

ELECTRONIC LETTER

Transmission disequilibrium test of stromelysin-1 gene variation in relation to Crohn's disease

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Crohn's disease (MIM 266600) and ulcerative colitis (MIM 191390) are the major forms of inflammatory bowel disease (MIM 601458), the prevalence of Crohn's disease being more than 1/1000 in the Western countries.¹ Inflammatory bowel disease is characterised by chronic relapsing intestinal inflammation, and its pathogenesis probably involves microbial, immunological, environmental, and genetic factors.²⁻³ Recent genetic association studies have shown that sequence variations in the Caspase Activating Recruitment Domain (*CARD15*) gene (MIM605956, formerly named NOD2) on chromosome 16q are a strong genetic factor for Crohn's disease but not for ulcerative colitis.⁴⁻⁶ *CARD15* represents the first major Crohn's disease susceptibility gene identified, and its identification might facilitate the uncovering of other genetic factors for the disease.

The matrix metalloproteinases (MMP) are a group of matrix degrading enzymes that play an important role in the pathogenesis of various inflammatory diseases including osteoarthritis, rheumatoid arthritis, atherosclerosis, cancers, and inflammatory bowel disease.⁷ We have shown that, of four MMPs studied (interstitial collagenase, gelatinase A and B, and stromelysin-1), stromelysin-1 in particular is directly involved in mucosal destruction following T cell activation in the human fetal gut.⁸ Furthermore, patients with Crohn's disease have increased expression of stromelysin-1 in the mucosa at both the mRNA and protein levels.⁹ Microarray techniques have demonstrated that stromelysin-1 expression is increased 8.7-fold in the mucosa of patients with Crohn's disease compared with healthy controls (Pender SLF, unpublished data), and have also shown that stromelysin-1 expression is 8.2-fold higher relative to controls in PWM stimulated human fetal gut explant culture.¹⁰ Thus, although the stromelysin-1 gene on chromosome 11q23 is not located within the particular chromosomal regions (19p13, 16q12, 16p, 14q11-q12, 12p13.2-q24.1, 6p, 5q31, and 1p36) that have been shown to be in linkage with inflammatory bowel disease (MIM 266600), it is a strong functional candidate gene that might have an influence on this multifactorial disorder.

We have previously identified a functional polymorphism in the promoter of the stromelysin-1 gene.¹¹ The polymorphism arises from insertion or deletion of an adenosine within a cluster of adenosines located at position -1612 and upwards, relative to the transcriptional start site of the gene, with one allele having a cluster of five adenosines (5A) and the other allele having six adenosines (6A). In vitro assays have shown that the 5A allele has a higher promoter activity than the 6A allele, with differential binding of a nuclear protein to the two allelic promoters.¹²

Given that increased stromelysin-1 expression plays an important role in the development of Crohn's disease and that the 5A/6A polymorphism has an allele specific effect on stromelysin-1 expression, individuals carrying the 5A allele might have increased susceptibility to Crohn's disease. We tested this hypothesis in the present study.

Key points

- Stromelysin-1, an extracellular matrix degrading enzyme, is involved in tissue destruction in Crohn's disease.
- To investigate whether the stromelysin-1 gene 5A/6A polymorphism was associated with susceptibility to Crohn's disease, this polymorphism was analysed in 468 German sporadic inflammatory bowel disease trios and 270 British and German multiplex inflammatory bowel disease families using the transmission disequilibrium test.
- There was overtransmission of the 5A allele to affected offspring in the German sporadic Crohn's disease trios ($p=0.0012$).
- There was an interaction between the stromelysin-1 gene 5A/6A polymorphism and the *CARD15* gene, a well established gene for Crohn's disease, such that overtransmission of the 5A allele to affected offspring in the German sporadic Crohn's disease trios was significant in *CARD15* variant carriers ($p=0.0054$) but not in non-carriers.
- In the *CARD15* variant carriers, overtransmission of the 5A allele was associated with stenosis ($p=0.0027$), fistulising disease ($p=0.0007$), previous surgical resection ($p=0.0023$), and disease of the ileum ($p=0.0001$) and right colon ($p=0.0115$).
- The stromelysin-1 gene 5A allele appears to represent a genetic factor for Crohn's disease.

