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OCTN genes: Susceptibility genes for autoimmune diseases?

E. Urcelay, E.G. de la Concha, A. Martínez

Departamento de Inmunología, Hospital Clínico San Carlos, Madrid.

LOS GENES OCTN: ¿GENES DE SUSCEPTIBILIDAD A ENFERMEDADES AUTOINMUNES?

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RESUMEN

El estudio genético de las enfermedades autoinmunes de base poligénica (artritis reumatoide, enfermedad inflamatoria intestinal, etc) ha evolucionado desde la identificación, mediante estudios de ligamiento, de regiones del genoma implicadas en la susceptibilidad, a la identificación dentro de esas zonas, mediante estudios de asociación, de las variantes concretas en genes específicos que están molecularmente relacionadas con la predisposición incrementada a la enfermedad. Una de las regiones que ha atraído más interés es 5q31, ligada a enfermedad inflamatoria intestinal y enfermedades alérgicas, puesto que en dicha región se encuentran los genes de importantes citocinas como IL4, IL5 e IL13. Un resultado sorprendente de los estudios de asociación que se hicieron a continuación, es que tanto en la enfermedad de Crohn como en la artritis reumatoide, los genes responsables presentes en la región resultaron ser, no esos genes de citocinas, sino dos transportadores de cationes orgánicos, OCTN1 y OCTN2, codificados por los genes *SLC22A4* y *SLC22A5*, respectivamente, y para los que nadie había anticipado una función relevante en el sistema inmune. En los últimos dos años ha existido un animado debate en la literatura inmunogenética acerca de si realmente esos genes son los auténticamente responsables de la enfermedad, o si simplemente son arrastrados pasivamente en el cromosoma 5, por desequilibrio de ligamiento, con la variante etiológica, que aún permanecería por identificar. En la presente revisión, pretendemos dar un breve panorama del estado de la cuestión.

PALABRAS CLAVE: OCTN1/ SLC22A4/ OCTN2/ SLC22A5/ Susceptibilidad genética/ Polimorfismo de Nucleótido Único/ Artritis Reumatoide/ Enfermedad de Crohn.

ABSTRACT

Genetic studies in polygenic autoimmune diseases (Rheumatoid arthritis, inflammatory bowel disease, etc) have moved from identifying by linkage studies those genomic regions involved in susceptibility, to the precise ascertainment of specific variants molecularly related to the disease by association studies. One of the regions which attracted more attention is 5q31, linked to inflammatory bowel and allergic diseases because it harbours the cytokine-cluster comprising IL4, IL5 and IL13, among others. A surprising result of subsequent association studies, both in Crohn's disease and in rheumatoid arthritis, was that the susceptibility genes in that region turned out to be, not any of the cytokine genes, but two organic cation transporters, OCTN1 and OCTN2 coded by the *SLC22A4* and *SLC22A5* genes respectively, not previously anticipated as relevant for the immune response. During the last two years there has been a lively debate in the immunogenetic literature on whether these genes are truly responsible of the increased susceptibility to the disease, or they are simply passively carried on chromosome 5q31 by linkage disequilibrium with an as-yet-unknown etiologic variant. In the present review, we aim at offering a brief glance of the current status in this field.

KEY WORDS: OCTN1/ SLC22A4/ OCTN2/ SLC22A5/ Genetic susceptibility/ Single Nucleotide Polymorphism/ Rheumatoid Arthritis/ Crohn's disease.

INTRODUCTION

Complex diseases arise from an interaction between genetic factors and environmental inputs that eventually act as triggers[1]. The main autoimmune inflammatory diseases (Inflammatory Bowel Diseases, Rheumatoid Arthritis, Multiple Sclerosis, Type 1 Diabetes, etc) are characterized by a non-mendelian pattern of inheritance. It is believed that many genes, each with a small overall effect, modulate the predisposition to suffer from those diseases. Some of the susceptibility genes appear to be very specific of a particular disease, but it is becoming increasingly clear that many genes act as "general" predisposition elements in several inflammatory conditions.

