Journal of Medical Virology 86:23–29 (2014)

Increased Prevalence of the Alpha-1-Antitrypsin (A1AT) Deficiency-Related S Gene in Patients Infected With Human Immunodeficiency Virus Type 1

Thalita Camêlo da Silva Ferreira[1]†, Erika Pereira Sampaio[1]†, Gustavo Adolfo Argañaraz[2], Marcos Vinícius Pereira Gondim[1], Leland Shapiro[3,4] and Enrique Roberto Argañaraz[1]

[1]Laboratory of Molecular Virology Faculty of Health Science, University of Brasília, Brasilia, Brazil
[2]Laboratory of Molecular Pathology, University of Brasília, Brasilia, Brazil
[3]Denver Veterans Affairs Medical Center in Denver, Denver, Colorado
[3]University of Colorado Denver Anschutz Medical Center in Aurora, Aurora, Colorado

thalitacamelofar@gmail.com, erikapsampaio@hotmail.com, gustavoa@unb.br, marvin.bio@hotmail.com, Leland.Shapiro@ucdenver.edu, enrique@unb.br

INTRODUCTION

Large variation exists in susceptibility to infection with Human Immunodeficiency Virus Type 1 (HIV) and disease progression. These observations demonstrate a role for antirretroviral host factors. Several reports describe a1-antitrypsin (A1AT), the most abundant circulating serine protease inhibitor, as a potent supressor of HIV infection and replication. In this study the prevalences of M, S, and Z A1AT genes in persons infected with HIV was assessed to determine possible associations with HIV disease progression or infection with HIV.

MATERIALS AND METHODS

Study Patients

DNA was isolated from peripheral blood mononuclear cells (PBMC) obtained from subjects infected with HIV enrolled in four multicenter cohorts. As shown in Table I, there were 39 subjects (12 Elite Controllers_EC, 12 Long-term non-progressors _LTNP and 15 Progressors_Prog) from a Canadian cohort, kindly provided by doctors Nicole Bernard and Cécile Tremplay from Research Institute of the McGill University Health Centre and the Centre de Recherche du Centre Hospitalier de l'Université de Montreal. Subject data from two U.S. cohorts were combined. These two cohorts included 10 subjects (1 LNTP and 9 Prog) from Osher Center blood bank for Integrative Medicine/University of California at San Francisco (UCSF)—UCSF Positive Health Program, San Francisco, California, EUA, provided by Dr. Frederick Hecht of University of California, San Francisco—UCSF, USA, and 13 subjects (13 Prog) contributed by New England Comprehensive Hemophilia Center of University of Massachusetts/ Memorial Health Center, Worcester, Massachusetts, EUA provided by Dr. Frank Kirchhof of Ulm University. Nine subjects were from an Argentinean cohort (2 EC, 4 LNTP, and 3 Prog), provided by Dr. Federico Gorini, Pueblo Evita hospital, Berazategui City, Provincia de Buenos Aires, Argentina, and eight subjects were from the public health network of the Federal District, Brasilia, Brazil (3 LNTP and 5 Prog).

Detection of A1AT Gene Mutations

M, S, or Z A1AT gene variants were identified using a multiplex PCR–RFLP technique as described previously [Settin et al., 2006].

Statistical Analysis

A1AT allele frequencies were calculated using the gene counting method (each individual gene represented by two alleles in each subject). Group differences in genotypes and allele frequencies were assessed using Fisher's exact test or the chi-square test. A type 1 error of 0.05 (P<0.05) was defined as statistically significant.

TABLE I. Subject Characteristics From Each Country of Origin

	EC (N = 12)	LTNP (N = 12)	Prog (N = 15)
Canada			
Gender	6M/4F/ND for N = 2	11M/1F	15M
Age	53.5 (34–73), ND for N = 2	49 (42–65)	38 (25–63)
Years followed	7.16 (2.65–14.5), ND for N = 2	10.0 (4.7–17.4)	ND for N = 15
Log_{10} viral load	All <1.69[a]	All <5[a]	5.20 (4.30–6.60)[b]
$CD4^+$ lymphocytes (mm^{-3} blood)	All >400[a]	All >400	260 (110–450)
	EC (N = 0)	LTNP (N = 1)	Prog (N = 22)
U.S.			
Gender	NA	ND for N = 1	ND for N = 22
Age	NA	ND for N = 1	23 (14–59), ND for N = 11
Years followed	NA	1.75 (NA)	5.33 (1.33–14.08)
Log_{10} viral load	NA	2.97 (NA)	4.34 (3.95–4.91)
ND for N = 13			
$CD4^+$ lymphocytes (mm^{-3} blood)	NA	832 (NA)	414 (192–803)[c]
	EC (N = 2)	LTNP (N = 4)	Prog (N = 3)
Argentina			
Gender	ND for N = 2	ND for N = 4	ND for N = 3
Age	37.5 (30–45)	32.5 (11–38)	29 (23–31)
Years followed	4 (3–5)	6.5 (2–15)	ND for N = 3
Log_{10} viral load	All <1.69	3.23 (2.60–3.65)	3.74 (3.5–3.92)
$CD4^+$ lymphocytes (mm^{-3} blood)	>911 and >1101	794 (486–806)	600 (200–877)
	EC (N = 0)	LTNP (N = 3)	Prog (N = 5)
Brazil			
Gender	NA	2M/1F	4M/1F
Age	NA	55 (46–55)	45 (28–55)
Years followed	NA	9 (9–10)	5 (1–5.5)
Log_{10} viral load	NA	<1.69 for N = 2, ND for N = 1	2.79 (1.69–5.69)
$CD4^+$ lymphocytes (mm^{-3} blood)	NA	712 (708–839)	136 (98–246)