METHODS

Subjects

The stromelysin-1 gene 5A/6A polymorphism was analysed in a collection of trios from Germany, each consisting of one patient with inflammatory bowel disease and their two unaffected parents (table 1). In addition, the polymorphism was analysed in a cohort of German families and a cohort of British families, each with multiple cases of inflammatory bowel disease (table 1). These samples were recruited by an international group of inflammatory bowel disease investigators at the Charité University Hospital (Berlin, Germany), the Christian-Albrechts-Universität Hospital (Kiel, Germany), St Mark's Hospital (London, UK), Guy's Hospital (London, UK), King's College Hospital (London,

Abbreviations: CARD, caspase activating recruitment domain; MMP, matrix metalloproteinase; PWM, pokeweed mitogen; TDT, transmission disequilibrium test

UK), and several additional German centres. The characteristics of the subjects have been described previously.^{5 13-16}

Informed, written consent was obtained from all study participants. Recruitment protocols were approved by ethics committees at the participating centres before the study began. The diagnosis of inflammatory bowel disease and the classification into Crohn's disease and ulcerative colitis were determined by standard diagnostic criteria.^{17 18} Clinical, radiological, and endoscopic examinations (type of lesions, distribution) were required for unequivocal confirmation of the diagnosis of either ulcerative colitis or Crohn's disease. Histological findings also had to be confirmative or compatible with this diagnosis. In cases of uncertainty, the diagnosis of indeterminate colitis was assigned and the patient excluded from the study.

Genotyping

Genomic DNA was prepared from 10 ml of fresh or frozen peripheral venous blood using the Puregene system (Gentra Systems, Minneapolis, Minnesota, USA). Individual DNA samples were arrayed in 96-well microtitre plates. The stromelysin-1 gene 5A/6A polymorphism was genotyped by TaqMan 5'-nuclease assay using the following primers and probes (designed on the reverse strand): forward primer 5' GCCACCACTCTGTTCTCCTTGTC 3', reverse primer 5' CACG GCACCTGGCCTAAAGA 3'; first probe (6A) 5' CAAGACATGG TTTTTCCTCCCATCA 3', second probe (5A) 5' CAAGACAT GGTTCCTCCCATCA 3'. Primers and probes were designed with the Primer Express program (Aplera, Foster City, California, USA) and synthesised by Eurogentec (Liège, Belgium). The amplification reaction, done in a Biometra T1 thermocycler (Biometra, Göttingen, Germany), involved two pre-polymerase chain reaction (PCR) steps of two minutes at 50°C and 10 minutes at 95°C, followed by 50 cycles including a denaturation step at 95°C for 15 seconds and an annealing and extension step at 64°C for one minute, in a total volume of 5 µl with 100 nM of probes and 300 nM of primers.

Statistical analysis

An integrated database¹⁹ was used to manage the genotyping data. Transmission disequilibrium tests (TDT) of the 5A/6A polymorphism in relation to inflammatory bowel disease, Crohn's disease, and ulcerative colitis in the German trios and in the German and British families were undertaken using the TRANSMIT program^{20 21} with the robust variance estimator option. TDT of the 5A/6A polymorphism in relation to various phenotypes of Crohn's disease in the German trios was also carried out using the TRANSMIT program. Significances were verified using 10 000 bootstrap replicates.

Possible interaction between the stromelysin gene and the *CARD15* gene was examined by stratifying the patients according to their *CARD15* genotype. Individuals carrying

one or more copies of the R702W, G908R, or 1007insC mutations⁴⁻⁶ were classified as *CARD15+*, and individuals not carrying these mutations as *CARD15-*.

RESULTS

Analyses in German sporadic inflammatory bowel disease trios

Transmission disequilibrium tests in the German sporadic inflammatory bowel disease trios showed a highly significant association between Crohn's disease and overtransmission of the 5A allele ($p = 0.0012$, table 2). No significant association between ulcerative colitis and the stromelysin-1 gene was detected.

There was an interaction between stromelysin-1 and *CARD15* genes, such that the association of the stromelysin-1 gene 5A allele with Crohn's disease was apparent only in individuals carrying one or more mutations in the *CARD15* gene ($p = 0.0054$, table 3). In *CARD15* mutation carriers, overtransmission of the 5A allele was associated with various Crohn's disease traits, including stenosis ($p = 0.0027$), fistulising disease ($p = 0.0007$), previous surgical resection ($p = 0.0023$), and disease of the ileum ($p = 0.0001$) and right colon ($p = 0.0115$; NS after correcting for multiple testing) (table 3).