The first approach to study the genetics underlying these diseases took the form of association studies, under case-control formats. When a polymorphic gene is tested, this type of analysis looks for a difference in allelic, genotypic or carrier frequencies between patients and healthy controls with similar ethnic background. Most of the first results identified the HLA locus in human chromosome 6 as the main susceptibility component in the most prevalent autoimmune diseases. Although the association of the autoimmune diseases with HLA alleles or haplotypes dates back to the 1970´s, in most cases, and because of the extensive linkage disequilibrium within the region, the precise identification of the causative gene in the HLA region is still awaited. The phenomenon of linkage disequilibrium (two alleles at different loci are present in the same individual more frequently than expected by chance) is useful for the genetic researcher, because it is possible to detect an association signal even when the polymorphism under scrutiny is not the etiological variant itself, but one closely related to it. However, this same linkage disequilibrium makes it often impossible to tell, on purely genetic grounds alone, which specific variant underlies the increased predisposition to suffer from a specific disorder. In short, linkage disequilibrium is the tool that allows detecting an association, but once an association has been found it becomes the problem when trying to further dissect the region. In some cases semi-formal proof of the involvement of a specific gene comes from smart deductions from available data, as was the case with the HLA-DQ2 heterodimer association with celiac disease[2] or the shared epitope in the *DRB1* gene, also located on the HLA complex, in rheumatoid arthritis[3]. In the first case, the observation that susceptibility to celiac disease was associated with the presence of the DQα1*05/DQβ1*02 heterodimer, encoded either in *cis* or in *trans*, led to the suggestion that the surface DQ glycoprotein was *per se* the etiological molecule, a fact later confirmed when it was found that only the DQ2 allele was able to bind transglutaminase-modified gliadin peptides. In the second case, the observation that every *DRB1* allele associated with rheumatoid arthritis (RA) presented a similar amino acid structure around the critical position 70 of the DRβ molecule, led to the suggestion that this amino acid structure (the shared epitope) was the intrinsic susceptibility factor. However, no clear functional data on the molecular mechanism of peptide binding to the shared epitope alleles are available to support this fact. This uncertainty highlights the difficulty inherent to determine with precision the susceptibility gene in a region of extended linkage disequilibrium, and to translate with precision this presumed determination to the molecular basis of the disease.

In the 1990s, the first genome-wide linkage studies (an approach previously used only with monogenetic traits) were published for IBD[4-8] and other diseases[9-17]. These studies seek the genomic regions shared more frequently than expected by chance among affected individuals in the same family. The regions identified in this manner usually contain many genes, because linkage in a family extends at a distance of several cM (approximately 5 Mb). Therefore, when a linkage peak is detected in a genomic scan, further studies using a denser collection of markers are necessary to restrict the region of interest to less than one megabase. Finally, an association study is performed to identify variants in specific genes that can be (ideally) functionally tested to ascertain their implication in the inflammatory process. Association studies relying not in linkage, but in linkage disequilibrium, which rarely extends more than 100 kb, are able to shorten the genomic susceptibility interval.

5q31: A REGION OF INTEREST

One of the first genomic regions detected in those pioneer linkage studies was 5q31[18], a region already known to contain a cytokine gene cluster. This cytokine locus was subsequently found to be associated with Crohn's disease, atopic dermatitis and asthma[19]. This region has been the focus of intense research during the last years and includes a plethora of immune-related genes: *IL4* (the main cytokine driving Th2 development), *IL13* (a Th2 cytokine involved in Th2 effector functions, as expulsion of intestinal parasites from infested animals and humans), *IL5* (a Th2 cytokine driving development of eosinophils, or isotype switch to IgA in mucosal B cells), *IRF1* (a transcription factor regulating to interferon expression), and other important immunoregulatory cytokines.

In 2001, Rioux et al described the association with Crohn's disease (one of the forms of inflammatory bowel diseases) of an extended haplotype covering 250 kb in the 5q31 locus, that could be tagged by 11 single nucleotide polymorphism or

SNPs[20]. The 250kb genomic region, embedded in a larger region of the 5q31 locus, was shown in an accompanying paper to be in tight linkage disequilibrium, with stretches of DNA with no detectable recombination separated from the next DNA block by a few recombination events[21]. In this case, these rare recombinations were not enough to completely disrupt the linkage disequilibrium along the region. Linkage disequilibrium was detectable even at 400 kb of distance or more. Once the susceptibility haplotype had been identified, a list was prepared with those SNPs present in the region and having an allele specific to that susceptibility haplotype. The 11 SNPs (out of 301 fully genotyped) identified in this way were, by definition, quasi-equivalent. It was therefore possible, accordingly to the authors, to recover all the genetic association found in the region with a single SNP. As described in this seminal paper, the 250 kb haplotype encompasses the etiological mutation with a probability of 90%; if the haplotype is extended to cover 350 kb, this probability raises to 99%. The core susceptibility region included only five genes *(IRF1, OCTN2, OCTN1, PDLIM, P4AH2)*, but the authors did not apparently exclude an involvement of the cytokine genes nearby *(IL4, IL5, IL13*, etc), although they are outside of the association peak. Curiously, a brief mention was made in that study about two polymorphisms located in the OCTN genes *(SLC22A4* coding for OCTN1 and *SLC22A5* coding for OCTN2), but they were considered irrelevant by the authors, probably because the OCTN genes encoding cationic transporters with no clear immune functions, were not considered good candidates in inflammatory diseases at that time.