All data are presented as median (range) unless described otherwise. NA, not applicable; M, male; F, female; ND, not determined.
[a]Data for viral load or $CD4^+$ lymphocytes represent 5 to more than 20 values for each subject.
[b]Viral load for each subject calculated as the mean of ≥5 time points.
[c]$CD4^+$ count values represent the mean of 2–3 time points for each of the 13 subjects from the New England Comprehensive Hemophilia Center of University of Massachusetts Memorial Health Center.

RESULTS

Table II shows the A1AT genotype and A1AT allele distributions for the groups EC, LTNP, and Prog. There were no statistically significant differences in frequencies of A1AT genotype or A1AT alleles comparing the EC, LTNP, and Prog groups.

In Table III, study subjects are grouped into respective countries of origin and A1AT genotype and allele frequencies shown. These frequencies are compared to the frequencies of A1AT genotypes and alleles reported for the general population in each respective country. In every country examined except Brazil, a genotype containing the S allele was significantly more prevalent in persons infected with HIV compared to population estimates (SS in Canada, SZ in the U.S., and MS in Argentina).

TABLE II. A1AT Genotype and Allele Distributions in Subjects Infected With HIV Grouped by Clinical Stages of Disease Progression

	N (%)		
	EC (N = 14)	LTNP (N = 20)	Prog (N = 45)
A1AT genotype			
MM	12 (85.7)	17 (85)	39 (86.7)
MS	2 (14.3)	3 (15)	4 (8.9)
SS	0 (0)	0 (0)	1 (2.2)
SZ	0 (0)	0 (0)	1 (2.2)
A1AT alleles			
M	26 (92.8)	37 (92.5)	82 (91.1)
S	2 (7.2)	3 (15)	7 (7.8)
Z	0 (0)	0 (0)	1 (1.1)

TABLE III. A1AT Genotype and Allele Frequency Distributions in Subjects Infected With HIV and in the General Population from Each Country of Origin

	A1AT genotype frequency (%)			A1AT allele frequency (%)	
	MS	SS	SZ	S	Z
Canada					
HIV^+ (N = 39)	7.69	2.56*	0	6.41	0
Population	7.40	0.15* $P < 0.0001$	0.10	3.91	1.29
U.S.					
HIV^+ (N = 23)	13.04	0	4.34*	8.69*	2.17
Population	4.46	0.05	0.04* $P < 0.0001$	2.32* $P = 0.033$	1.05
Argentina					
HIV^+ (N = 9)	33.33*	0	0	16.66*	0
Population	6.33* $P < 0.032$	0.11	0.04	3.35* $P < 0.032$	0.62
Brazil					
HIV^+ (N = 8)	0	0	0	0	0
Population	9.17	0.24	0.05	4.85	0.57

Population, population frequencies reported in each country [de Serres and Blanco, 2012].
*Statistically significant difference, with *P*-values written below each significant comparison.

DISCUSSION

Since A1AT genes are not altered by HIV infection, the increased frequency of the A1AT S gene in patients infected with HIV (Table II) preceded infection. This suggests that presence of the S A1AT gene comprised a risk factor for HIV infection. Also, since the S A1AT gene product is associated with serum A1AT concentrations 60% of levels associated with the M A1AT gene product, a similar relationship between low serum A1AT concentration and HIV infection is suggested. It is therefore possible that lower serum A1AT levels in patients infected with HIV [Bryan et al., 2010] reflect increased frequency of deficiency-associated A1AT genes. Therefore, low serum A1AT concentrations likely preceded HIV infection [Bryan et al., 2010]. Collectively, these considerations imply A1AT deficiency-associated genes and low A1AT serum concentrations comprise risk factors for HIV infection but not disease progression.

In summary, our results suggest that deficiency of A1AT related to the presence of the abnormal S A1AT gene enhances susceptibility to HIV infection.

REFERENCES

Settin A, El-Bendary M, Abo-Al-Kassem R, El Baz R. 2006. Molecular analysis of A1AT (S and Z) and HFE (C282Y and H63D) gene mutations in Egyptian cases with HCV liver cirrhosis. J Gastrointestin Liver Dis 15:131–135.

Bryan CL, Beard KS, Pott GB, Rahkola J, Gardner EM, Janoff EN, Shapiro L. 2010. HIV infection is associated with reduced serum alpha-1-antitrypsin concentrations. Clin Invest Med 33:E384–E389.

UnB
CNPq Conselho Nacional de Desenvolvimento Científico e Tecnológico
CAPES