

# Association of Single-Nucleotide Polymorphisms in *IL28B*, but Not *TNF- $\alpha$* , With Severity of Disease Caused by Andes Virus

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**Background.** Andes virus (ANDV) is the sole etiologic agent of hantavirus cardiopulmonary syndrome (HCPS) in Chile, with a fatality rate of about 35%. Individual host factors affecting ANDV infection outcome are poorly understood. In this case-control genetic association analysis, we explored the link between single-nucleotide polymorphisms (SNPs) rs12979860, rs8099917 and rs1800629 and the clinical outcome of ANDV-induced disease. The SNPs rs12979860 and rs8099917 are known to play a role in the differential expression of the interleukin 28B gene (*IL28B*), whereas SNP rs1800629 is implicated in the expression of tumor necrosis factor  $\alpha$  gene (*TNF- $\alpha$* ).

**Methods.** A total of 238 samples from confirmed ANDV-infected patients collected between 2006 and 2014, and categorized according to the severity of the disease, were genotyped for SNPs rs12979860, rs8099917, and rs1800629.

**Results.** Analysis of *IL28B* SNPs rs12979860 and rs8099917 revealed a link between homozygosity of the minor alleles (TT and GG, respectively), displaying a mild disease progression, whereas heterozygosity or homozygosity for the major alleles (CT/CC and TG/TT, respectively) in both *IL28B* SNPs is associated with severe disease. No association with the clinical outcome of HCPS was observed for *TNF- $\alpha$*  SNP rs1800629 (*TNF* -308G>A).

**Conclusions.** The *IL28B* SNPs rs12979860 and rs8099917, but not *TNF- $\alpha$*  SNP rs1800629, are associated with the clinical outcome of ANDV-induced disease, suggesting a possible link between *IL28B* expression and ANDV pathogenesis.

**Keywords.** ANDV; HCPS; *IL28B*; *TNF-alpha*; SNP.

Andes virus (ANDV), member of the genus *Hantavirus* within the family *Bunyaviridae* [1], is endemic in Argentina and Chile. The main reservoir host for ANDV is the long-tailed pygmy rice rat (*Oligoryzomys longicaudatus*) [2]. Transmission to humans occurs mainly via exposure to aerosolized rodent urine, saliva, and

feces containing the virus [1]. However, human-to-human transmission has also been described [3]. ANDV causes a respiratory disease known as hantavirus cardiopulmonary syndrome (HCPS), characterized by the development of a vascular leakage syndrome, eventually leading to massive pulmonary edema, shock and, in many cases, death [4, 5]. HCPS was first recognized in Chile in 1995 and serologically confirmed in retrospective cases from 1993 [6]. As of April 2015, a total of 925 confirmed cases had been reported with a current case fatality rate of about 35% (Department of Epidemiology Chilean Ministry of Health; <http://www.minsal.cl>).

To date, no Food and Drug Administration-approved antiviral drugs, immunotherapeutics, or

Received 31 May 2015; accepted 4 September 2015; electronically published 22 September 2015.

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**Clinical Infectious Diseases**® 2015;61(12):e62-9

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DOI: 10.1093/cid/civ830

vaccines are available for HCPS [7]. Patient survival rates hinge largely on early diagnosis, hospital admission and aggressive pulmonary and hemodynamic support in an intensive care unit (reviewed in [4, 5]). There is currently no blood biomarker to predict the outcome of ANDV-induced HCPS. Interestingly, several reports have established links between host single-nucleotide polymorphisms (SNPs) and disease progression for other members of the *Hantavirus* genus (reviewed in [8]). For example, a study conducted in Brazil showed that the host SNP rs1800629 in the tumor necrosis factor  $\alpha$  (*TNF- $\alpha$* ) gene promoter, involving the substitution of guanine (G) to adenosine (A), linked with the outcome of Araraquara virus-induced HCPS [9]. Individual host factors affecting ANDV infection outcome are poorly understood but are likely to prove important for predicting disease progression in hospitalized patients.

One example of how the knowledge of the patients' genetic background can be used in the clinic has emerged from the study of the hepatitis C virus (HCV) (reviewed in [10–12]). Several genome-wide association studies reported SNPs near the interleukin (IL) 28B gene (*IL28B*) locus on chromosome 19 that are associated with sustained virological response to antiviral therapy [10–12]. These studies defined rs12979860 CC and rs8099917 TT as a favorable *IL28B* genotype during HCV infection. *IL28B* expression is higher in individuals with rs12979860 CC and rs8099917 TT genotypes than in those with rs12979860 non-CC and rs8099917 non-TT genotypes [13–15]. With HCV, elevated expression of *IL28B* is associated with virus clearance, a positive response to therapy, and a better disease outcome [11, 12, 16].