OCTN GENES

In 2003, a report on the Japanese population described a novel association of one of the OCTN genes within 5q31 with rheumatoid arthritis[22]. *SLC22A4* encodes a transporter of cationic organic molecules (OCTN1), which is expressed in haematological and other tissues. A combination of genetic and functional studies led the authors to propose that the slc2F2 SNP, located in a RUNX consensus binding site present in the *SLC22A4* gene, was the primary source of association in this region. RUNX family members are DNA-binding transcription factors that regulate the expression of genes involved in cellular differentiation and cell cycle progression[23]. Moreover, in this case, a dual association was found, besides the SNP located in the OCTN1 gene *(SLC22A4)*, another polymorphism located in the *RUNX* gene itself was also found to be associated with rheumatoid arthritis. Those results were intriguing, because previously several genetic associations were observed between some diseases and polymorphisms in RUNX binding sites[24,25].

In the year 2004, a report from Canada identified the OCTN genes as the source of the 5q31 association in Crohn's disease[26]. The authors re-sequenced the five genes located in the IBD5 interval, and they identified 10 new SNPs. Two of them were located in the organic cation transporter gene mini-cluster *(SLC22A4* and *SLC22A5*, encoding the OCTN1 and OCTN2 transporters, respectively) and they were predicted to have functional effects. The first is a C>T transition that causes the amino acid substitution leucine (a conserved amino acid at that protein site) to phenylalanine. The second SNP is a G>C transversion in the *SLC22A5* promoter, which disrupts a heat shock element 207 basepairs upstream of the start codon. The 1672T and -207C alleles are in linkage disequilibrium and they form a susceptibility TC haplotype, which was found at a higher frequency in Crohn's disease (CD) patients (haplotypic frequency=0.52) than in controls (haplotypic frequency=0.42). When taking into account the previously described association of one of the quasi-equivalent eleven SNPs which served as proxies of the susceptibility 250 kb haplotype described three years earlier, the two OCTN SNPs were found to be at an increased frequency in patients compared to controls even in individuals without the IGR2078a_1, a surrogate marker for the extended IBD5 250 kb haplotype. The converse (association of IGR2078a_1 in absence of the susceptibility TC haplotype) was not true, and it was therefore concluded that the association observed in the 5q31 region was essentially due to the association observed at (any of) the two OCTN genes. Additional functional studies were performed; it was determined that the Leu503Phe polymorphism, located in the critical 11th transmembrane segment, substantially altered the kinetics properties of the transporter protein. Carnitine uptake into the cell was 2.7 times lower in cells expressing 503Phe than in those expressing 503Leu. Besides, electrophoretic mobility shift assays studies showed that the SNP located at the *SLC22A5* promoter affected the binding of HSF1, a heat-inducible transcription factor. It was also reported that both SLC22A4 and *SLC22A5* genes are expressed in the intestinal cell types that are the main targets in Crohn's disease: epithelial cells, macrophages and T cells. Intriguing as these results are, the study did not address what was the supposed role of carnitine uptake in the pathology or etiology of the inflammatory bowel diseases. Nevertheless, taken together with the previous Japanese results in rheumatoid arthritis, the published results suggested that an alteration in the RUNX1-OCTN axis might unexpectedly underlie inflammatory conditions.

It is interesting that the mutations found associated with Crohn's disease in the European populations were absent in the Japanese population[27], and that the converse was true

(i.e., the Japanese susceptibility RA allele was significantly less frequent in Caucasian populations[28]). Logically, the specific association found for European Crohn's disease could not be replicated in the Japanese population, but additional polymorphisms in the *SLC22A4* gene did indeed show a trend towards association, although the significance observed (p=0.03) could not withstand multiple comparisons[27]. This result was not confirmed by a subsequent Japanese study[29]. At present, it seems that no predisposition variant exist for Crohn's disease in 5q31 in the Japanese population[29, 30]. It was also reported that in Caucasian populations, an additive effect existed with the NOD2 gene[30], a locus situated in human chromosome 16 that encodes a muramyl-dipeptide receptor[31], which is a strong susceptibility factor in Crohn's disease[32, 33].

