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HYPOTHESIS ABOUT THE PROTECTIVE ROLE OF CCR5DELTA32 MUTATIONS IN JUVENILE IDIOPATHIC ARTHRITIS: FICTION OR REALITY?

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Resume. It is suspected that the prevalence in different ethnic groups of HLA-genotype and of mutation CCR5delta32 – factors which alter adhesion of protein CCR5 – are the causes of different prevalence of juvenile idiopathic arthritis in different ethnic populations. Prerequisites to the fact that the mutation CCR5delta32 may have importance in determining susceptibility to the disease were the observations showing that CCR5 deletion polymorphism reveals a population and geographic diversity in addition to ethnic specificity. But reports on the role of gene deletion in the CCR5 chemokine receptor susceptibility to JIA rather contradictory. 234 DNA samples of patients with systemic JIA (soJIA) were ana-lyzed. The diagnosis was made according to the ILAR criteria. DNA was isolated using QIAamp Mini Kit (QIAGEN) according to the protocol provided. Our results didn't reveal any differences in prevalence of mutation in patients with soJIA, in patients with soJIA + macrophage activation syndrome and in total population. Our results do not support the idea of protective role of the muta-tion CCR5delta32 against soJIA, which conclusion can be explained also by probable association of soJIA with HLA-genotype or other factors of ethnicity. At the same time, it can be considered as an additional evidence of expediency of soJIA being an original disease different from the rest of JIA group of diseases.

Key words: system onset juvenile idiopathic arthritis; mutation; CCR5delta32; ethnicity.

Introduction. Juvenile idiopathic arthritis is not a single disease, but a term that encompasses all forms of arthritis that begin before the age of 16 years, persist for more than 6 weeks, and are of unknown cause [10].

Different classification criteria have been used to identify distinct clinical subsets.

There are 3 international classifications. The American College of Rheumatology (ACR) classification uses the term of Juvenile Rheumatoid Arthritis (JRA). The European League Against Rheumatism (EULAR) prefers the term Juvenile Chronic Arthritis (JCA) for such arthritides. The international committee under the auspices of the World Health Organization and the International League of Associations for Rheumatology (ILAR) proposed the term Juvenile Idiopathic Arthritis (JIA) (Table 1).

Juvenile idiopathic arthritis is the most common chronic rheumatic disease in children and an important cause of disability. The incidence rate of JIA is 2–16 cases per 100 000 children under 16 years old. The mortality is 0.5–1 % [10]. The prevalence of JIA differs in different countries (Table 2).

Systemic arthritis is the most distinct category of JIA and it is diagnosed in 10–20 % of all JIA patients. At onset, it is characterized by prominent systemic features, such as fever, rash, and serositis, hepatosplenomegaly, generalized lymphadenopathy. The mortality of dJIA constitutes about 2/3 of the mortality associated with JIA in general [11].

About 5–8 % of children with systemic juvenile idiopathic arthritis develop a life-threatening complication known as macrophage activation syndrome. This syn-

Table 1

Classification of juvenile idiopathic arthritis

ACR (American College of Rheumatology)	EULAR (European League Against Rheumatism)	ILAR (International League Against Rheumatism)
Juvenile rheumatoid arthritis (JRA) Systemic JRA Polyarticular JRA Pauciarticular JRA	Juvenile chronic arthritis (JCA) Systemic JCA Polyarticular JCA, RF-negative Juvenile rheumatoid arthritis, RF-positive Pauciarticular JCA Juvenile psoriatic arthritis Juvenile ankylosing spondylitis	Juvenile idiopathic arthritis (JIA) Systemic JIA Polyarticular JIA, RF-positive Polyarticular JIA, RF-negative Oligoarticular JIA Persistent Extended Psoriatic arthritis Enthesis-related arthritis Other arthritis

Table 2

Prevalence and annual increase of rheumatoid arthritis in a population of different countries (Alamanos Y. et al., 2005)

