LETTER TO THE EDITOR

Considerations About the Role of the CCR5 Gene in Juvenile Idiopathic Arthritis - Look at the Whole or Put All Parts Together?

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DEAR EDITOR,

The CCR5 is an important chemokine receptor. The gene coding for this protein initially gained attention when a variant called CCR5Δ32 (due to the occurrence of a 32 base pair deletion in its coding region) was associated to resistance against HIV infection. Thus, homozygous CCR5Δ32 individuals were shown to be protected against HIV-1 infection and heterozygous individuals presented a delay on AIDS development [1, 2]. From this sparkling start, the CCR5 gene, and specifically the CCR5Δ32 allele, become a candidate and a target to several studies intending to understand and explore such “beneficial allelic variant”. In this way, in 1998 the CCR5Δ32 variant was suggested to act as a protective factor against the development of rheumatoid arthritis (RA) [3] and since then several works were published attempting to corroborate or refute this initial idea and also attempting to inhibit this chemokine receptor, as a therapeutic approach in order to modulate rheumatoid arthritis symptoms [4-9].

Considering the potential association of this chemokine receptor and rheumatoid arthritis, it is tempting to analyze the effect of this same genetic variant in other rheumatological conditions. Juvenile idiopathic arthritis (JIA), for instance, is the most common chronic rheumatic disease of childhood and is defined as a chronic inflammatory condition that affects the synovial joints of individuals aged up to 16 years and that persists for at least six weeks. JIA is of unknown etiology, although there is evidence that genetic and immunological factors are involved in its development. A recently meta-analysis, performed by Hinks et al. suggested an association of the CCR5 gene with juvenile idiopathic arthritis [10]. Although we also believe that CCR5 is an important molecule in JIA, our results point to opposite directions. While Hinks et al. affirm that the CCR5Δ32 gene variant is associated with protection from developing JIA, our results suggest that this variant is associated with the most severe forms of the disease [11].

As our study was not included in the meta-analysis performed by Hinks et al., we believe that some considerations should be done in order to not avoid important information concerning the involvement of the CCR5 molecule in JIA. The reason for the non inclusion of our work on the meta-analysis was “significant heterogeneity between the studies”. Although we can agree that the CCR5Δ32 allelic frequency among our control sample was low (3.8%) as compared to those on the other three studies included at the meta-analysis (10.0% in a cohort from the United States [6], 11.5% in a population from Norway [9] and 11.4% for the United Kingdom study [10]), the frequency of the CCR5Δ32 allele among JIA patients was quite similar amongst all studies, including ours (9.4, 8.8, 9.7, and 9.2 respectively). The Brazilian population is considered to be highly miscegenated, nevertheless, in our sample we only included individuals classified as European-desendent and from the same geographic region (Rio Grande do Sul, the southernmost Brazilian state). Rio Grande do Sul is a state where African-derived genetic contribution to individuals classified as Euro-descendent is restricted, as previously discussed [12]. Also, different works have already assessed the CCR5Δ32 allelic frequency in the South population of Brazil, with frequency values ranging from 0.035 to 0.066 [12-16]. The ethnic classification used by our group (based on phenotypic characteristics of individuals and ethnicity data of parents/grandparents reported by the participants) is widely adopted in our country. Although we must admit that individuals classified as European-derived or African-derived can present a certain degree of admixture, a recent study which assessed individual interethnic admixture using a 48-insertion-deletion Ancestry-Informative Marker panel, identified a very high level of European contribution (94%) and far fewer Native American (5%) and African (1%) genes in a sample of 81 European-derived individuals from southern Brazil [17]. Therefore, the ethnic classification of the individuals in our work as European-desendent is supported both by the CCR5Δ32 allelic frequencies among Southern Brazilian populations and by the low degree of admixture in this region.

The ethnic background of a given population certainly interferes in the expression of any given feature. For example, the analysis performed by Lindner et al. [9] in the
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Norwegian cohort do not supported an association between the CCR5Delta32 allele and Norwegian RA or JIA patients. Nevertheless, when their data was included in a meta-analysis, overall results still provide evidence for a role for CCR5Delta32 in RA, once again highlighting the importance of consider the genetic/ethnic background of the analyzed population.

Even considering that data should be analyzed in a way to minimize the effects of genetic/inter-ethnic diversity, other aspects are also relevant to establish the real role of the CCR5 molecule on JIA. For instance, in the Brazilian cohort it was possible to identify a CCR5Delta3 allele frequency gradient that correlated with JIA subtypes classified according to the number of affected joints, the presence of rheumatoid factor (RF), and the degree of systemic inflammation, suggesting a relationship between the absence of the CCR5 chemokine receptor and the JIA subtypes with a broader inflammatory involvement (namely polyarticular CCR5 molecule on JIA. For instance, in the Brazilian cohort other aspects are also relevant to establish the real role of the population.

Analysis, overall results still provide evidence for a role for Nevertheless, when their data was included in a meta-analysis, the CCR5Delta32 allele and Norwegian RA or JIA patients. Norwegian cohort do not supported an association between the CCR5Delta32 allele and Norwegian RA or JIA patients. Therefore, it will be quite important not only to consider all the studies approaching human populations as a whole, but also to analyze specific subgroups of individuals, i.e. affected by certain JIA subtypes, with specific disease courses and so on. In conclusion, in JIA, the CCR5Delta32 allele seems to be much more a disease modifying factor than a susceptibility factor and should, therefore, be analyzed under this perspective. We believe that the absence or the reduced expression of a functional CCR5 molecule on JIA patients provokes a dysregulated pro-inflammatory response on such individuals. More studies on the genetics and expression of this molecule in different human populations should be performed in order to clearly identify the involvement of the CCR5 molecule in JIA and in other rheumatologic conditions as well as the potential consequences of anti-CCR5 therapies.

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CONFLICT OF INTEREST

We declare that we have no conflicts of interest in the authorship or publication of this contribution.

ABBREVIATIONS

CCR5 = Chemokine receptor gene 5
JIA = Juvenile idiopathic arthritis
RA = Rheumatoid arthritis
RF = Rheumatoid factor

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Juvenile Idiopathic Arthritis is a complex disease, characterized by the existence of a number of subtypes correlated to different clinical features. Taking together, all data from the literature indicates that JIA individuals with different disease subtypes will be distinctly affected by the absence, or by a lower expression, of the CCR5 molecule. Therefore, it will be quite important not only to consider all the studies approaching human populations as a whole, but also to analyze specific subgroups of individuals, i.e. affected by certain JIA subtypes, with specific disease courses and so on. In conclusion, in JIA, the CCR5Delta32 allele seems to be much more a disease modifying factor than a susceptibility factor and should, therefore, be analyzed under this perspective. We believe that the absence or the reduced expression of a functional CCR5 molecule on JIA patients provokes a dysregulated pro-inflammatory response on such individuals. More studies on the genetics and expression of this molecule in different human populations should be performed in order to clearly identify the involvement of the CCR5 molecule in JIA and in other rheumatologic conditions as well as the potential consequences of anti-CCR5 therapies.
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