Genetic linkage and association studies in celiac disease: discoveries from whole genome analysis

Akademisk avhandling

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Avhandlingen baseras på följande arbeten:

I. ***Meta and pooled analysis of European coeliac disease data***. Babron MC, Nilsson S, Adamovic S, Naluai AT, Wahlström J, Ascher H, Ciclitira PJ, Sollid LM, Partanen J, Greco L, Clerget-Darpoux F; European Genetics Cluster on Coeliac Disease. Eur J Hum Genet. 2003 Nov;11(11):828-34. PMID: 14571266

II. ***Fine mapping study in Scandinavian families suggests association between coeliac disease and haplotypes in chromosome region 5q32.*** Adamovic S, Amundsen SS, Lie BA, Hellqvist A, Gudjónsdóttir AH, Ek J, Nilsson S, Wahlström J, Ascher H, Sollid LM, Naluai AT. Tissue Antigens. 2008 Jan;71(1):27-34. PMID: 17971050

III. ***A comprehensive screen for SNP associations on chromosome region 5q31-33 in Swedish/Norwegian celiac disease families.*** Amundsen SS, Adamovic S, Hellqvist A, Nilsson S, Gudjónsdóttir AH, Ascher H, Ek J, Larsson K, Wahlström J, Lie BA, Sollid LM, Naluai AT. Eur J Hum Genet. 2007 Sep;15(9):980-7. PMID: 17551518

IV. ***Replication of chromosome region 5q31-33 and celiac disease: A complex image emerges.*** Adamovic S, Amundsen SS, Lie BA, Gudjónsdóttir AH, Ek J, Ascher H, Wahlström J, Nilsson S, Sollid LM, Naluai ÅT. **In manuscript**.

V. ***Association study of IL2/IL21 and FcgRIIa: significant association with the IL2/IL21 region in Scandinavian coeliac disease families***. Adamovic S, Amundsen SS, Lie BA, Gudjónsdóttir AH, Ascher H, Ek J, van Heel DA, Nilsson S, Sollid LM, Torinsson Naluai A. Genes Immun. 2008 Jun;9(4):364-7. PMID: 18418394

ABSTRACT

Celiac Disease (CD) or Gluten Sensitive Enteropathy (GSE) is a life-long disorder. It is characterized by inflammation in the small intestine of genetically predisposed individuals caused by inappropriate immune response to gluten, a protein enriched in some of our common grains (wheat, rye and barley). The toxicity of gluten is manifested by the autoimmune action of T-lymphocytes on mucosal cells in the small intestine, disrupting its vital function of absorbing nutrients from the food. The disease affects predominantly children, but it can develop later in life as well. Untreated CD involves risk for major complications: *Dermatitis herpetiformis* ("the celiac disease of the skin"), nutritional deficiencies, osteoporosis, anaemia, fertility problems, neurological disturbances and malignancies. The only known treatment for CD is a lifelong adherence to gluten-free diet (GFD).

In a Scandinavian genome wide scan, performed by our group and published in 2001, eight chromosomal regions apart from HLA showed nominal significance ($p < 0,05$), among them 5q31-33. This region was previously suggested as a susceptibility region in other complex diseases: asthma, type 1 diabetes, rheumatoid arthritis and inflammatory bowel disease.

The main goal of this study was to explore the region of 18cM on 5q31-33, identify genetic risk factors and evaluate their contribution to the development of CD. In 2003 a joint analysis of four independent genome scans was performed by the European Genetics Cluster on Coeliac Disease, a collaborative work between six European research groups, including our. Data from Italian, Finnish, UK and Swedish/Norwegian cohorts, a total of 442 families, was pooled together and analysed. The meta-analysis using pooled data confirmed 5q31-33 as the second most significant region after the HLA region.

After the meta-analysis, we applied a fine mapping strategy on the 18cM region on 5q31-33. The most essential result of this study was the strengthened linkage signal on 5q31-33

In 2006 we used the Illumina platform (GoldenGate assay technology) to perform an extensive screen of the region on 5q31-33. This study identified seven associated regions within 5q31-33 and a number of associated haplotypes but none of the association signals could explain the linkage peak observed in the families previously.

In 2007 we performed a follow-up study of the association to the region comprising IL2/IL21 genes on 4q27, reported in the first genome-wide association study (GWAS) in celiac cases and controls. We confirmed that the IL2/IL21 region is a susceptibility region in CD.

Unfortunately, the first GWAS failed to identify specific genes predisposing to CD. The GWAS as well as our own fine mapping study pointed out the difficulties scientists face in searching for the causing variants in complex diseases. It appears that causing variants may be hard to detect with association analysis alone because of the strong linkage disequilibrium in associated regions. However, the GWAS detected a number of CD associated genomic regions which remain to be explored.

Keywords: Celiac Disease, genome-wide scan, linkage, association, GWAS, complex disease, autoimmune, HLA, IL2/IL21, 5q31-33.

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