Population	Prevalence (%)	The annual increase (%)
U.S. in general	*0.9–1.1*	*0.02–0.07*
U.S. native	*5.3–6.0*	*0.09–0.89*
United Kingdom	0.8–1.10	0.02–0.04
Finland	0.8	0.03–0.04
Sweden	0.5–0.9	
Norway	0.4–0.5	0.02–0.03
Netherlands	0.9	0.05
Denmark	0.9	
Ireland	0.5	
Spain	0.5	
France	0.6	0.01
Italy	0.3	
Greece	0.3–0.7	0.02
Bulgaria	0.9	

drome is characterized by the sudden onset of sustained fever, pancytopenia, hepatosplenomegaly, liver insufficiency, coagulopathy with hemorrhagic manifestations, and neurological symptoms [12].

The etiology and pathogenesis of juvenile idiopathic arthritis are still poorly understood but seem to include both genetic and environmental components. Moreover, the heterogeneity of this disease implies that different factors may contribute to the pathogenesis and etiology in various JIA categories. Distinct associations with both MHC or non-MHC genes have been described in various subsets of juvenile idiopathic arthritis, and many of these associations have been reproduced in different ethnic groups.

T cells play a major role in the pathogenesis of juvenile idiopathic arthritis. Synovitis in JIA is characterized by the expansion of synovial tissue driven by infiltration with immune cells including T cells, plasma cells, and macrophages as well as proliferation of synoviocytes. The migration of inflammatory cells to the synovial membrane is driven by local production of chemokines that selectively attract predominantly Th1-cells. These T cells produce various cytokines including IL-2, IFN-γ, and TNF-β [1]. Chemokines control the movement of lymphocytes by regulating cell motility and expression of adhesion molecules [7].

Human CCR5 (CC chemokine receptor 5, CC chemokine receptor type 5) is a protein encoded by the gene *CCR5*. CCR5 receptor is a member of a subclass of beta-chemokines, a family of integral membrane proteins. The gene encoding CCR5 is located on the short arm of chromosome 3. The natural chemokine ligands that bind to this receptor are CC chemokines, such as CCL3 (macrophage inflammatory protein 1a), CCL4 (macrophage inflammatory protein b), and CCL5 (regulator of growth, activation, secretion of T-cells). CCR5delta32 is a deletion of 32 base pairs, that leads to the decreased ability of the CCR5 protein expressed on T-lymphocytes and other immune cells to bind its ligands [2].

In 1997, researchers found that the homozygous deletion of 32 bp (bp — base pair) in the gene encoding the chemokine receptor CCR5 had a protective effect in HIV infection. It has been shown that some forms of HIV initially use CCR5 as a receptor to enter and infect host cells. The deletion in the CCR5 gene leads to the decreased ability of the HIV virus to enter T cells. While in the heterozygous state this mutation greatly reduces the likelihood of infection of cells with HIV, the homozygocity leads to a complete protection from HIV infection.

CCR5 is a protein receptor that is coupled with the G protein. CCR5 protein is expressed primarily by T cells, macrophages, dendritic cells and microglia cells [6]. It promotes trafficking of T-helper 1 lymphocytes to the inflamed synovium, where they accumulate and produce proinflammatory cytokines such as IL-2 and IFN-γ. In turn, this leads to the development of synovitis and joint destruction. Several CCR5 ligands including CCL3, CCL4, and CCL5, have been found in high concentrations in synovial fluid of patients with rheumatoid arthritis suggesting that, the selective accumulation of CCR5 + T-cells in the synovial fluid is likely to occur in response to the presence of these chemokines [8].

Consistent with this idea, it was noted that the number of CCR5 on the cell surface determines the intensity of T cell migration to the inflamed synovium and stimulation of CCL5. Indeed, the level of CCR5 expression can influence the proinflammatory effects of T cells in the synovial fluid, facilitating the accumulation and in-

crease their responsiveness to chemokines. It has been suggested that the number of CCR5 on the cell surface may be a predictor of disease activity [2].