IL 28B or interferon (IFN)  $\lambda$ 3 together with IFN- $\lambda$ 1 (IL-29), IFN- $\lambda$ 2 (IL28A), and IFN- $\lambda$ 4, constitute the type III IFN family (reviewed in [17, 18]). The members of the IFN- $\lambda$  family interact through unique receptors that are distinct from type I (IFN- $\alpha/\beta$ ) and type II (IFN- $\gamma$ ) IFN receptors [17–19]. The expression of the IFN- $\lambda$  receptor is limited primarily to epithelial and immune cells. IFN- $\lambda$  is coexpressed together with other type I IFNs by virus-infected cells, triggering the Jak-STAT pathway [17, 18] and resulting in the expression of IFN-stimulated genes involved in the antiviral response [17].

ANDV infection induces IFN- $\lambda$  expression in Vero E6 cell lines, suggesting a possible link between IFN- $\lambda$  expression and a cellular antiviral response [20]. In addition, pretreatment of cultured cells with IFN- $\lambda$  inhibits infection by Hantaan virus [21], the prototypic hantavirus. Based on these reports linking hantavirus infection and disease outcome with IFN- $\lambda$  and TNF- $\alpha$  [9, 20, 21], we designed this case-control genetic association analysis study specifically to address whether there is a link between the outcome of ANDV-induced disease in Chilean patients and *IL28B* SNPs rs12979860 and rs8099917, known to affect *IL28B* protein expression [13–15], or SNP rs1800629, known to play a role in determining TNF- $\alpha$  levels [22].

**Table 1. Characteristics of Andes Virus-Infected Patients (n = 238)**

Variable	Patients, No. (%) <sup>a</sup>
Sex <sup>b</sup>	
Male	167 (70)
Female	70 (30)
Age, mean (SD), y <sup>c</sup>	34 (16)
Age group	
0–15 y	22 (9.8)
16–30 y	77 (34.2)
31–50 y	89 (39.6)
51–80 y	37 (16.4)
Area (south latitude) <sup>d</sup>	
North (17°30' to 32°16')	2 (0.9)
Center (32°02' to 36°33')	71 (30.3)
South (36°00' to 56°30')	161 (68.8)
Area of infection <sup>e</sup>	
Urban	22 (10.1)
Rural	197 (89.9)
Risk factor <sup>f</sup>	
Rural resident	120 (73.6)
Farm worker	47 (37.0)
Forestry worker	9 (8.3)
Excursionist	44 (34.4)
Contact case	16 (14.5)
Mouse bite	1 (0.9)
Outcome	
Mild	104 (43.7)
Severe <sup>g</sup>	134 (56.3)
Death	59 (24.8)

Abbreviation: SD, standard deviation.

<sup>a</sup> Data represent No. (%) of patients unless otherwise specified.

<sup>b</sup> Data were available for 237 patients.

<sup>c</sup> Data were available for 225 patients.

<sup>d</sup> Data were available for 234 patients.

<sup>e</sup> Data were available for 219 patients.

<sup>f</sup> Risk factors were calculated for 163, 127, 109, 128, 110, and 107 patients respectively.

<sup>g</sup> Including the 59 deceased patients.

## MATERIAL AND METHODS

### Study Population and Biological Samples

This study included 238 peripheral blood, plasma, or serum samples from patients infected with ANDV, collected at the time of hospital admission, between January 2006 and January 2014. Sample selection was based on availability. Approval for the use of the samples and for the designed research protocol was obtained from the Ethical Review Board of the Facultad de Medicina, Pontificia Universidad Católica de Chile (code 12–292). ANDV infection was confirmed by positive hantavirus immunoglobulin M serology or by ANDV genome detection using reverse-transcription polymerase chain reaction [23, 24]. According to the

