Significance of Polymorphism in 2',5'-Oligoadenylate Synthetase Genes in HIV Infection

DOI: 10.17691/stm2016.8.1.13
Received June 15, 2015

© **L.B. Bakhteeva,** Infectionist[1];
S.F. Khaibullina, MD, PhD, Researcher[2]; Leading Researcher, Institute of Fundamental Medicine and Biology[3];
V.K. Lombardi, PhD, Leading Researcher, Whittemore Peterson Institute[2]; Leading Researcher, Institute of Fundamental Medicine and Biology[3];
V.A. Anokhin, MD, DSc, Professor, Head of the Department of Pediatric Infections[4];
A.A. Rizvanov, DSc, Chief Researcher, Professor, Genetics Department, Institute of Fundamental Medicine and Biology[3];
S.V. Boichuk, MD, DSc, Professor, Head of the Department of Pathologic Physiology[4];
F.I. Nagimova, MD, PhD, Deputy Chief Doctor for Medical Affairs[1]

[1]Republican Center for the Prevention and Fighting of AIDS and Infections Diseases, Ministry of Health of the Republic of Tatarstan, 2a Vishevskogo St., Kazan, the Republic of Tatarstan, 420097, Russian Federation;
[2]The University of Nevada, 1664 North Virginia St., Reno, Nevada 89557, USA;
[3]Kazan (Volga Region) Federal University, 18 Kremlyovskaya St., Kazan, the Republic of Tatarstan, 420008, Russian Federation;
[4]Kazan State Medical University, 49 Butlerova St., Kazan, the Republic of Tatarstan, 420012, Russian Federation

The aim of the investigation was to assess the prognostic value of polymorphism of genes encoding 2',5'-oligoadenylate synthetase (OAS) synthesis in HIV infection.

Materials and Methods. The DNA of 94 HIV infected patients have been sequenced using multiplex polymerase chain reaction. For molecular genetic testing we used DNA samples isolated from the scraping of oral epithelial cells. We studied interferon-induced genes, namely: OAS enzyme. It was a case–control study. Depending on the decrease rate of CD4-lymphocytes, the patients were divided into two groups: with typical disease progression and those with slow progression. We determined the frequencies of mutant alleles and genotypes in patients with different progression rates, and assessed genotype associations with different outcomes.

Results. There have been found oligonucleotide polymorphisms of OAS genes of different enzyme forms: *OAS2* rs2072137 (chr12:113440921) and *OAS3* rs1859330 (chr12:113376388). The frequency of mutant allele C of *OAS2* rs2072137 polymorphism appeared to be significantly higher in a group with a typical disease progression (p=0.03). The frequency of mutant allele A of *OAS3* rs1859330 polymorphism had no difference in the groups. In a group with mutant genotypes TC and CC of *OAS2* rs2072137 polymorphism, the frequency of typical disease progression was significantly higher than that in the group with the main ("wild") genotype TT (p=0.0125). Logistic regression revealed typical HIV infection progression in patients to be significantly associated with *OAS2* rs2072137 polymorphism and age.

Conclusion. *OAS2* rs2072137 polymorphism is associated with typical progressive HIV infection, and, probably, presents a new genetic prognostic marker of the disease.

Key words: HIV infection; gene polymorphism; 2',5'-oligoadenylate synthetase; 2',5'-OAS; OAS.

Interferon (IFN) is a significant component of innate immunity. Interferon system plays a key role in antiviral immune protection regulation. In addition to interferons themselves the system also involves the products of the genes they induce (protein kinase R, 2',5'-oligoadenylate synthetase (OAS)). Three interferon types have been distinguished [1, 2].

Type I IFN includes IFN-α (leukocyte), IFN-β (fibroblastic), IFN-τ (trophoblastic), IFN-ω, IFN-σ, IFN-κ and IFN-ε. The production of these interferons is induced by viral infection, and most infected cells have this ability. IFN-α is actively synthesized by plasmacytoid dendritic cells [3].

Type II interferons (immune) (γ) are synthesized in response to mitogenic and antigenic stimuli only by certain immune cells: NK-lymphocytes, $CD4^+$ and Th1 cells, $CD8^+$ cytotoxic suppressor cells [4].