In 1998, it was suggested that the CCR5delta32 variant might act as a protective factor against the development of rheumatoid arthritis (RA). Furthermore, Hinks et al. have shown that the CCR5delta32 gene variant is also associated with protection from developing JIA [9].

The CCR5 receptor takes part in the T1-response in different autoimmune diseases, and therefore, the presence of the CCR5delta32 gene variant may influence susceptibility to different diseases. The genetic studies, however, have been complicated by the fact that the distribution of CCR5 mutations in various populations has ethnic and racial differences [5]. This gene occurs in 20% of the White race. In the African-American population, the frequency is up to 6%, 7% in the Hispanic group, and less than 1% in Asians. Deletions in of CCR5 have not been reported among West Africans, Thais, Japanese and Koreans. The frequency of the CCR5delta32 variant in North Africa is 2% [14]. In Europe, the CCR5delta32 mutation in the heterozygous state occurs with a frequency of 5–14% [11]. It is more common in Northern Europe. In Central and Western Europe, the average frequency is 10%, while in the southern countries, such as Portugal and Greece, the frequency is 4–6%. The highest frequency in the world of CCR5delta32 variant was observed in coast-dwellers (33%, of which 3% — in the homozygous state). Among Russians and Ukrainians the frequency of this mutation is about 21%. [14]. The uneven distribution of CCR5delta32 in Europe appears to be associated with climatic and geographical factors. Early studies of Stephens et al. suggested that the CCR5delta32 variant arose either because of genetic drift or appeared suddenly. It has been speculated that this allele was favored by natural selection during the Black Plague of 1348, but further research has revealed that the gene did not protect against the Plague [1].

The predominance of CCR5-positive synovial mononuclear cells in patients with various types of arthritis suggests that CCR5 plays an important role in synovial inflammation. In children with juvenile idiopathic arthritis synovial T cells express higher levels of CCR5. The association with the CCR5delta32 variant was investigated in rheumatoid arthritis in adults with conflicting results. Homozygous for CCR5delta32 leads to the lack of expression of CCR5 on the cell surface. This allele was found to be associated with protection against rheumatoid arthritis in adults. In 2006, Prahalad S. with colleagues tested the hypothesis that genetic variations in CCR5 were associated with susceptibility to JIA. The results showed that two variants (CCR5–1835T and CCR5delta32) of the gene encoding CCR5 were associated with juvenile idiopathic arthritis, especially in children with disease onset before the age of 6 years. The frequency CCR5delta32 was significantly lower in probands with early-onset juvenile idiopathic arthritis suggesting a protective effect [9].

The aim of the study performed by Lindner E. et al. (2007) was to assess whether the polymorphism of CCR5delta32 was associated with rheumatoid arthritis and juvenile idiopathic arthritis in the Norwegian population. About 853 patients with rheumatoid arthritis, 524 patients with juvenile idiopathic arthritis and 658 controls were geno typed for the CCR5delta32 polymorphism. The frequency of CCR5delta32 allele was 11.5% in controls, 10.4% in patients with rheumatoid arthritis, and 9.7% in patients with juvenile idiopathic arthritis. These results did not show a relationship between CCR5delta32 variant and either rheumatoid arthritis or juvenile idiopathic arthritis in the Norwegian population [4].

Scheibel I. et al. (2008) studied the association between CCR5delta32 polymorphism and juvenile idiopathic arthritis, rheumatoid arthritis patients in patients from Brazil. This study included 203 patients with rheumatoid arthritis, 101 patients with juvenile idiopathic arthritis and 104 healthy controls. The Delta32 allele frequency was higher in patients with juvenile idiopathic arthritis (9.4%) as compared with controls (3.8%) and patients with rheumatoid arthritis (3.2%). Among patients with juvenile idiopathic arthritis, CCR5delta32 allele was observed in 4.1% of patients with oligoarthritis, in 11.2% of patients with polyarthritis (9.5% in RF-negative and 33.3%- in RF-positive), and in 25% with systemic juvenile idiopathic arthritis. The results of this study suggest that at least in some types of juvenile idiopathic arthritis, in contrast with rheumatoid arthritis, CCR5delta32 not only does not have a protective effect, but may be a factor associated with more severe disease [13].