**Table 2. Available Clinical and Laboratory Findings at the Time of Sample Collection**

Variable	Patients, No. (%)		P Value
	Severe Disease <sup>a</sup>	Mild Disease <sup>a</sup>	
Fever (>38.5°C)	127 (94.5)	97 (96.9)	.30
Gastrointestinal symptoms	115 (69.6)	86 (65.1)	.30
Headache	118 (85.6)	92 (92.4)	.09
Myalgia	123 (84.6)	93 (91.4)	.10
Respiratory distress	127 (94.5)	88 (69.3)	<.001
Infiltrates on chest radiograph	118 (94.1)	88 (80.7)	.003
Blood shift (>10% bands)	80 (66.3)	57 (49.1)	.33
Atypical lymphocytosis <sup>b</sup>	56 (46.4)	42 (38.1)	.27
Thrombocytopenia <sup>c</sup>	117 (98.3)	83 (96.4)	.34
Increased hematocrit <sup>d</sup>	110 (58.2)	71 (42.2)	.03

<sup>a</sup> Classified according to clinical outcome.

<sup>b</sup> Defined as >10% atypical lymphocytes.

<sup>c</sup> Defined as <150,000 mm<sup>3</sup>.

<sup>d</sup> Defined as >52% for men and >48% for women.

patients' final clinical outcome, samples were grouped by the authors into mild and severe infection categories (Tables 1 and 2). A mild hantavirus infection was characterized as a febrile illness with nonspecific symptoms (eg, headache, myalgias, chills, gastrointestinal symptoms) with no or minimal respiratory compromise. Severe cases were characterized as exhibiting rapid and progressive impaired lung function requiring oxygen support and the use of vasoactive drugs, followed by the onset of shock, or death.

### DNA Extraction and SNP Genotyping

The distribution of the evaluated SNPs was determined with total genomic DNA from 500 nonrelated and ANDV-uninfected individuals, obtained from a well-characterized DNA library considered representative of the Chilean population [25–28], the control cohort. Genomic DNA was extracted from samples using the QIAamp DNA Mini Kit (Qiagen), according to protocols described elsewhere [25, 29]. Genotyping of SNPs rs12979860 and rs8099917 was performed as described elsewhere [25]. Genotyping of the rs1800629 SNP was performed using a TaqMan pre-designed SNP assay (Applied Biosystems; reference C\_7514879\_10). The amplification reaction was conducted in a Stratagene Mx3000P thermal cycler (Agilent Technologies), and the correct assignment of alleles in each sample was attributed automatically by MXPro QPCR software version 4.10 (Agilent Technologies), as described elsewhere [25]. Positive and negative controls, described in a previous study [25], were used in each genotyping assay.

### Statistical Analysis

The clinical symptoms exhibited by patients at admission were analyzed using a 1-tailed Fisher exact test for each variable;

analyses were performed with GraphPad software (version 5.1; GraphPad). The association between polymorphisms and the severity of infection was calculated using a 2-tailed Fisher exact test with a 2 × 2 contingency table assuming a minor allele recessive effect model for rs12979860 and rs8099917 and a minor allele dominant effect model for rs1800629; analyses were performed with GraphPad (version 5.1) and OpenEpi (version 3.01) software [30]. A  $\chi^2$  test was used to verify any discrepancies of distribution from Hardy–Weinberg equilibrium in the ANDV-infected population [31]. A Wilcoxon matched pairs test was used to determine differences between genotype frequencies in the control and ANDV-infected groups. Differences were considered significant at  $P < .05$ .