There was no evidence of interaction between the stromelysin gene and smoking in relation to the development of Crohn's disease. In individuals carrying one or more mutations in the *CARD15* gene, there was significant overtransmission of the 5A allele in the trios, regardless whether the offspring had smoked (observed/expected 5A allele transmission ratio, 69/59.65; $p = 0.0147$) or had never smoked (observed/expected 5A allele transmission ratio, 76/65.87; $p = 0.0239$).

In non-carriers of the *CARD15* gene mutations, there was no significant overtransmission of the 5A allele in the trios, regardless of whether the offspring had smoked or not ($p = 0.6231$, $p = 0.6379$, respectively).

Analyses in the multiplex inflammatory bowel disease families

No significant association between the stromelysin-1 5A/6A polymorphism and Crohn's disease or ulcerative colitis was detected in the German and British families with familial inflammatory bowel disease (table 2), and this was not affected by stratification for *CARD15* genotype.

DISCUSSION

In this study we showed an association of Crohn's disease susceptibility with the stromelysin-1 gene 5A/6A polymorphism in a cohort of German sporadic Crohn's disease trios. As increased stromelysin-1 gene expression plays an important

Table 1 Subjects genotyped for the stromelysin-1 gene 5A/6A polymorphism

	Disease	Number of trios or families	Number of affected offspring per family	Number of trios or families where both parents were genotyped
German sporadic IBD trios	CD	320	1	318 (ie, in 99.4% of the collection)
	UC	148	1	147 (ie, in 99.3% of the collection)
German multiplex IBD families	CD	135	1 in 47 families, 2 in 82 families, 3 in 6 families	115 (ie, in 85.2% of the collection)
	UC	83	1 in 44 families, 2 in 39 families	70 (ie, in 84.3% of the collection)
British multiplex IBD families	CD	91	1 in 40 families, 2 in 44 families, 3 in 7 families	78 (ie, in 85.7% of the collection)
	UC	49	1 in 28 families, 2 in 17 families, 3 in 4 families	42 (ie, in 85.7% of the collection)

CD, Crohn's disease; IBD, inflammatory bowel disease; UC, ulcerative colitis.

Table 2 Results of transmission disequilibrium test

	Crohn's disease		Ulcerative colitis	
	O/E	p Value*	O/E	p Value*
German sporadic IBD trios	279/250.63	0.0012	129/128.98	0.9955
German multiplex IBD families	252/247.51	0.5133	124/119.91	0.4331
British multiplex IBD families	151/152.69	0.7600	62/64.46	0.4642

*After 10 000 bootstrap replicates.
IBD, inflammatory bowel disease; O/E, observed/expected 5A allele transmission ratio.

role in the development of Crohn's disease, the association of the stromelysin-1 gene 5A allele with increased Crohn's disease susceptibility is likely to reflect increased expression of stromelysin-1 in 5A allele carriers, which would be consistent with results of functional studies showing that the 5A allele had a higher transcriptional activity than the 6A allele. We also found that there is an interaction between the stromelysin-1 gene and the *CARD15* gene in determining Crohn's disease susceptibility. The underlying mechanism for this observation is unclear. One possibility would be that non-genetic factors play a greater role in the non-carriers of the *CARD15* gene mutations than in the carriers, making the modest effect of the stromelysin-1 gene less detectable in the non-carriers of the *CARD15* gene mutations. The possibility that stromelysin-1 and *CARD15* interact at the cellular or molecular level could not be ruled out.

As smoking is an established environmental risk factor for Crohn's disease, and previous studies have shown an interaction between the 5A/6A polymorphism and smoking in relation to the risk of coronary heart disease,²²⁻²³ we explored whether there was an interaction between the 5A/6A polymorphism and smoking in Crohn's disease, but did not find evidence of such an interaction.