Given the conflicting results of the CCR5delta32 association studies in juvenile idiopathic arthritis published to date (i.e. protective role of CCR5delta32 in in one study [9], neutral effect in another [4], and a risk factor in the third study) [13]), Hinks et al. (2010) studied the relationship between the presence of the CCR5delta32 variant and juvenile idiopathic arthritis in the British population. CCR5delta32 was typed in 1054 patients with juvenile idiopathic arthritis and 3129 healthy controls. CCR5delta32 was significantly associated with protection against the development of juvenile idiopathic arthritis in the UK population. Interestingly, the most pronounced protective effect was observed in the group of RF-positive polyarthritis group, although no significant differences were observed between the sub-

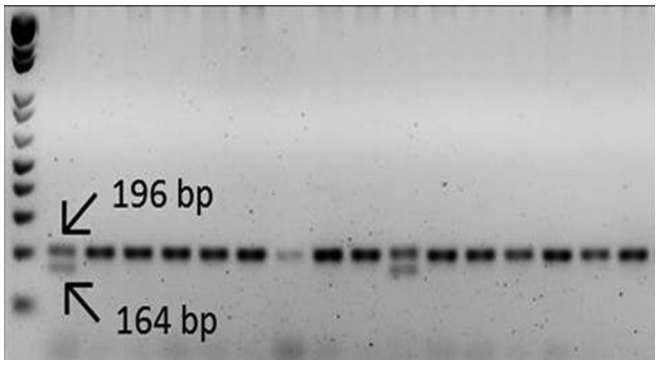

Fig. 1. Gel documentation of the results of PCR with primers

types. Meta-analysis of previously published studies had confirmed the protective CCR5delta32 connection with JIA. The CCR5delta32 may influence the number of CCR5 receptors expressed on the surface of T cells, and, in turn, the level of CCR5 expression can influence the migration of inflammatory cells to the synovial membrane, and thus can have an impact on the susceptibility to juvenile idiopathic arthritis [3].

The aim of our study was to evaluate the protective role of CCR5delta32 mutation in groups of children of other ethnic origin suffering from systemic juvenile idiopathic arthritis (sJIA).

MATERIALS AND METHODS

We analyzed 234 DNA samples obtained from patients with systemic JIA. 210 DNA samples were provided for this study by the tertiary Pediatric Rheumatology Center at the Cincinnati Children's Hospital Medical Center (Ohio, USA). Of 234 patients in this cohort, 175 were Caucasian American, 20 — Hispanic or Latino, 12 — African American, 1 — American Indian, 1 — Asian, and 1 — multi-racial. Additional 24 samples in the form of blood dried on filter paper were collected in Clinic of Pediatrics № 3 at the St. Petersburg Pediatric Medical Academy. DNA was isolated using a QIAamp Mini Kit (QIAGEN) in accordance with the manufacturer's instructions. The diagnosis was established according to the ILAR criteria; all patients were informed and consented to participate in the study. Of 259 SJIA patients included in this study, in 25 patients the course of SJIA was complicated by macrophage activation syndrome.

The CCR5 delta32 deletion was identified using the polymerase chain reaction (PCR) with the following primers: CCR5-D32-F: 5 `CTTCATTACACCTGCAGTC3`, CCR5-D32-R: 5 `TGAAGATAAGCCTCACAGCC3`. The PCR reaction was performed under the following conditions: 95°-5'x1; 95°-15'' → 55°-15'' → 72°-60''x40; 72°-10'x1 → 4° — ∞, and the products of the reaction were separated in 2% agarose gel within 1.5 hours. The gel documentation was read using a Gel Doc XR Plus (Bio-Rad, USA) (Figure 1).