Type III interferons have been recently identified (IFN-λ1/IL-29, IFN-λ2/IL-28A, IFN-λ3/IL-28B). They are produced by epithelial cells of the respiratory tract, especially by plasmacytoid dendritic cells, monocytes and macrophages in response to their excitation by pathogen-associated molecular structures of infectious agents [5].

After interferon binding to appropriate receptors, there has been induced intracellular signaling through YAK2 (Janus kinase) and transcription factors STAT [6]. Interferon ceases virus replication affecting the transcription of their genomes by various ways. The mechanism under consideration in the present

For contacts: Liliya B. Bakhteeva, e-mail: chulpan190885@mail.ru

paper is based on the induction of OAS enzyme synthesis. OAS is activated in viral-infected cells and catalyses oligoadenylate synthesis with unusual 2',5'-phosphodiester bond, the cells activate latent endoribonuclease L (RNA L) by binding. Activated RNA L catalyses the degradation of both: virus and cell RNA resulting in the inhibition of elongation and decreased protein synthesis rate [7, 8]. According to their sizes, it is practice to distinguish three OAS enzyme forms: OAS1, OAS2 and OAS3. They are associated with different subcellular fractions, the membrane, cytoplasm, nucleus, and differ in the concentration of double-stranded RNA necessary for their activation. However, their complete physiological significance is unclear [1].

There are a few researches aimed at revealing clinically significant OAS gene polymorphism. Most of them concern such infections as chronic viral hepatites C and B, Dengue fever, West Nile Fever, and tick-borne encephalitis [9–13]. We have found no reports on the study of the effect of different OAS genes on HIV infection. Previous studies showed the relationship of HIV genes with OAS enzyme [14, 15]. HIV transactivated responder (TAR) exhibits the ability to activate two interferon-induced enzymes, protein kinase and OAS, which potentially should provide HIV replication control by interferon system. However, Tat virus protein binding to TAR blocks TAR-mediated OAS enzyme activation [16]. Moreover, RNA L inhibitor activated in infected HIV cells breaks the mechanism of OAS/RNA L system resulting in the twofold increase of HIV replication [17]. Antisense RNA expression against mRNA RNA L decreases the level of the protein, increases HIV production, and reduces antiviral effect of IFN-α [18]. Thus, OAS activation in HIV-infected cells reflects the response of congenital protection, and thus, genetic alterations in the genes encoding OAS, can influence the OAS/RNA L system reaction, and, subsequently, the course of the infection.

The aim of the investigation was to assess the prognostic value of polymorphism of genes encoding 2',5'-oligoadenylate synthetase synthesis in HIV infection.

Materials and Methods. The study was carried out on the basis of Republican Center for the Prevention and Fighting of AIDS and Infectious Diseases (Republic of Tatarstan, Russia), Central Research Laboratory of Kazan State Medical University (Republic of Tatarstan, Russia), and Whittemore Peterson Institute (Reno, Nevada, USA). The case–control study was carried out on 94 HIV infected patients. The study was performed in outpatient settings during scheduled preventive medical examination.

The study was carried out in accordance with the declaration of Helsinki (adopted in June, 1964 (Helsinki, Finland) and revised in October, 2000 (Edinburg, Scotland)) and approved by the Ethics Committee of Republican Center for the Prevention and Fighting of AIDS and Infectious Diseases. All patients gave their written informed consent.

Inclusion criteria included:

HIV infection;

patient's informed consent;

CD4-lymphocyte level being higher or equal to 350 cells/μl at the moment HIV infection was diagnosed, or at follow-up starting;

no opportunistic infections at the moment HIV infection was diagnosed, or at follow-up starting;

a follow-up period at Republican Center for the Prevention and Fighting of AIDS and Infectious Diseases, being at least five years.

The date of laboratory confirmation of HIV infection was considered to be the "entry point" of the study.

