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GLOBAL PERSPECTIVES: SOUTH AMERICA (MO SILVA, SECTION EDITOR)

IL28B Polymorphisms Among Latin American HCV Patients

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Abstract Latin America is a diverse region with more than 500 million people and approximately 8 million HCV infected individuals. The recent description of genetic polymorphisms associated to the interleukin 28B gene that predicts the response to treatment in these patients has impacted the clinical algorithms of management. In this review we examine the studies of prevalence of the IL28B genotypes in the general population and in HCV infected patients in the region and its relationship with treatment response to peginterferon and ribavirin. We show that the prevalence in the different studies in the region show a CC genotype of the rs12979860 between 18 to 35 %. This particular SNP is more consistently associated with treatment response than rs8099917 in Latin America, as well as around the world.

Keywords IL28B · Interleukin 28B · Lambda 3 · Hepatitis C virus · HCV · Latin America

Introduction

Latin America is defined as the Spanish, Portuguese and French speaking American countries. As such, Latin America comprises 14 % of the world territory and 590 million people. This territory has a great diversity in terms of geography, economic development, cultural background and ethnicity. Specifically regarding ethnicity, the self-reported ethnic background in Latin America is as follows: Mestizo 44 %, White 27 %, Amerindian 9 %, Mulatto 6 %, Black 5 %, Asian 1 % and others 1 % [1]. This makes more difficult to generalize conclusions to the projected 8 million people infected with hepatitis C virus in the region [2•, 3].

In the following article we will review the available information regarding interleukin 28B (IL28B) polymorphisms and hepatitis C virus (HCV) infection in Latin America. For most of this review, mainly IL28B rs12979860 variants will be discussed.

Review Strategy

A search was conducted in MEDLINE with the terms IL28B, Latin America and the combined search term: IL28B[All Fields] AND (("argentina"[MeSH Terms] OR "argentina"[All Fields]) OR ("bolivia"[MeSH Terms] OR "bolivia"[All Fields]) OR ("brazil"[MeSH Terms] OR "brazil"[All Fields]) OR ("chile"[MeSH Terms] OR "chile"[All Fields]) OR ("colombia"[MeSH Terms] OR "colombia"[All Fields]) OR ("costa rica"[MeSH Terms] OR ("costa"[All Fields] AND "rica"[All Fields]) OR "costa rica"[All Fields]) OR ("cuba"[MeSH Terms] OR "cuba"[All Fields]) OR ("ecuador"[MeSH Terms] OR "ecuador"[All Fields]) OR ("el salvador"[MeSH Terms] OR ("el"[All Fields] AND "salvador"[All Fields]) OR "el salvador"[All Fields]) OR ("guatemala"[MeSH Terms] OR "guatemala"[All Fields]) OR ("haiti"[MeSH Terms] OR "haiti"[All Fields]) OR ("honduras"[MeSH Terms] OR "honduras"[All Fields]) OR ("mexico"[MeSH Terms] OR "mexico"[All Fields]) OR ("nicaragua"[MeSH Terms] OR "nicaragua"[All Fields]) OR ("panama"[MeSH Terms] OR "panama"[All Fields]) OR ("paraguay"[MeSH Terms] OR "paraguay"[All Fields]) OR ("peru"[MeSH Terms] OR "peru"[All Fields]) OR

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Table 1 Allelic frequency CC genotype in ethnic groups of Latin America (general population; non-HCV infected individuals). The allelic frequencies are reported from references [5, 6•, 8]. Genotypes frequencies were calculated when not available

Population	N	C allelic frequency	CC genotype
Pima (Mexico)	198	0.56	31 %
Maya, Yucatán (Mexico)	104	0.38	14 %
Guahibo (Colombia)	24	0.63	40 %
Karittiana (Brazil)	108	0.82	67 %
Quechua (Peru)	44	0.64	41 %
Surui (Brazil)	94	0.78	61 %
Ticuna (Brazil)	124	0.20	4 %
Santiago (Chile)	405	0.63	40 %
Central area (Argentina)	NR	0.66	43 %

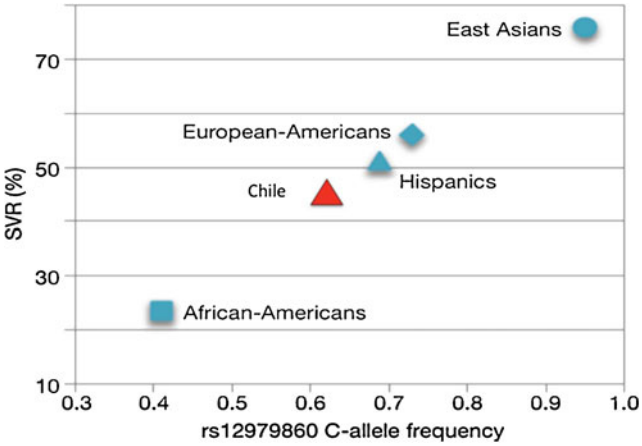

Fig. 1 Sustained virological response (SVR) according to C-allele frequency in different ethnic groups. Graph modified, with permission, from [9] with Chilean data from [16]

("dominican republic"[MeSH Terms] OR ("dominican"[All Fields] AND "republic"[All Fields]) OR "dominican republic"[All Fields]) OR ("uruguay"[MeSH Terms] OR "uruguay"[All Fields]) OR ("venezuela"[MeSH Terms] OR "venezuela"[All Fields]) OR ("puerto rico"[MeSH Terms] OR ("puerto"[All Fields] AND "rico"[All Fields]) OR "puerto rico"[All Fields])). A total of 15 articles were retrieved. Additionally, the references in the aforementioned papers were reviewed. Abstracts presented in local conferences were included when available.

