Newsletter June 2010

This is the newsletter for PREVENTCD, Prevent Coeliac Disease: a project investigating the possibility of inducing tolerance to gluten in genetically predisposed children by means of early dietary intervention. The project is sponsored by the European Union and involves 10 European countries.

WP3: FAMILY STUDY

Recruitment of the families is almost completed; only those children born up to June 2010 will be included. The targeted number of one thousand neonates has been exceeded. Many of these children have turned 3 years of age and completed their participation in the project. It was agreed that they will be followed up by at least telephone contact and autoantibodies determination once per year.

Two subprojects were formed within PREVENTCD:

"Autoimmune disease Analyses (AidA)" to determine the presence of autoanitibodies related to type 1 diabetes and autoimmune thyroiditis at the age of 36 months.

"Impact of HLA screening on families of children with CD" that will answear how much the screening affects the quality of life.

WP4: POPULATION STUDY

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Anneli Ivarsson, Associate Professor and work package leader, presented preliminary results from the ongoing multisite field phase of WP4 at the Annual Meeting of the Swedish Paediatric Society on the 19th of April 2010 in Jönköping, Sweden.

Anneli Ivarsson

WP 5: GENETICS

In the past decade, tremendous progress has been achieved in unraveling the genetic etiology of coeliac disease. Twin- and family-based studies clearly show a strong genetic component to coeliac disease development, with inherited risk mainly attributable to the HLA-DQ2 and –DQ8 variants. These HLA risk variants are carried by more than 95% of coeliac patients, and they explain approximately 35% of the heritability of coeliac disease. On the other hand, these variants are also present in 30%-40% of the healthy population, which means that having HLA risk variants is necessary but not sufficient for the development of coeliac disease.

In 2007, Van Heel et al. published the first genome-wide association study (GWAS) which identified the *IL2/IL21* locus as a risk locus for coeliac disease. Subsequent studies probing GWAS information in greater depth have identified a further 12 non-HLA risk loci. Most of these loci contain a candidate gene that functions in the immune system. To identify additional risk variants and broaden our knowledge about the functional background of coeliac disease, Dubois et al. performed a second-generation GWAS using more than six times as many samples as the previous GWAS of Dutch, UK, Italian and Finnish origin *(Dubois et al., Nature Genetics, 2010)*.

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WP 5: GENETICS

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This new GWA study confirmed all 13 previously identified non-HLA loci to be strongly associated with coeliac disease. In addition, 13 loci showed an association with coeliac disease at the genome-wide significance level. Most of these loci again contain genes with immune functions (*BACH2*, *CCR4*, *CD80*, *CIITA-SOCS1-CLEC16A*, *ICOSLG, ZMIZ1, ETS1*, *RUNX3*, *THEMIS* and *TNFRSF14*). The new risk loci *ETS1*, *RUNX3*, *THEMIS* and *TNFRSF14* play key roles in thymic T-cell selection, a pathway that previously has not been implicated in coeliac disease pathogenesis. In addition to the 13 loci associated with celiac disease at the genome wide significance level, there was also evidence to suggest associations for a further 13 loci. All findings were replicated in 7 additional cohorts from the USA, Hungary, Ireland, Poland, Spain, Italy and Finland.

We hope that the identification of these new coeliac susceptibility genes will improve diagnostic and prognostic markers, provide a better understanding of the disease etiology, permit development of new therapeutics and clarify the clinical overlap of coeliac disease with other autoimmune disorders.

Recent publications

Dubois PCA , Trynka G, Franke L, Hunt KA, Romanos J et al. Multiple common variants for celiac disease influencing immune gene expression. Nat Genet. 2010;42:295-302. Epub 2010 Feb 28.

Caja S, Myrsky E, Korponay-Szabo IR, Nadalutti C, Sulic AM, Lavric M, Sblattero D, Marzari R, Collighan R, Mongeot A, Griffin M, Mäki M, Kaukinen K. Inhibition of transglutaminase 2 enzymatic activity ameliorates the anti-angiogenic effects of coeliac disease autoantibodies. Scand J Gastroenterol. 2010;45:421-7.

Hogen Esch CE, Csizmadia GD, van Hoogstraten IM, Schreurs MW, Mearin ML, von Blomberg BM. Childhood coeliac disease: towards an improved serological mass screening strategy. Aliment Pharmacol Ther. 2010;3:760-6. Epub 2009 Dec 25.

Zhernakova A, Elbers CC, Ferwerda B, Romanos J, Trynka G et al. Evolutionary and functional analysis of celiac risk loci reveals SH2B3 as a protective factor against bacterial infection. Am J Hum Gen 2010; 86, 1–8.

Decker E, Engelmann G, Findeisen A, Gerner P, Laa M. Cesarean delivery is associated with celiac disease but not inflammatory bowel disease in children.*Pediatrics* 2010;125;e1433-e1440.

Others

Hjördís ÓA, Pedersen MG, Thorsen P, Mortensen PB, Deleuran B, Eaton WW, Parner ET. Disorders Association of Family History of Autoimmune Diseases and Autism Spectrum. *Pediatrics* 2009;124;687-694.

5th Progress Meeting
Brussels, February 2010

This time the biannual progress meeting was organized in Brussels, where we debated in the close neighbourhood of the European Commission.

The possibility of a neutral prolongation of the project was discussed. Since relatively high costs will be related to the follow up of the cohort after the project and the completion of the EU sponsorship, the issue of potential sources of financial support was also raised.

PREVENTCD team at the Progress Meeting: Brussels, 11&12nd Feb 2010.