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Crohn’s disease course is not different in familial than in sporadic cases: A case–control population-based study

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Background: Having a first degree relative (siblings, children, parents) with Crohn’s disease (CD) is the main risk factor to develop the disease. This genetic risk could influence the natural history of the disease; particularly in multiplexes families (MF) defined by at least 3 members with CD linked at the first degree. The aim of our study was to compare disease course between patients with CD in MF and sporadic families.

Methods: MF were identified in a French population-based study on inflammatory bowel disease (Epimad Registry). Each patient from MF was matched to at least one sporadic case also issued from this Registry. Matching criteria were: gender, age at CD diagnosis, phenotype at diagnosis (disease location and disease behaviour) according to Montreal classification [1] and date of CD diagnosis. Primary outcomes were assessed at the end of the follow up and included: disease extension, change of behaviour from inflammatory (B1) to complicated type of CD (structuring B2 and/or penetrating B3), occurrence of extra-intestinal manifestations (EIMs), the need for immunosuppressor (IS) treatment or anti-TNF biologic agent, and at least one intestinal resection. Case–control comparisons were performed using a mixed model for multivariate analysis, adjusted to smoking status.

Results: Fifty-nine patients belonging to 24 MF were included matched to 88 sporadic patients. The median follow-up was 16 years [Q1 = 12–Q3 = 20]. Patients from MF were significantly more often smokers or former smokers than controls (93% vs 53%, p < 0.05). No differences between MF and sporadic cases were observed regarding disease extension (75% vs 70%), change of behaviour (56% vs 65%) or prevalence of EIMs (27% vs 31%). Similar proportions of sporadic cases and MF patients received at 10 and 20 years; (1) IS (46% vs 62% and 61% vs 73%, respectively), (2) anti-TNF therapy (14% vs 24% and 46% vs 52%, respectively), and (3) underwent surgical intestinal resection (42% vs 50% and 49% vs 57%, respectively).

Conclusions: In this case–control population-based study we find none difference in the CD disease course between patients from multiplex and sporadic families. These findings could suggest that genetic and environmental risk factors affecting the CD disease course are different from those affecting its occurrence.

Reference(s)

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Case–control study and meta-analysis of glutathione S-transferase polymorphisms in patients with inflammatory bowel disease

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Background: Glutathione S-transferases (GSTs) are important in the detoxification of a wide variety of exogenous and endogenous compounds, including reactive oxygen species (ROS). Since ROS are involved in the aetiology of inflammatory bowel diseases (IBD), polymorphisms in GSTs might modulate the risk for Crohn’s disease (CD) or ulcerative colitis (UC). In more detail, the null alleles GSTM1*0 and GSTT1*0, which cannot be detected by immunochips used in genome wide association studies, lead to a failed protein synthesis. For GSTP, the single nucleotide substitutions A>G at codon 105 and C>T at codon 114, are considered as the most important polymorphisms and lead to a reduced enzyme function. Previous studies highlighting GST polymorphisms in IBD patients showed divergent results, therefore we conducted a case–control study and a meta-analysis of GST polymorphisms in GST Mu (GSTM1), GST Pi (GSTP1) and GST Theta (GSTT1) in IBD patients.

Methods: Genomic DNA of 552 patients with CD, 223 patients with UC and 972 healthy controls from our centre was genotyped for polymorphisms in GSTM1, GSTP1 and GSTT1 using polymerase chain reaction techniques. Results of the case–control study were included in the meta-analysis. A search on Pubmed and EMBASE was conducted comprising the search terms: GST, glutathione S-transferase, IBD, Crohn’s disease and ulcerative colitis. Case–control studies examining GST polymorphisms in patients with IBD compared to healthy controls were included, provided that absolute numbers of genotype distributions were given. With the most common homozygous GSTP1 genotype or homozygous + heterozygous GSTM1 or GSTT1 genotypes set as reference, data were pooled and weighed odds ratios (OR) were calculated with a random effect model using RevMan® V5.2 software.

Results: The search for the meta-analysis identified 118 articles. After screening for title and abstract 10 articles remained. Three were excluded because of Chinese language (n = 2) or overlapping data (n = 1). A total of 1613 patients with CD, 1759 patients with UC and 4098 healthy controls, including our data, was used for further analysis. Pooled analysis showed an increased susceptibility for UC with the homozygous GSTT1*0 genotype (OR 2.27, 95% CI 1.31–3.92). In contrast to GSTT1, the GSTP1 114 Ala/Val + Val/Val genotypes had lower risk for UC (OR 0.70, 95% CI 0.54–0.90). For CD, pooled analysis showed a slight protective effect for the combination of homozygous GSTM1*0 + GSTT1*0 genotype (OR 0.73, 95% CI 0.55–0.98). Conclusions: The homozygous GSTT1*0 genotype, associated with a decreased detoxification of ROS, may increase the susceptibility for UC, whereas the GSTP1 114 genotypes associated with reduced enzyme activity, may result in a lower risk for UC.

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BAX, a novel susceptibility gene for Crohn’s disease

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Background: Autophagy and apoptosis play a major role in Crohn’s disease (CD). We present the first study in our population of polymorphisms (SNPs) involved in these scenarios (NOD2, ATG16L1). We have previously shown that NOD2 and ATG16L1 possess a joint effect model using RevMan® V5.2 software. The search for the meta-analysis identified 118 articles. After screening for title and abstract 10 articles remained. Three were excluded because of Chinese language (n = 2) or overlapping data (n = 1). A total of 1613 patients with CD, 1759 patients with UC and 4098 healthy controls, including our data, was used for further analysis. Pooled analysis showed an increased susceptibility for UC with the homozygous GSTT1*0 genotype (OR 2.27, 95% CI 1.31–3.92). In contrast to GSTT1, the GSTP1 114 Ala/Val + Val/Val genotypes had lower risk for UC (OR 0.70, 95% CI 0.54–0.90). For CD, pooled analysis showed a slight protective effect for the combination of homozygous GSTM1*0 + GSTT1*0 genotype (OR 0.73, 95% CI 0.55–0.98). Conclusions: The homozygous GSTT1*0 genotype, associated with a decreased detoxification of ROS, may increase the susceptibility for UC, whereas the GSTP1 114 genotypes associated with reduced enzyme activity, may result in a lower risk for UC.

Reference(s)