To statistical analysis of the obtained data included methods of statistical description, as well as methods of verification of statistical hypotheses. The results are presented in Table 3.

In this study, the frequency of heterozygous forms of CCR5delta32 in patients with systemic juvenile idiopathic arthritis was 16%. At the same time, the mutation CCR5delta32 was not found among Hispanics, or African Americans, most likely due to the small number of patients (20 and 12, respectively) and a low prevalence of this mutation in these ethnic groups. Among the Caucasian American patients of the European origin, the prevalence of heterozygotes for the CCR5 delta32 was 16%, while in patients from Russia it was 21%. The prevalence of heterozygotes CCR5delta32 among SJIA patients with MAS history was 17%. No patients with homozygous deletions of the chemokine receptor

Table 3

Results of own researches

	Total of patients	CCR5/ CCR5	CCR5/ CCR5delta32	CCR5delta32/ CCR5delta32
Caucasian American	175	147	28	0
Russian	24	19	5	0
Hispanic or Latino	20	20	0	0
African American	12	12	0	0
American Indian	1	1	0	0
Asian	1	1	0	0
Multiracial	1	1	0	0

CCR5 gene (CCR5delta32/CCR5delta32) were identified in this study.

CONCLUSIONS

It has been suggested that the varying frequencies of certain of MHC alleles and the *CCR5delta32* variant in different ethnic groups is one of the reasons for unequal incidence of juvenile idiopathic arthritis in different populations. However, the published data on the effect of deletions in the chemokine receptor CCR5 gene on susceptibility to JIA are quite contradictory.

Results of our study showed no differences between the frequency of the *CCR5delta32* variant in patients with the systemic form of JIA (including patients with or without MAS) and in the general population.

Our results do not support the idea that the CCR5delta32 variant may have a protective effect on the susceptibility to sJIA. The lack of association between SJIA and the CCR5delta32 variant that may dampen the IFN-induced Th1 responses, is also consistent with the idea that the role of Th1 cells in this type of arthritis may be limited [15]. This specific problem requires further study.

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ГИПОТЕЗА О ПРОТЕКТИВНОЙ РОЛИ МУТАЦИИ CCR5DELTA32 ПРИ ЮВЕНИЛЬНОМ ИДИОПАТИЧЕСКОМ АРТРИТЕ: МИФ ИЛИ РЕАЛЬНОСТЬ?

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◆ **Resume.** Предполагается, что неодинаковая распространенность в различных этнических группах HLA-генотипа и мутации CCR5delta32, приводящей к нарушению адгезивных свойств кодируемого белка CCR5, является одной из причин неодинаковой распространенности ювенильного ревматоидного артрита в различных популяциях. Предпосылками к тому, что мутация CCR5delta32 может иметь значение в определении подверженности к этому заболеванию, явились наблюдения, показавшие, что делеционный полиморфизм CCR5 кроме этнической специфичности обнаруживает также популяционное и географическое разнообразие. Но сообщения о роли делеции гена хемокинового рецептора CCR5 в восприимчивости к ЮИА достаточно противоречивы. Было проанализировано 234 образца ДНК

пациентов с системными формами ЮИА. Диагноз был установлен в соответствии с критериями ILAR. ДНК была выделена с использованием QIAamp Mini Kit (QIAGEN) в соответствии с прилагаемым протоколом. Наши результаты не выявили различия в наличии мутации у пациентов с системным ЮИА, у пациентов с системным ЮИА, осложненным синдромом макрофагальной активации, и в популяции в целом. Наши результаты не позволяют считать доказанной протективную роль мутации CCR5delta32 относительно с ЮРА, что может быть обусловлено возможной взаимосвязью с HLA-генотипом либо с прочими факторами, ассоциированными с этнической принадлежностью. Вместе с тем, это может быть расценено, как дополнительное свидетельство целесообразности выделения системного ЮРА в качестве самостоятельного заболевания.

◆ **Key words:** системный ювенильный идиопатический артрит; мутации; CCR5delta32; этничность.

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