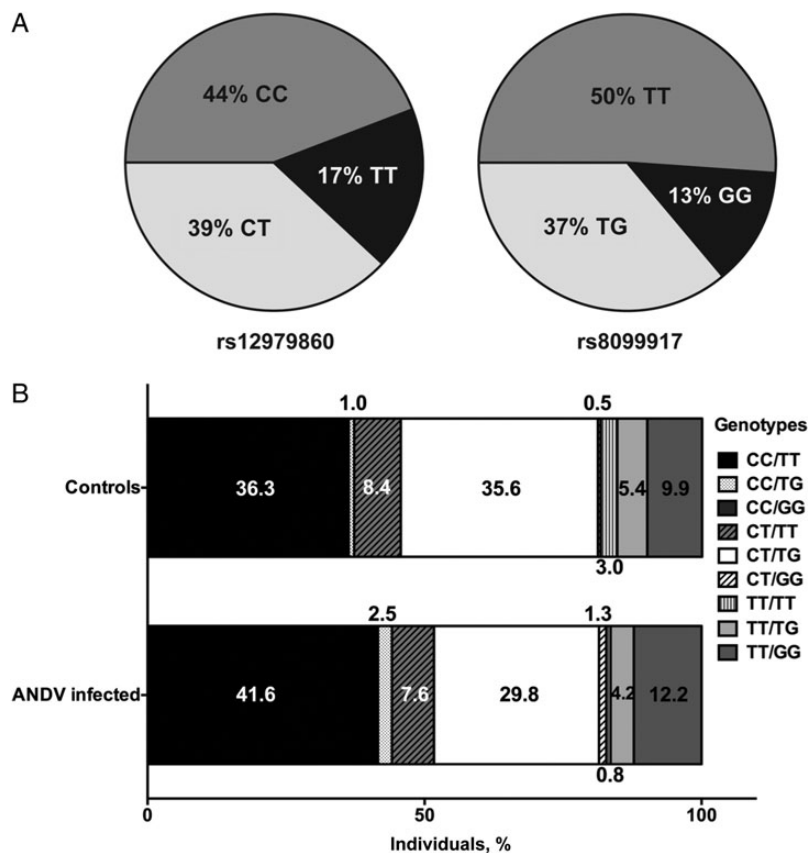
## RESULTS

### Analysis of *IL28B* SNPs in ANDV-Infected Patients

Demographic information available for patients is included in Table 1. Clinical information reported at the time of sample collection is in Table 2. Most samples ( $n = 232$ ) were obtained from hospitals located in regions that overlap with the geographic distribution of the virus reservoir (Table 1; center and south) [2]. The mean (standard deviation) age of the patients was 34 (16) years, and 70% were male (Table 1). Most patients declared themselves as having been in a high-risk geographic location (Table 1) and exhibited symptoms typical of hantavirus-induced distress (Table 2).

The classification of HCPS cases into severe, mild, and self-limited forms has been shown to have a prognostic value, with statistically significant differences between survivors and non-survivors [32]. Thus, based on the available clinical information, the ANDV-infected patients were divided into 2 main groups, mild or severe infection, depending on the final clinical outcome [32]. That outcome was not associated with the patient's sex; 55.7% of all males and 58.6% of all female patients were classified as having severe infection. A univariate analysis revealed that respiratory distress, radiographic signs of pulmonary disease, and high hematocrit levels at the time of sample collection differed significantly according to clinical outcome (Table 2).

SNP analysis in ANDV-infected patients revealed that the frequencies for the rs12979860 CC, CT, and TT genotypes were 0.44, 0.39, and 0.17, respectively, compared with 0.50, 0.37, and 0.13 for the rs8099917 TT, GT, and GG genotypes (Figure 1A). The allele frequencies of rs12979860 and rs8099917 within the group of ANDV-infected patients were similar to those reported for a the control cohort, in which the rs12979860 CC, CT, and TT genotype frequencies are 0.37, 0.44, and 0.19, respectively, and the rs8099917 TT, GT and GG genotype frequencies were 0.47, 0.43, and 0.10 [25]. A direct comparison of the



**Figure 1.** Interferon  $\lambda$  single-nucleotide polymorphisms (SNPs) among the studied population. *A*, Distribution of rs12979860 and rs8099917 SNP genotypes among 238 Andes virus (ANDV)-infected patients. *B*, Frequency of the genotype combination for the 2 SNPs rs12979860 and rs8099917 in control population ( $n = 405$ ) and ANDV-infected ( $n = 238$ ) population. The total number of individuals in each group was defined as 100%, and the percentages of individuals with 1 of the 9 possible genotypes were calculated. The numbers within each box correspond to the percentage of individuals with a particular genotype. Control group data were sourced from a previous report [25].

different combinations of genotypes for SNPs rs12979860 and rs8099917 between noninfected and ANDV-infected individuals showed no significant variations in the genotype distribution (Figure 1*B*).