A recent study suggested that the OCTN-associated susceptibility might not be related to their transporter activity[34]. It was described that the susceptibility variant 503Phe presents higher homology with peptides derived from bacteria *(Campylobacter jejuni* and *Mycobacterium paratuberculosis)*, suggesting that a molecular mimicry phenomenon could result in antibodies raised against the mutant receptors. The already less-than-optimal functional allele would consequently be even less able to transport carnitine, and therefore, beta oxidation of fatty acids in the mitochondrial matrix would be compromised. The specific breakdown of fatty acid oxidation in intestinal epithelial cells has been proposed as a primary event leading to Crohn's disease. It was even suggested that a high-dose L-carnitine regime would benefit patients harbouring the mutation to compensate its poor transporter ability. Unfortunately, this elegant theory was questioned because it was described that the main solute transported by OCTN1 is not carnitine, but ergothioneine[35]. Ergothioneine is made exclusively by fungi and mycobacteria and it is captured by plants from the soil; when mushrooms or vegetables are consumed by humans, ergothioneine enters the body, where its precise role remains unknown. It has been proposed to be a powerful anti-oxidant, but this role seems to be critical only under certain conditions. How an altered transport of this anti-oxidant could be related to inflammatory conditions remains an obscure issue. This result, though, has fuelled interest in this metabolite, and recently an increased concentration of the molecule has been found in rheumatoid arthritis patients relative to that found in healthy controls[36]. Moreover, the OCTN1 503Phe variant is a more efficient ergothioneine transporter as shown by *in vitro* studies[37]. However, even this observation *per se* does not presuppose the directionality of the causal relationship. If the 503Phe allele is in linkage disequilibrium with another true causative allele, ergothioneine levels would be anyway different in patients and in controls. Besides, as a matter of fact, it has to be taken into account that the study of ergothioneine levels was performed in a Caucasian population and that there is no association between the exonic C1672T (Leu503Phe) polymorphism and rheumatoid arthritis in Caucasian populations[38, 39]. Since the specific association of the *SLC22A4* gene with rheumatoid arthritis observed in the Japanese population (with an intronic SNP located in a RUNX1 binding site)[22] has not been replicated in European populations[28,39,40], the relevance of the study dealing with ergothioneine levels remains unclear. It would be interesting to measure ergothioneine levels in a cohort of Japanese rheumatoid arthritis patients, where the association of the disease with a functional polymorphism in the *SLC22A4* gene does exist, to evaluate the relationship between those levels, the genetic data and the susceptibility to suffer from the disease.

A follow-up study in the Canadian population[41] has hinted towards a more specific association of these OCTN variants with ileal disease, the same clinical form that is associated with the *CARD15/NOD2* mutations, and therefore an interaction between both genes was suggested. Moreover, no effect was discernible in ulcerative colitis patients, in which no association with *CARD15/ NOD2* gene variants seems to exist.

ARE OCTN GENES PRIMARILY ASSOCIATED?

More recent genetic results have questioned the validity of previous findings (see Table I, for a summary). In celiac disease, where 5q has been shown also to be linked to the disease[42-47], no evidence was found regarding *SLC22A* genes, which suggested that the causal variant in this genomic region may lie elsewhere[48]. In this Irish study, four SNPs, each specific of one of the four haplotypes present in the core susceptibility region (IGR2230a_1, the IBD5-risk-specific tag; IGR3018a_1, haplotype2; IGR3020a_1, haplotype 3; and IGR3066a_1, haplotype 1) were genotyped using primer-introduced restriction analysis after polymerase chain reaction. Those polymorphisms were included in the 7th block, according to the nomenclature of Rioux and Daly[20, 21], where OCTN1 and OCTN2 genes map. No association was found with celiac disease. Since the SNPs were selected based on their ability to recover most of the information present in the OCTN haplotypes, it seems unlikely that some of those genes are related to increased susceptibility to celiac disease. One note of caution is necessary in this case, because the small sample size (150 celiac patients and 150 healthy controls) could lead to false-negative results.