The range of normal values of CD4-lymphocytes is very wide: from 500 to 1,400 cells in 1 μl. "Typical" progression of the disease was characterized by the decrease of CD4-lymphocytes by 50–100 cells a year [19]. According to protocols, antiretroviral therapy is administered when CD4 level is 350 cells in 1 μl [20]. This level of immune cells is considered to provide the protection against opportunistic infections.

According to the criteria specified, as well as the rate of annual decrease of CD4 cells, during the first five years of a follow-up, the patients were divided into two groups based on archival data (*AIDSNET* and medical treatment records of the AIDS centre): with typical and slow progressive states of the disease.

A group of "typical progressors" (n=54) involved the patients with decreased CD4-lymphocyte level, less than 350 cells in 1 μl within a five-year follow-up, the annual decrease rate being over 50 cells. Due to clinical laboratory indications, some of these patients (n=13) during the follow-up were administered antiretroviral therapy. The second group ("slow progressor", n=40) included the patients with CD4-lymphocyte level persisting over 350 cells in 1 μl within the whole follow-up period, the loss rate being less than 50 cells a year (Table 1).

For genetic analysis we sequenced DNA samples by multiplex polymerase chain reaction (Ion Ampliseq Library kit; Life Technology, USA). The study was focused on the genes coding for synthesis of different OAS enzyme forms.

For molecular genetic analysis we used DNA samples isolated by a sorbent method according to the instruction enclosed to "DNA-sorb-B" (Central Research Institute of Epidemiology, Ministry of Health, Russia). Scrapping of oral epithelial cells served as biological material. Primers were designed using the equipment of Ion Ampliseq Designer (Life Technologies, USA). A sensor chip (Ion 318 Chip) was used for the study. Final sequencing was performed on a sequencer Ion PGM Next-Generation Sequencing Platform. Nucleotide sequences obtained by AmpliSeq technique were compared to human reference-genome (NCBI37/hg19) using Bowtie2 Aligment tools [21]. The variability in single nucleotides of each amplicon was determined by SAMtools and BCFtools [22]. Possible genotypes and the probability of their detection in each position were calculated by SAMtools mpileup. Revealed variants and genotypes were denoted using BCFtools. By means of AmpliSeq

Table 1

The characteristic of the groups under study (as of the start of a follow-up period)

Demographic and clinical laboratory characteristics of the patients	"Slow progressors" (n=40)	"Typical progressors" (n=54)	p
Gender (abs. number/%):			
male	24/60	33/61	
female	16/40	22/39	
Age (years), Me [25; 75]	24.0 [21.5; 28]	26 [22; 32]	**0.02**
Infection route (abs. number/%):			
sexual	14/35	23/43	0.4
parenteral (injection)	26/65	31/57	0.4
HIV infection stage (abs. number/%):			
stage III	40/100	54/100	1.0
Comorbidities (abs. number/%):			
chronic viral hepatitis	27/68	34/63	0.6
Number of CD4-lymphocytes at the moment of a follow-up starting (cells/μl), Me [25; 75]	655 [511; 868]	479 [374; 658]	**0.0014**
Viral load at the moment of a follow-up starting (*log* copies/ml), Me [25; 75]	3.89 [3.30; 4.40]	4.30 [3.80; 4.59]	**0.03**

method we obtained complete sequences of the genes under study that enabled to detect both known and yet unknown single nucleotide polymorphisms (SNP).

The findings were statistically processed using Statistica 10.0 and Epiinfo 6. We grouped the patients with hetero- and homozygous genotypes by a mutant allele. Data complying with the normal distribution law were presented in the form of a mean value and standard deviation. The data, which are not subject to this law, were represented as medians and extreme values of an ordered sample. Mann–Whitney U-test was used to compare the quantitative characters of two parts, which are not subjects to the normal distribution law. When comparing relative frequencies in two groups we used null statistic hypothesis for relative frequency equation.

We checked the distribution of genotypes by polymorphic loci under study for compliance with Hardy–Weinberg's law. The significance of differences in allele and genotype frequencies between the samplings compared was determined using Fischer's exact test (for small samplings) and χ-square test, respectively. To compare the frequencies of outcomes we calculated "odds ratio" (OR) and 95% confidential intervals (95% CI).