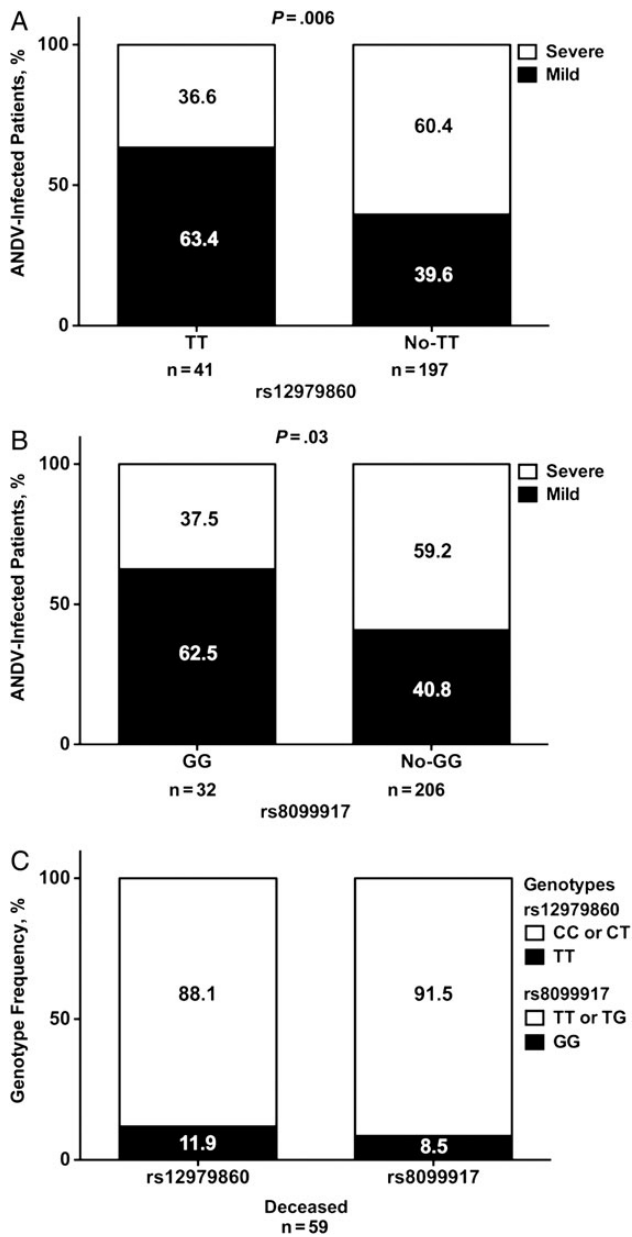
There was an increase in individuals showing homozygosity for the major C allele in rs12979860 and major T allele in rs8099917 among the ANDV-infected population (Figure 1*B*). Within the control cohort, both SNP genotypes were in Hardy-Weinberg equilibrium ( $\chi^2$  test,  $P > .1$ ) [25]. In contrast, in infected patients these SNPs were found not to be in equilibrium (rs12979860 ( $\chi^2 = 6.61$ ;  $P = .01$ ); rs8099917 ( $\chi^2 = 5.80$   $P = .01$ )), suggesting a possible selection effect.

#### Link Between *IL28B* SNPs and the Severity of ANDV-Associated Pathogenesis

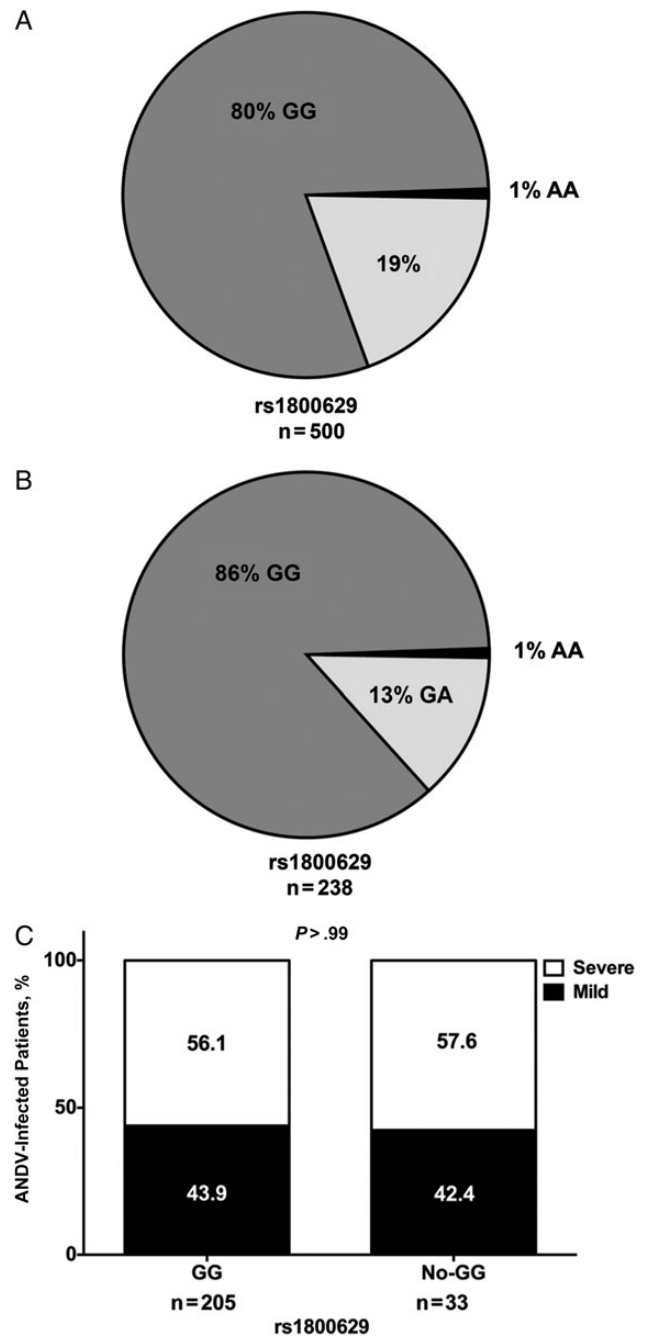
Next, we evaluated whether a correlative link existed between *IL28B* SNPs and the severity of ANDV-associated pathogenesis. Analysis of SNP rs12979860 revealed a link between the