A British study has not found evidence of association of these genes with rheumatoid arthritis[39]. The SNPs studied were those described as etiologic in RA or in CD, and several

TABLE I. Summary of the most important published association papers on OCTN genes and 5q31. The results of the association test for polymorphisms located in the SLC22A4 or SLC22A5 genes are included; the final column shows whether these results are independent of other 5q31 genetic markers

Author	Year	Population	Disease	OCTN Susceptibility	Independent?
Rioux et al.[20]	2001	Canadian	Crohn´s disease	Yes	No
Tokuhiro et al.[22]	2003	Japanese	RA	Yes	Yes
Peltekova et al.[26]	2004	Canadian	Crohn´s disease	Yes	Yes
Ryan et al.[48]	2004	Irish	Celiac disease	No	-
Yamazaki et al.[27]	2005	Japanese	Crohn´s disease	No	-
Barton et al.[39]	2005	British	RA	No	-
Gazouli et al.[56]	2005	Greek	Crohn´s disease	Yes	Not tested
Ho et al.[50]	2005	British	Psoriatic Arthritis	Yes	Not tested
Kuwahara et al.[65]	2005	Japanese	RA	No	-
Newman et al.[41]	2005	Canadian	Crohn´s disease	Yes	Not tested
Torok et al.[66]	2005	German	Crohn´s disease	Yes	?*
Newman et al.[38]	2005	Canadian	RA	No	-
Fisher et al.[58]	2006	British	Crohn´s disease	Yes	No
Friberg et al.[52]	2006	Swedish	Psoriasis	No	-
Martínez et al.[67]	2006	Spanish	Crohn´s disease	Yes	Yes
Martínez et al.[28]	2006	Spanish	RA	No	-
Onnie et al.[62]	2006	British	Crohn´s disease	Yes	No
Orozco et al.[49]	2006	Spanish	Lupus	No	-
Orozco et al.[40]	2006	Spanish	RA	No	-
Russel et al.[60]	2006	British	Crohn´s disease	Yes	No
Santiago et al.[53]	2006	Spanish	Type 1 diabetes	Yes	Not tested
Smyth et al.[68]	2006	European	Type 1 diabetes	No	-
Tosa et al.[29]	2006	Japanese	Crohn´s disease	No	-
Waller et al.[63]	2006	British	IBD	Yes	No
Cucchiara et al.[61]	2007	Italian	Crohn´s disease	Yes	No
Silverberg et al.[57]	2007	USA/Canadian	Crohn´s disease	Yes	No

**OCTN1/2 (SLC22A41672T//SLC22A5-207C) haplotype protective in 5q31 IBD5 carriers, in contrast with Peltekova et al.(26). RA: Rheumathoid arthritis; IBD: inflammatory bowel disease.*

additional markers were also included in order to cover the OCTN genes with high density. The negative result obtained would imply that there is no association at all at 5q31 in RA or, alternatively, that the etiologic variant is not the same in rheumatoid arthritis (RA) as in Crohn's disease. This conclusion is stressed by the findings from the same authors showing that there was a difference between RA patients and Crohn's disease patients when Crohn's associated mutations were compared between both groups of patients. It would be very interesting to determine the role of the variants associated with Crohn's disease in a set of RA samples in which previous evidence of linkage had been found. It is important to note that no linkage has been convincingly detected between 5q31 and rheumatoid arthritis in the genomic scans performed to date.

A study in the Spanish population described no association with the polymorphism located in the *SLC22A4* gene and susceptibility to systemic lupus erythematosus[49]. The polymorphisms studied included those previously associated with Crohn's disease in a Caucasian population and with rheumatoid arthritis in the Japanese population. Therefore, in both rheumatic diseases (rheumatoid arthritis and lupus) there is no evidence of association in Caucasian populations with OCTN variants or with any variant in linkage disequilibrium with them.