The association between the stromelysin-1 gene 5A/6A polymorphism and Crohn's disease was not detected in the multiplex families in this study. There are several possible explanations for the presence of an association of Crohn's disease with the stromelysin-1 gene 5A/6A polymorphism in the sporadic Crohn's disease trios, and the absence of such an association in the multiplex families. First, it is possible that the stromelysin-1 gene 5A/6A polymorphism is associated with a subset of Crohn's disease phenotypes that are enriched in the sporadic Crohn's disease trios but underrepresented in the multiplex Crohn's disease families. However, we did not find a significant difference between the trios and the

multiplex families in the frequencies of the phenotypes listed in table 3. Second, as the trios represent sporadic inflammatory bowel disease whereas the multiplex families represent familial disease, it is possible that other not yet identified genes have greater effects on the development of Crohn's disease in the multiplex families than in the sporadic Crohn's disease trios, and thus the modest effect of the stromelysin-1 gene would be more easily detectable in the latter than in the former. Another possible explanation might be the lack of statistical power in the family samples, as the sample sizes of the German and British multiplex families and the case-control set were substantially smaller than those of the trio collection. In addition, in about 15% of the German and British families only one parent was genotyped, which would further reduce the statistical power in these samples. In comparison, in nearly 100% of the trios, both parents were genotyped.

In this study, no association between ulcerative colitis and the stromelysin-1 gene 5A/6A polymorphism was detected. Although Crohn's disease and ulcerative colitis are both major forms of inflammatory bowel disease, previous studies have shown that *CARD15* gene mutations are associated with Crohn's disease but not with ulcerative colitis,⁴⁻⁶ suggesting that they have different pathological mechanisms.

Functional studies have revealed that the 5A allele has a higher transcriptional activity than the 6A allele, with preferential binding of a transcription repressor to the latter.¹²⁻²⁴⁻²⁵ Stromelysin-1 plays an important role in the development of several diseases where the pathogenesis involves inflammation and matrix degradation and remodeling. An association between the 5A/6A polymorphism and phenotypes of coronary heart disease has been shown in various studies, such that carriers of the 5A allele have increased risk of myocardial infarction—a clinical event associated with matrix degradation in coronary atherosclerotic plaques—whereas 6A homozygotes have greater atherosclerotic plaque growth, which is associated with matrix accumulation.¹¹⁻²⁶⁻²⁸ Taken together, the functional data and genetic epidemiological observations indicate that genetic variation in the promoter of the stromelysin-1 gene can alter the levels of stromelysin-1 expression, leading to an imbalance between synthesis and degradation of vascular matrix—that is, an imbalance favouring matrix degradation in individuals carrying the 5A allele, contrasted by an imbalance favouring matrix accumulation in 6A homozygotes.

In addition to atherosclerosis, several other pathological conditions have been associated with the stromelysin-1 gene 5A/6A polymorphism. For example, a recent study showed that this polymorphism is associated with susceptibility and progression of primary sclerosing cholangitis.²⁹ An association between this genetic variation and rheumatoid arthritis has also been reported.³⁰ The results of our present study suggest that the stromelysin-1 5A/6A polymorphism might also be related to Crohn's disease. However, the findings of this study need confirmation in an independent study before the stromelysin-1 gene may be considered an established

Table 3 Results of transmission disequilibrium test in German sporadic inflammatory bowel disease trios stratified for *CARD15* genotype

	<i>CARD15</i>	O/E	p Value*
Crohn's disease	+	166/147.49	0.0054
	-	170/167.04	0.6718
Stenosis	+	116/98.56	0.0027
	-	100/100.89	0.871
Fistulae	+	103/84.60	0.0007
	-	90/90.39	0.942
Resection	+	106/89.39	0.0023
	-	89/87.87	0.8284
Ileal	+	147/124.78	0.0001
	-	124/124.84	0.891
Right colon	+	124/109.3	0.0115
	-	114/114.84	0.8805
Left colon	+	57/52.19	0.2165
	-	113/113.56	0.9206

*After 10 000 bootstrap replicates.
CARD15 mutation, + indicates carriers of the R702W, G908R, or 1007insC mutation; - indicates non-carriers.
O/E, observed/expected 5A allele transmission ratio.

genetic risk factor for this disease. In contrast to rare mutations with large functional effects, such as the *CARD15* mutations, the 5A/6A polymorphism is a common variant and would probably have only moderate effects on stromelysin-1 expression and disease susceptibility.

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