent Neoplasia Equations (DDW 2022) the chance of having AAID was calculated; a linear relationship is observed between age (16, 39, 53) and risk for AAID. **B-C**. 3D Ribbon drawing of HLA-DQ2.5 (**B**) and HLA-DQ8 (**C**) showing a frontal view into the epitope-binding groove. Amino acids encoding HH are shown in red (perfect match) or in dark blue (one mismatch RGYW); GC-rich sequence is shown in yellow. At-risk amino acids are located on the floor or beta-chain helices (light blue) of the binding groove.

	Type 1 Diabetes	Graves' Disease	Celiac Disease
Main GWAS signal	HLA	HLA	HLA
Autoantigen GWAS signal	Insulin	TSHR	None?
Amplifier GWAS signal in FinnGen Release 7 (top 3) **Cases / Controls**	Insulin PTPN22 HIST1H2BA 7,337 / 255,551	TSHR PTPN22 CTLA4 1,421 / 231,654	LPP SH2B3 CCR3 2,953 / 296,917
Antibodies against GWAS signal	Yes	Yes	No
Germline mutations in autoantigen cause disease like AID	Yes	Yes	No
Symptom prevention	No	No	Gluten-free diet
Tissue affected by AID	Local cell destruction	Local cell activation	Inflammation small bowel mucosa
Contact with external antigen	No	No	Yes - small bowel
External antigen as cause of AID	No	No	Yes

Conclusions

- Existing epidemiological and genetic data are compatible with a somatic DNA mutation mechanism as the cause of CD.
- The configuration and composition of the peptides causing CD within the mutated epitope-binding groove require a specific baseline configuration – hence only a few DQ alleles are associated with CD risk – and one or more mutations – hence inheritance with incomplete penetrance that depends on the number of HH and the number of mutations required to initiate disease.
- Tissue transglutaminase is not an autoantigen causing CD but anti-tissue transglutaminase antibodies are a result of the gluten-induced chronic inflammatory process of the small bowel mucosa.

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Disclosures

None