Using those same two genetic markers (1672T and -207C) a genetic relationship was evidenced between psoriatic arthritis and Crohn's disease[50], in addition to the previously described association of this complication of psoriasis with CARD15/ NOD2 mutations[51]. It is interesting to note that no association was observed with psoriasis without arthritis or with undifferentiated arthritis without psoriasis. No analysis was undertaken in this study to ascertain if the OCTN genes themselves or other genes nearby were the

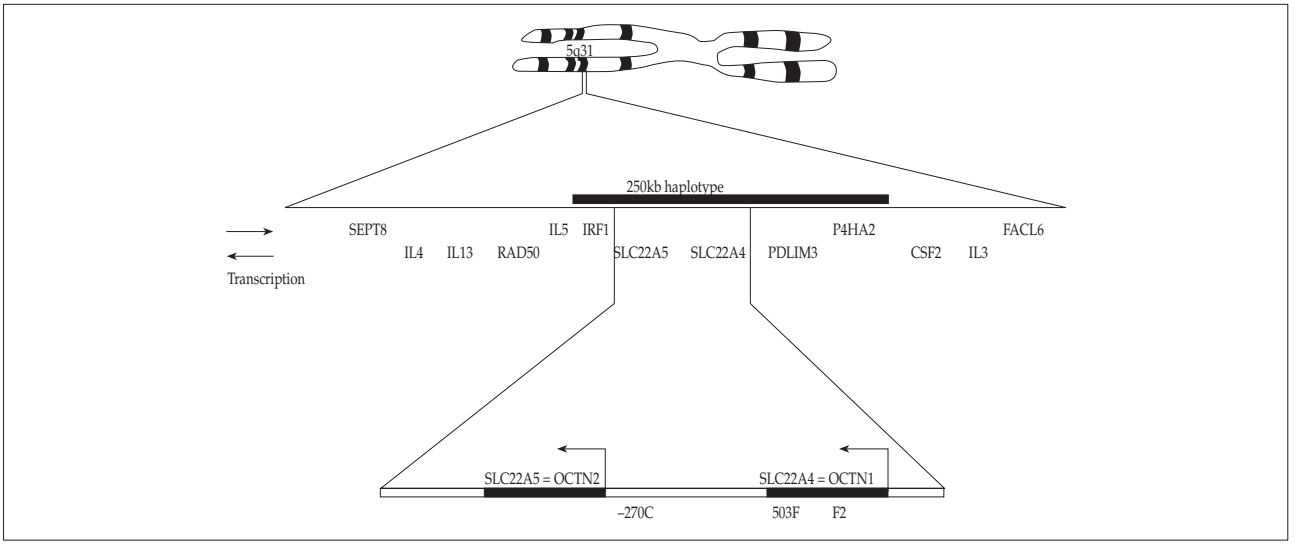

Figure 1. *Schematic depiction of the 5q31 region. Genes with their transcriptional directionality and the 250 kb core region associated with Crohn's disease are represented. The polymorphisms associated with Crohn's disease in Caucasian populations (-207C in the SLC22A5 promoter and 503F in SLC22A4), and another polymorphism associated with rheumatoid arthritis in the Japanese population (F2 located in a RUNX binding site in the SLC22A4 gene) are also included.*

primary source of the observed association signal. This situation (association of OCTN genes without evidence for them being primarily causative) was reversed in a study on psoriasis[52]. In this case a susceptibility signal was detected at 5q31-32, but no association was found with the OCTN polymorphisms. In IBD it is not possible to ascertain to what extent the observed associations are primarily derived from the OCTN genes or from another gene in linkage disequilibrium with them. However, as OCTN variants are not associated with psoriasis, it can be suggested that causal susceptibility variant located in 5q31-32 might be different in Crohn's disease and in psoriasis.

Only one study addressed the susceptibility conferred by OCTN genes to Type 1 diabetes, and it was performed in the Spanish population[53]. In this case, a small increase in the Crohn's disease associated 1672T/-207C haplotype was found (p=0.05), suggesting a genetic link between Type 1 diabetes and Crohn's disease, two Th1 diseases. Additionally, the presence of an additional protective haplotype conformed by the four OCTN SNPs included in the study would imply that several risk factors might be present in the region. The presence of more than one susceptibility gene in a genomic region is not often discussed in the OCTN literature, but the experience with HLA genetics[54, 55] indicates that this possibility should not be completely disregarded.

Turning back to inflammatory bowel diseases, a Greek study[56] reported an association of the 1672T and -207C alleles with Crohn's disease, but no attempt was made to discern between a specific role of these markers as opposed to a mere association due to linkage disequilibrium with 5q31. Therefore, those results cannot be interpreted as confirming a role for OCTN genes in Crohn's disease susceptibility.