For numeric evaluation of risk factors of typical HIV infection progression we used a binary logistic regression, which enabled to calculate the event probability depending on the values of free variables. The analyzed independent characteristics and their symbols are as follows (the encoding used in the present study): genotype ("1": "wild", "0": mutant); gender ("1": female, "0": male); age (years) at the beginning of a follow-up (absolute value); infection route ("1": intravenous, "0": sexual); hepatitis C virus infection at the moment of the follow-up start ("1": chronic viral hepatitis C, "0": no chronic viral hepatitis C).

Critical level of significance (p) was taken equal to 0.05 when carrying out all parts of the study. The patients were grouped by simple random sample.

Results. While carrying out the study we detected SNP of genes of different OAS enzyme forms: *OAS2* rs2072137 (chr12:113440921) and *OAS3* rs1859330 (chr12:113376388). SNP of *OAS2* rs2072137 is known to result in the change of T for C [23], and SNP of *OAS3* rs1859330 leads to the change of G for A consisting in the substitution of arginine for lysine [24]. Clinical significance of these gene variants is unknown. Tables 2 and 3 show the findings.

The frequency analysis of mutant alleles in subgroups of patients with different HIV infection progression rates revealed the significant increase of allele C frequency polymorphism *OAS2* rs2072137 in the group of "typical progressors" (p=0.03). The analysis of genotype frequencies also found the significant difference (p=0.019): the frequency of mutant genotypes was higher in a group of "typical progressors" (See the Table 2).

No significant differences were found when analyzing the frequency of mutant allele A polymorphism *OAS3* rs1859330. A significant difference (p=0.041) was found in the frequency of genotypes (See the Table 3).

We compared the frequency of outcomes in two groups with different genotypes. In our study an outcome was considered as the decrease of CD4-lymphocytes: less than 350 within 5 years at average rate of over 50 cells a year. In a group of patients with mutant genotypes TC and CC by *OAS2* rs2072137 gene polymorphism, the frequency of typical disease progression was significantly higher than that in a group with a "wild" genotype TT (p=0.0125; OR=3.44; 95% CI=1.38–8.59) prompting suggestions that the presence of a mutant allele C by *OAS2* rs2072137 polymorphism increases

Table 2

Distribution of frequencies and genotypes by gene polymorphism *OAS2* rs2072137 among "slow" and "typical" progressors

Group	Genotype (abs. number/%)			Allele (%)		
	TT	TC	CC		C	
"Slow progressors" (n=40)	31/77.5	7/17.5	2/5	p_1=0.019	13.75	p_2=0.03 OR — 2.4 (1.12–5.18)
"Typical progressors" (n=54)	27/50	24/44.4	3/5.6		27.7	

N o t e. p_1: statistical significance in genotype frequency between the groups; p_2: significant difference in allele C frequency.

Table 3

Distribution of frequencies and genotypes by gene polymorphism *OAS3* rs1859330 among "slow" and "typical" progressors

Group	Genotype (abs. number/%)			Allele (%)		
	TT	TC	CC		C	
"Slow progressors" (n=40)	34/85	5/12.5	1/2.5	p_1=0.041	10.3	p_2=0.63 OR — 1.4 (0.54–3.76)
"Typical progressors" (n=54)	47/87	1/2	6/11		12.0	

N o t e. p_1: statistical significance in genotype frequency between the groups; p_2: significant difference in allele A frequency.

Table 4

Frequency of "wild" and mutant genotypes of *OAS2* gene by polymorphism rs2072137 in groups with different HIV infection progression types

Genotypes	"Typical progressors"	"Slow progressors"	
TC+CC (n=36)	27	9	p=0.0125 OR — 3.44 (1.38–8.59)
TT (n=58)	27	31	

Table 5

Frequency of "wild" and mutant genotypes of *OAS3* gene by polymorphism rs1859330 in groups with different HIV infection progression types

Genotypes	"Typical progressors"	"Slow progressors"	
GA+AA (n=13)	7	6	p=0.98 OR — 0.84 (0.26–2.70)
GG (n=81)	47	34	

Table 6

Logistic regression analysis of factors associated with HIV infection progression rate

Characteristics included in the model	B	p	OR	95% CI
OAS2 rs2072137	**1.33**	**0.0069**	**3.79**	1.45–9.87
Age	–0.0699	0.0495	0.93	0.87–0.999
Gender	0.047	0.93	1.05	0.37–2.96
Infection route	0.3	0.72	1.35	0.25–7.20
Chronic virus hepatitis C	–0.048	0.95	0.95	0.19–4.78

the probability of typical progression of HIV infection by 3.4 times (Table 4).

