Clinical and genetical aspects of celiac disease

Akademisk avhandling

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Av
Audur Heida Gudjónsdóttir
Legitimerad läkare

Fakultetsopponent
Docent Bo Lindquist
Läkarhuset Odenplan, Stockholm

Avhandlingen baseras på följande delarbeten:

I. Gudjónsdóttir AH, Nilsson S, Ek J, Kristiansson B, Ascher H.
The risk of celiac disease in 107 families with at least two affected siblings.
J Pediatr Gastroenterol Nutr 2004;38:338-42.

II. Naluai AT, Nilsson S, Gudjónsdóttir AH, Louka AS, Ascher H, Ek J, Hallberg B, Samuelsson L, Kristiansson B, Martinsson T, Nerman O, Sollid LM, Wahlström J.
Genome-wide linkage analysis of Scandinavian affected sib-pairs supports presence of susceptibility loci for CD on chromosomes 5 and 11.
Eur J Hum Genet 2001;9:938-44.

III. Gudjónsdóttir AH, Nilsson S, Naluai ÅT, Ek J, Amundsen SS, Wahlström J, Ascher H.
Association between genotypes and phenotypes in CD.
In press J Pediatr Gastroenterol Nutr 2008

IV. Gudjónsdóttir AH, Nilsson S, Hugot J-P, Mustalahti K, Clot F, Coto I, Percopo S, Ascher A.
Clinical features of DQ2-negative compared to DQ2-positive celiac disease.
In manuscript.

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Abstract

Celiac disease (CD), or gluten-sensitive enteropathy, is one of the most common chronic diseases in childhood but is diagnosed in all ages. CD is a genetically driven immunological intolerance to dietary gluten. The treatment is a gluten-free diet. The diagnostic criteria are the ESPGHAN criteria, which include the histological characteristics of villous atrophy, crypt hyperplasia and increased number of intraepithelial lymphocytes (IEL). The clinical manifestations in CD range from severely affected young children to children and adults with milder symptoms as well as patients with silent CD. There is a strong heredity in CD with the well-known HLA components DQ2 and DQ8. The genetics in CD are believed to confer up to 40% HLA genetics and otherwise non-HLA genetics. The knowledge of the genotype-phenotype association in CD is limited. The aim of this study has been to estimate the risk of a third sibling being affected in CD sib-pair families, identify the chromosomal region containing susceptibility genes in CD and study the genotype-phenotype association in CD. Material was collected from 107 families with at least two affected siblings, making a total of 224 CD siblings, as well as their healthy siblings and parents. Screening for CD was performed in these apparently healthy members and the estimated risk for CD in the third sibling and parent was then calculated. Thirteen new CD cases were diagnosed, six siblings and seven parents. The estimated sibling risk was 26.3% and the parent risk was 12.9%. The risk of a sibling of two affected siblings having CD was approximately three times higher compared to siblings of one affected sibling. Considering the high level of knowledge of CD in these families, the number of undiagnosed cases was surprisingly high. We suggested that serological screening should be offered all first-degree relatives of CD patients. Genome-wide linkage scan was performed in the same material. This work showed significant evidence of linkage to CD with an interesting region on chromosome 5q31-33 and on chromosome 11q. Simplex CD family material was collected for further genetic association studies. The phenotype-genotype association was examined in two studies. An investigation was made of a possible interaction between the phenotypes and HLA class II risk alleles, the CTLA4 +49 A/G polymorphism, the haplotype MH30*G:-1147*T:+49*A:CT60*G:CT61*A and the 5q31-33 locus, in CD**.** The patients were grouped according to symptoms at presentation, the age at diagnosis and gender. The heritability of the phenotype was estimated to be 0.45. The AA genotype at the CTLA4 +49A/G polymorphism was associated with clinically silent disease. No other correlations were found between genotypes and clinical presentation, age at diagnosis or gender. A genotype-phenotype analysis was made of phenotypes in DQ2-negative CD patients in the largest DQ2-negative CD group that has been published compared to DQ2-positive CD controls in a European population. The finding was that the clinical presentation differed significantly between DQ2-negative and DQ2-positive CD patients in Italy and Sweden. In both samples there was an association between DQ2-negative cases and classic symptoms. In the Italian sample there was also an association between silent grade and DQ2-negative cases. Autoimmune disease was significantly overrepresented in DQ8-positive patients. This thesis shows that the risk for third sibling and parents is, as expected, increased in sib-pair families, as the expected risk of being affected in polygenic diseases is higher in families with multiple cases compared to single-case families. The genome scan indicated significant linkage to 11q and 5q, which makes these regions interesting for further fine mapping of these regions using association analysis. Genotype-phenotype analysis of both HLA and non-HLA locus showed some significant correlation between silent CD and both CTLA4 +49 AA genotype and the DQ2-negatives. In addition, an association was shown between classic symptom grade and DQ2-negative cases.

Key words: celiac disease, sib-pair, screening, genome-wide scan, linkage analysis, heritability, genotypes, DQ2-negative, phenotypes, autoimmune disease

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