genotypes that carry the minor T allele homozygosity (41 patients) and the severity of ANDV infection (odds ratio, 2.644; 95% CI, 1.317–5.309;  $P = .006$ ) (Figure 2*A*). These observations suggest that homozygosity for the minor T allele is associated with a mild disease progression. Analysis of SNP rs8099917 also revealed a link between homozygosity for the minor G allele (32 patients) (odds ratio, 2.421; 95% CI, 1.123–5.217;  $P = .034$ ) and mild disease progression (Figure 2*B*).

We then evaluated *IL28B* SNPs in the subpopulation of individuals who died due to HCPS (59 patients; 24.8% of all studied cases) (Table 1). Consistent with our findings for SNP rs12979860 in the whole infected cohort, 88.1% of deceased patients showed heterozygosity or homozygosity for the major C allele, while for SNP rs8099917, 91.5% of deceased patients were heterozygote or homozygote for the major T allele (Figure 2*C*). This observation strongly suggests that heterozygosity or homozygosity for the major alleles in both *IL28B* SNPs is associated with the severity of the disease caused by ANDV.



**Figure 2.** Association between the severity of Andes virus (ANDV) pathogenesis and interferon  $\lambda$  single-nucleotide polymorphism (SNP) genotype. Patients were grouped according to the SNP rs12979860 (A) and rs8099917 (B) genotypes. Each genotype was divided into 2 groups: those with a homozygous status for the minor allele, and those with a heterozygous or homozygous status for the major allele. The total number of patients in each group was defined as 100%, and the severity of ANDV-associated disease was evaluated as a dichotomous variable using a Fisher exact test. The number within each box corresponds to the percentage of patients with mild or severe disease. C, Total number of deceased patients was grouped according to the genotype for SNPs rs12979860 and rs8099917. The number within each box corresponds to the percentage of patients with a protective genotype (homozygous for the minor allele) and with a risk genotype (heterozygous or homozygous status for the major allele).



**Figure 3.** Polymorphism analysis for tumor necrosis factor  $\alpha$  gene (*TNF- $\alpha$* ). A, Distribution of *TNF- $\alpha$*  single-nucleotide polymorphism (SNP) rs1800629 among 500 noninfected individuals obtained from a well characterized DNA library considered e representative of the Chilean population [25–28]. The total number of individuals was defined as 100%. B, Distribution of *TNF- $\alpha$*  SNP rs1800629 among 238 patients infected with Andes virus (ANDV). The total number of patients was defined as 100%. C, ANDV-infected patients were grouped into those with a homozygous status for the major allele (GG) and those with a heterozygous or homozygous (non-GG) status for the minor allele. The total number of patients in each group was defined as 100%, and the severity of ANDV-associated disease was evaluated as a dichotomous variable using a Fisher exact test. The number within each box corresponds to the percentage of patients with mild or severe disease.