Similar analysis on *OAS3* rs1859330 polymorphism revealed no mutation influence on the disease progression rate (Table 5).

Table 6 shows the values of coefficients of binary logistic regression (B) and the odds ratio (OR) of a typical HIV infection progression in response to a joint effect of several factors. This model does not include *OAS3* rs1859330 polymorphism since the previous analysis it showed no significant effect.

The obtained regression model is significant (p=0.02), though, unfortunately, it exhibits low prognostic value: χ^2=13.3; df=5; percentage of correct prognoses described by the model is 64.89%. Among the five characteristics the table shows, the genotype of *OAS2* rs2072137 gene polymorphism plays the most important role in HIV infection progression. According to the model, *OAS2* rs2072137 polymorphism and age are significantly associated with "typical" infection progression.

Discussion. The whole history of HIV infection study clearly demonstrates it is the effect of adaptive immunity functioning that researchers have taken their main interest in. It is no surprise. At the same time innate immunity has been started studying relatively recently. One of its components is the system of interferons. IFN-α and IFN-β have been shown to suppress directly HIV infection *in vitro* [25, 26]. Plasma dendritic cells produce

type I IFN in response to single- and double-strand RNA and unmethylated parts of CpG DNA (in this case TLR7 and TLR9 are used) [3]. One of the mechanisms of antiviral protection of interferons is their ability to influence viral replication through *OAS* genes. Antiviral protective effectiveness seems to depend on the ability of infected cells to prevent OAS enzyme inhibition.

As early as during the first years of surveillance over HIV infection epidemic, some infected people were observed to have slow progression of the disease or just no progression at all; such patients succeed in maintaining normal level of $CD4^+$-lymphocytes without any treatment and avoiding opportunistic infections. Due to the capabilities of developing HIV infection control methods, the phenomenon is still in the field of researchers' attention. There have been carried out many studies aimed at searching genetic factors, which influence HIV infection prognosis. The best known and numerous studies describe polymorphism of genes encoding co-receptors for HIV [27, 28]. They are devoted to the thoroughly studied deletion of 32^{th} base pair of the gene encoding the protein CCR5 of T-cells, and CCR2b gene polymorphism. These genetic factors are associated with slow AIDS progression. HLA phenotype is also reported to be significant in HIV infection prognosis. So, HLA-B57 of class 1 and HLA-B27 are associated with the survival within a long period of time [29].

Thus, according to the findings, polymorphism in *OAS2* rs2072137 is related to typical HIV infection progression. Age in our study appears to be an additional predictor of typical disease progression, and it is consistent with numerous previous researches, where seroconversion in old patients is associated with rapid disease progression [30, 31].

Conclusion. The findings of the study enable to consider *OAS2* rs2072137 a new genetic prognostic marker of the infection progression. The data supply the knowledge on the relationship of innate immunity with HIV, and the description of genetic prognostic markers if HIV infection. Most probably, this gene variant results in qualitative or quantitative alterations of OAS, by that reducing an antiviral effect of IFN-α. It is evident that the hypothesis needs further extension studies to confirm the significance of these genes in HIV infection pathogenesis.

Study Funding. The study was funded by the grant given to Kazan Federal University in the sphere of scientific activities. The research was carried out using the equipment of Interdisciplinary Core Facility, with financial support of the state represented by Ministry of Education and Science of the Russian Federation (ID RFMEFI59414X0003) and Education Research Pharmaceutical Center of Kazan (Volga Region) Federal University.

Conflicts of Interest. The authors have no conflicts of interest related to the present study.

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