A more recent paper by the Rioux group[57] has directly addressed the issue of OCTN susceptibility versus background susceptibility present in 5q31, extending previous case-control data with a familial analysis[58]. This is the most extensive attempt trying to localize the susceptibility variant within that genomic locus. The authors did not find any evidence of an independent role of the OCTN polymorphisms against the 5q31 haplotype background. Moreover, the authors rule out a direct susceptibility role for the *SLC22A5* promoter polymorphism; they showed that removing this SNP from the analysis did not eliminate the association signal observed in a score of nearby SNPs. However, when other SNPs more strongly associated were removed instead, significant p values were no more apparent. These results are hardly compatible with a primary role of the -207 *SLC22A5* promoter polymorphism in disease susceptibility. Coming from the same group that first described the 11 equivalent SNPs along the whole 250 kb region, it seems a rather devastating blow for the OCTN genes being the primary responsible genes for the genomic signal identified at 5q31. Additionally, it was described that the 5q31 effect was seemingly present only in non-Jew patients. Besides the OCTN genes themselves, three additional genes *(IRF1, PDLIM* and *P4HA2)* in the vicinity were claimed to be equally associated with the disease, with no genetic

basis to decide among them. The reasons behind the ethnic discrepancy between Jews and non-Jews are not entirely clear, as the haplotype structure is rather similar in Ashkenazi Jews and in Caucasian populations. It might be that to operate as a susceptibility locus, 5q31 must interact with another genetic polymorphism, perhaps in another chromosome; this additional coadjutant genetic component might be absent from Ashkenazi Jews.

These results are in agreement with previous reports from the Satsangi group[59, 60]. Although they use the OCTN SNPs as useful markers to examine the implication of the 5q31 cluster, the OCTN1/2 variants were not independent of the background IBD5 risk haplotype in conferring disease susceptibility. A very similar result was recently obtained in the Italian population: although a significant association was found for both *SLC22A4* 1672T and -207C on the *SLC22A5* promoter[61], a strong linkage disequilibrium was also found between those two markers and the IGR2096a_1 and IGR2198a_1, which, according to the original paper by Rioux et al.[20], could act as surrogate markers of the general 250 kb susceptibility haplotype present in the locus 5q31. A multivariate analysis did not reveal any independent role of the OCTN markers when the general 5q markers were taken into account, and, therefore, it does not constitute evidence for a primary susceptibility role of the cationic transporters (although it does not constitute evidence against such a role, either).

Interestingly, a recent study suggests that the region associated with Crohn's disease might also include the RAD50 gene, lying just outside of the 250kb core 5q31 region[62]. It is interesting that the *RAD50* gene is known to contain a locus control region for the Th2 cytokine gene cluster, located several kilobases away. This suggests that even when the primary association source is identified, the gene in which the polymorphism resides is not necessarily the "disease" gene.

Another group studied the implication of OCTN markers and other 5q31 markers in susceptibility to Crohn's disease and ulcerative colitis[63], the other main form of inflammatory bowel disease (IBD). In this study it was shown that any of the markers could account for the complete susceptibility observed in 5q31. There was no evidence of a specific role of the OCTN genes, and an effect was also observed in ulcerative colitis, as opposed to previous findings, but in keeping with another previous report[64].

CONCLUSION

To summarize: 5q31, as a large genomic region, has been found to be a susceptibility locus in several autoimmune inflammatory conditions, including IBD and celiac disease, and, although no conclusive evidence exists for rheumatoid arthritis in our population, a strong case can be made about the implication of the locus in this disease in the Japanese population. The OCTN genes, in particular, are associated with IBD in Caucasian populations and with RA in the Japanese population, but in no case it has been demonstrated that the effect is due to the OCTN genes themselves: contrary to the results by Peltekova et al.[26], OCTN polymorphisms do not seem to be independent risk markers in IBD. This is not to say that OCTNs are clearly not responsible for the association, but it evidences that caution is mandatory when trying to ascertain the etiologic variant in a region of high linkage disequilibrium. Studies in other ethnic groups having a different but well defined haplotype structure (as the Yoruba from Nigeria), are warranted in order to gain a comprehensive view of the genetic alteration(s) behind the susceptibility conferred by 5q31 to several inflammatory conditions.

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CORRESPONDENCE TO:
Dr. Alfonso Martínez Doncel
Departamento de Inmunología
Hospital Clínico San Carlos, Madrid
C/ Martín Lagos, s/n.
28040 Madrid, Spain
Phone number: 34-91 330 33 47. Fax: 34-91 330 33 44
E-mail: alfmdoncel@terra.es

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