### No Link Between *TNF- $\alpha$* Gene Polymorphism –308G>A and the Severity of ANDV-Associated Pathogenesis

No data are available regarding the allelic frequencies of SNP rs1800629 polymorphism within the Chilean population. Thus, we analyzed the genomic DNA from 500 noninfected individuals, obtained from a well-characterized DNA library considered representative of the Chilean population [25–28]. The frequencies for the rs1800629 GG, GA, and AA genotypes were 0.80, 0.19, and 0.01, respectively (Figure 3A). Next, we evaluated SNP rs1800629 in ANDV-infected patients; frequencies for the rs1800629 GG, GA, and AA genotypes were 0.86, 0.13, and 0.01, respectively (Figure 3B). For both control and ANDV-infected groups, the SNP was in Hardy–Weinberg equilibrium ( $\chi^2$  test,  $P > .1$ ). The allele frequencies of SNP rs1800629 were similar in the control cohort and in ANDV-infected patients. *TNF- $\alpha$*  SNP rs1800629 was then compared between patients with mild versus severe disease pathogenesis. The distribution of *TNF- $\alpha$*  alleles of SNP rs1800629 were not observably correlated with the severity of outcome of the infection (Figure 3C).

## DISCUSSION

There is considerable evidence to suggest that immune mechanisms rather than direct viral cytopathology are responsible for the massive vascular dysfunction and plasma leakage displayed by HCPS (reviewed in [4, 5]). A robust T-cell response is generated in humans during hantavirus infection, followed by a long-lived memory T-cell response [33]. However, experiments conducted in Syrian hamsters (*Mesocricetus auratus*), which develop a disease similar to HCPS on infection with ANDV, suggest that ANDV-induced disease is not the result of T-cell-mediated immunopathology [34–36]. At the same time, findings of some studies indicate that specific HLA alleles can be associated with either mild or severe disease [33, 37]. In Sin Nombre virus–infected patients with HCPS, the HLA-B\*35 allele has been associated with a severe disease [37], whereas in ANDV-infected patients with HCPS, HLA-B\*35 restricted memory T-cell responses were associated with a mild disease outcome [33]. Even though results for Sin Nombre virus and ANDV seem contradictory, both reports raise the possibility that host factors, distinct from T-cell involvement, might be linked to the pathogenesis and outcome of ANDV infection [33, 37].

Infection of Vero E6 cells by ANDV induces the expression of IFN- $\lambda$  [20]. The level of expression of IFN- $\lambda$  influences the outcome of infection by several different viruses including the prototype hantavirus Hantaan [11, 21, 38]. These observations led us to evaluate the potential effect of *IL28B* genetic variation on the outcome of ANDV infection. We analyzed samples from a total of 238 patients, all confirmed as ANDV infected (Figures 1 and 2). Although the sample size may seem marginal

and a limitation to the present study, it nevertheless corresponds to 60.4% of all ANDV infections reported in Chile between January 2006 and January 2014.

In recent years, public and private healthcare systems in Chile have worked together to improve the diagnosis of HCPS and the intensive care therapeutic approach to cases of ANDV infection. The clinical guidelines for management of ANDV-infected patients are followed by all intensive care units throughout the country (Hantavirus Clinical Guidelines/Department of Epidemiology Chilean Ministry of Health; <http://www.minsal.cl>). On this basis, we believe it is fair to assume that the outcomes of ANDV infection observed in the studied cohort were not unduly influenced by variability in the application of management procedures across the locations of sample collection (Table 1). *IL28B* genotyping revealed that in the analyzed cohort SNPs seemed biased toward a genotype associated with a poor disease outcome, rs12979860 CC and rs8099917 TT (Figure 1). This observation was somewhat expected, because serological studies conducted in endemic regions of Chile have reported a nonnegligible proportion of clinically asymptomatic ANDV infections [39, 40].

Results suggest that heterozygosity or homozygosity for the major alleles of *IL28B* SNPs rs12979860 C and rs8099917 T, known to be associated with high levels of *IL28B* expression [13–15], are linked with a poor disease outcome in ANDV-infected patients (Figure 2). These data represent a reversal of what is observed in HCV infections where *IL28B* SNP rs12979860 CC and rs8099917 TT are considered protective [11, 12]. Albeit unexpected and counterintuitive, our findings suggest that in contrast to what has been described for HCV, the innate immune system might play an important, yet not fully characterized, role in ANDV pathogenesis.