Prevalence of IL28B Polymorphisms in the General Population in Latin America

There is scanty information regarding the prevalence of the different IL28B associated polymorphisms in the Latin American population. The ALFRED database (ALlele FREquency Database), form Yale University [4], contains information of DNA samples from diverse ethnic origin. The 394 samples from South America show a C allelic frequency of 0.61 (CC genotype 37 %), compared to a CC genotype prevalence of 28 % in North America, 45 % in Europe, 13 % in Africa, 77 % in Asia and 85 % in Oceania [5].

When looking at the CC genotype population frequencies in different countries or ethnic groups, the AFRED database again may shed some light in Latin America, showing very important differences in genotype frequency among different racial groups.

The largest population study prevalence of the IL28B genotypes among non-HCV infected individuals shows a CC genotype prevalence of 40 % at the rs12979860 in Chile [6•]. This study shows also that the rs8099917 has the following genotype distribution: TT 47 %, TG 43 % and GG 10 %. The DNA for this study comes from a well-characterized sample of the general Chilean population [7]. A study form the central area of Argentina shows an allelic frequency of the

Table 2 IL28B rs12979860 CC genotype prevalence in HCV infected patients in Latin America. Sustained virological response to peginterferon alfa plus ribavirin in CC versus non-CC genotype patients

Country	Reference	n	CC prevalence in HCV patients	Reported CC prevalence in the population*	SVR in CC patients	SVR in non-CC patients
Argentina	Ridruejo et al. [18]	102	18 %	N/A	67 %	33 %
Brazil	Cavalcante et al. [13]	221	24 %	4 %-67 %	67 %	31 %
Brazil	Ramos et al. [17]	66	32 %	4 %-67 %	62 %	28 %
Brazil **	Ferreira et al. [14]	26	35 %	N/A	78 %	N/A
Chile	Pavez et al. [16]	78	22 %	41 %	59 %	22 %
Mexico	Sixtos et al. [19]	80	21 %	14 %-31 %	76 %	41 %
Mexico	Martínez-Gómez et al. [15]	83	24 %	14 %-31 %	45 %	28 %

* See Table 1.

** HCV – HIV co-infected patients

C allele of 0.66 [8]. All these studies are summarized in Table 1.

Prevalence of IL28B Polymorphisms in HCV Infected Patients in Latin America and Response to Treatment

Relatively soon after the publication of the GWAS showing the association of IL28B polymorphisms and HCV treatment response [9–11], a report from Chile confirmed this association in patients form Latin America [12]. Unfortunately, this paper doesn't allow calculating the IL28B genotype prevalence in infected patients since they selected patients based in response, but didn't analyze a complete cohort of treated patients.

Currently there are at least seven reports in the region studying the prevalence of CC genotype at rs12979860 in Latin America [13–19]. It is interesting to note that there is ample variation in the CC genotype at rs12979860 among the different studies, going from 18 to 35 %. These studies are summarized in Table 2.

All the studies confirm a strong association between this genotype and a higher sustained virological response, with more than doubling the SVR in CC patients compared with no-CC patients. Figure 1 superimposes the Chilean data to the previously published information regarding IL28B C allele frequency and response to treatment in different ethnic groups. In the studies where the rs8099917 was studied, it failed to be consistently associated with SVR in the Latin American population. Specifically, when the predictive power of the two SNPs polymorphisms were analyzed in combination, it was shown that the rs8099917 didn't add to the predictive power of the rs12979860.

Other Relationships of IL28B Polymorphisms in HCV Infected Patients in Latin America

We couldn't identify studies of association of IL28B variants to triple therapy (including boceprevir or telaprevir) response in Latin America. Interestingly, one Brazilian report confirms that the CC genotype conferred increased the chance of spontaneous clearance of HCV infection, with an OR 2.78 [20]. An additional study from Sao Paulo in HIV-HCV co-infected patients shows that the IL28B genotype influences the early viral kinetics in response to peginterferon alfa and ribavirin [21, 22]. IL28B has also been associated with the detection of HCV RNA in peripheral blood mononuclear cells (PBMCs) and treatment response in a study from Chile [6•].

Conclusions

Latin America is a diverse region, with a very different ethnic background. The IL28B CC genotype at rs12979860 varies from 18 to 35 %. Only seven studies from four countries of Latin America could be identified. As in other regions, the analysis of IL28B polymorphisms is strongly associated to treatment response to PEG-IFN and RBV in our region. Analysis of variants at different SNPs related to the gene don't seem to add significantly to the predictive power of this genetic marker in the context of hepatitis C. The role of this polymorphism seems to still be relevant in the context of the first wave of direct acting antivirals (boceprevir or telaprevir based therapies combined with peginterferon and ribavirin). Particularly in our region, where health care resources are limited, strategies including IL28B polymorphisms to aid in the identification of patients that could be treated with dual therapy with similar efficacy compared to triple therapy may have significant economic impact. Anyway, the utility of these polymorphisms in interferon free treatment regimens with very high SVR remains to be proven.

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Compliance with Ethics Guidelines

Conflict of Interest Alejandro Soza is a paid board member of MSD, Vertex, Roche, Gilead, and Janssen, receives payment for development of education presentations from MSD, Roche, and BMS, and has stock/stock options from Gilead. Marcelo Lopez-Lastra declares no conflicto of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by either of the authors.

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