The precise mechanisms underlying the association between severe ANDV infection and the *IL28B* genotype are still obscure because this study was not designed to evaluate cytokine expression through time. Therefore, no direct conclusions can be drawn on any association between *IL28B* expression and ANDV disease progression. Nonetheless, the direct connection between *IL28B* SNPs rs12979860 and rs8099917 and the differential expression of *IL28B* has been well documented by others [13–15]. Results presented herein establish a clear link between genotypes rs12979860 CC/CT and rs8099917 TT/TG, an elevated *IL28B* expression phenotype [13–15], and severe ANDV-induced disease. In turn, this is potentially suggestive of excessive cytokine production and signaling, with resulting effects on *IL28B* expression playing a role in the progression of ANDV-associated disease. In agreement with this possibility, high levels of cytokine-producing cells are seen in the lungs of patients with HCPS after death [41], the pulmonary fluid of patients with HCPS seems to be exudative [42], and proinflammatory mediators are found at elevated levels in the plasma as

well as the renal interstitium of patients with acute hantavirus-induced illness [43, 44]. It is well documented that IFN- $\lambda$  cytokines, including IL28B, promote a prolonged inflammatory cytokine response to pathogens [17]. It is plausible to predict that an increased magnitude of this response might make pathogen clearance in the immune system less efficient and promote disease [45, 46].

Our discovery of an apparent association between *IL28B* SNPs and the severity of ANDV-induced pathogenesis, however, might not be a general phenomenon applicable to all hantavirus induced illnesses. The disease caused by New World hantaviruses HCPS shares many (though by no means all) clinical features of the disease caused by the Old-World hantaviruses, known as *hemorrhagic fever with renal syndrome*. This might indicate that the biological mechanisms underlying HCPS and hemorrhagic fever with renal syndrome are not equivalent. The level of IFN- $\lambda$  induction varies in Vero E6 cells infected with different hantaviruses indicating that not all viruses induce a similar IFN- $\lambda$  response [20].

Patients with Puumala virus infection have been shown to have significantly lower serum levels of IFN- $\lambda$  during the acute phase than during the convalescent phase [21]. The clinical importance of this observation and its possible relation to what is being reported herein remain to be addressed, but the finding may suggest that the level of IFN- $\lambda$  expression is central to the resolution of the infection [21]. It should be noted that all patients included in the current study are expected to express *IL28B* in response to ANDV infection. What is likely to vary between individuals is the level of *IL28B* production, according to genotypes in *IL28B* SNPs [13–15]. It remains to be elucidated what level of *IL28B* production is required to clear ANDV infection, as opposed to excessive expression levels that may lead to severe disease.

A previous report described an association between *TNF- $\alpha$*  rs1800629 and the outcome of Araraquara virus-induced HCPS [9]. In the case of Puumala virus infection, Kanerva et al [47] reported an association between SNP rs1800629 and severe nephropathia epidemica in Finnish patients. It was tempting to predict that a similar association may exist for ANDV-induced HCPS. Our results show that a link between *TNF- $\alpha$*  rs1800629 and the outcome of ANDV-induced HCPS could not be established in the studied cohort (Figure 3). This may suggest that ethnic background should be accounted for when establishing genetic associations. As shown, rs1800629 AA genotype is poorly represented within the Chilean population (Figure 3A).

To date, there are few examples of the use of patient genetic information in routine clinical practice. Here we present compelling evidence that knowledge of host genomic background allows the severity of ANDV-induced disease to be predicted. In conclusion, our findings show that *IL28B* SNPs rs12979860

and rs8099917, but not *TNF- $\alpha$*  SNP rs1800629, are associated with the severity of ANDV-induced disease, potentially allowing these molecular markers to be used as predictors of clinical outcome in ANDV-infected patients.

## Notes

**Acknowledgments.** We thank Drs Alejandro Soza, Jaime Cerda, and Michael Kann for critical reading of the manuscript and Dr Michael Rau for editing it.

**Financial support.** This work was supported by the Iniciativa Científica Milenio del Ministerio de Economía, Fomento y Turismo, Instituto Milenio de Inmunología e Inmunoterapia (project P09/016-F to M. L. L.), the National Institute of Allergy and Infectious Diseases, National Institutes of Health (grant U01AI045452 to M. F. and M. L. L.), Fondo Nacional de Desarrollo Científico y Tecnológico (grant 1130303 to J. F. M.), Fondo de Financiamiento de Centros de Investigación en Áreas Prioritarias Center for Genome Regulation (grant 15090007 to J. F. M.), Comisión Nacional de Investigación Científica y Tecnológica (doctoral fellowship to J. A.), and the Uruguayan Comisión Sectorial de Investigación Científica (research fellowship to N. E. C.).

**Potential conflicts of interest.** All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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