IL7RA rs10491434 POLYMORPHISM IS RELATED TO SPONTANEOUS HIV INFECTION CONTROL IN NAÏVE HIV-INFECTED PATIENTS: A RETROSPECTIVE STUDY

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Title page

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Short title: *IL7RA* SNPs and HIV elite control

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Abstract

Introduction: Interleukin 7 receptor (IL7R) is vital in the adaptive immune response against HIV. We assessed *IL7RA* polymorphisms (SNPs) in antiretroviral therapy (ART)-naïve HIV patients for their association with spontaneous HIV infection control.

Methods: We conducted a retrospective cohort study involving 667 ART-naïve patients categorized by HIV progression (ordinal variable): 150 rapid progressors, 334 moderate/typical progressors, 86 long-term nonprogressors elite controllers (LTNPs-EC), and 97 LTNPs-non-EC. We genotyped three *IL7RA* SNPs using Agena Bioscience's MassARRAY platform. The association between *IL7RA* SNPs and spontaneous HIV infection control was evaluated using ordinal logistic regression.

Results: Individuals carrying the rs10491434 G allele have a higher likelihood of spontaneous HIV infection control (adjusted odds ratio (aOR)=1.33; p=0.023). Moreover, the *IL7RA* GCT haplotype, consisting of three specific SNPs (rs6897932, rs987106, and rs10491434), demonstrated an association with the control of untreated HIV infection (aOR=1.34; p=0.050). Remarkably, the rs10491434 SNP and the *IL7RA* GCT haplotype exhibited similar aOR values, suggesting that rs10491434 may be primarily responsible for the observed effect of the haplotype.

Conclusions: *IL7RA* rs10491434 G allele is associated with a higher likelihood of spontaneous HIV infection control, indicating its significant role in the pathogenesis of HIV, possibly influencing infection course and viral replication control.

Keywords

LTNPs; HIV elite controllers; Single nucleotide polymorphisms; IL7 Receptor

Background

The people living with HIV (PLWH) who do not receive antiretroviral therapy (ART) progress to AIDS in 10-15 years, being the clinical course highly variable and categorized into three major groups [1]: (i) rapid progressors (RPs) who rapidly progress to AIDS within the three first years after HIV seroconversion; (ii) moderate progressors (MPs) who slowly develop AIDS 3-10 years after HIV seroconversion; and (iii) long-term nonprogressors (LTNPs) who do not progress to AIDS over at least 8-10 years and have plasma viral load (pVL)≤10,000 HIV-1 RNA copies/mL, ≥500 $CD4^+$ T-cells/mm^3, and absence of clinical symptoms. Within LTNPs, HIV elite controllers (LTNP-ECs) can maintain pVL<50-75 copies/mL for at least one year [2], proving to be a potential phenotype to achieve the HIV functional cure [3]. This wide array of clinical evolution in PLWH is mainly due to complex interactions between the virus, host, and genetic factors [4].

Interleukin 7 (IL7) and its receptor (IL7R) play a central role in the adaptive immune system by regulating the development and homeostasis of T-cells, contributing to host defense against HIV [5]. IL7 stimulates de novo thymic production of naïve T cells and maintains the memory T cell pool through an antiapoptotic effect on IL7RA-expressing memory T cells. The progression of HIV infection is related to a dysregulation of the IL7/IL7R pathway, where increased levels of IL7 and decreased $CD4^+$ and $CD8^+$ T-cells expressing IL7RA have been observed [5]. In contrast, high levels of IL7RA expression on $CD4^+$ T-cells and reduced plasma levels of IL7 have been observed in LTNPs [5].

IL7R is a heterodimer consisting of the α-chain (CD127 or IL7RA) and the common γ-chain (CD132 or IL2RG) shared by several cytokines, such as IL2, IL4, IL9, IL15, and IL21 [5]. *IL7RA* single-nucleotide polymorphisms (SNPs) have previously been related to $CD4^+$ T-cell homeostasis and AIDS progression in ART-naïve PLWH [6,7] and $CD4^+$ T-cell recovery in PLWH under ART [8-12]. Nevertheless, a previous study by our group did not find an association between *IL7RA* SNPs and AIDS progression in ART-naïve PLWH stratified by the clinical pattern of AIDS progression (RP, MP, and LTNP) [13]. In the current study, we aimed to reevaluate the association between *IL7RA* SNPs and spontaneous HIV infection control in this same cohort of ART-naïve PLWH, where LTNPs have been stratified according to elite control of HIV infection into LTNP-non-ECs and LTNP-ECs.

Methods

We conducted a retrospective cohort study in 667 ART-naïve PLWH from the Cohort of the Spanish AIDS Research Network (CoRIS, see **Appendix 1**) and the Spanish Cohort of LTNPs (see **Appendix 2**). The study was approved by the Instituto de Salud Carlos III Research Ethics Committee and adhered to the principles of the Declaration of Helsinki. Additionally, the article was prepared following the STREGA guidelines (**Supplementary Table 1**).

PLWH were classified into four groups based on their disease progression and control of HIV infection: a) 150 RPs who had, within three years of HIV seroconversion, two or more values of $CD4^+$ T-cell ≤350 cells/mm^3 and/or an AIDS-related event (including death). b) 334 MPs with a continuous decrease in $CD4^+$ T-cells at a rate of 50-100 cells/mm^3 per year), at least two years after the diagnosis of HIV infection. c) 86 LTNP-EC who met the criteria of spontaneous HIV elite control, which means they had undetectable pVL for at least 90% of measurements for at least one year in the absence of ART. d) 97 LTNP-non-EC who were asymptomatic with $CD4^+$ T-cell counts ≥500 cells/mm^3 and pVL≤10,000 copies/mL for at least ten years after HIV seroconversion. However, they did not meet the criteria for spontaneous HIV elite control.

Blood samples were collected in different centers and hospitals from 2004 to 2014 and sent to the HGM HIV Biobank, where they were processed and frozen for future use. The DNA was extracted from the blood samples using the Wizard® SV Genomic DNA Purification System (Promega, Madison, WI, USA). The extracted DNA was genotyped at the Spanish National Genotyping Center (http://www.cegen.org/-CeGen) using the MassARRAY iPLEX Gold (Agena Bioscience, San Diego, CA, USA). Three *IL7RA* SNPs located at three putative regions were genotyped: rs6897932 (exon 6), rs987106 (intronic region), and rs10491434 (3′UTR). The DNA genotyping success rate was reported to be greater than 95%.

All statistical analyses were performed using Stata 17.0 (StataCorp, Texas, USA) with two-tailed statistical significance values of *p*-value ≤0.05. Categorical variables were described as absolute counts and frequencies, and the chi-square test was employed to compare them. The median and interquartile ranges were used to describe continuous variables, and the Kruskal-Wallis test was used to compare them. The Stata's *genhwi* package analyzed Hardy-Weinberg equilibrium (HWE). Three inheritance models (additive, recessive and dominant) were evaluated for the genetic association study. The linear-by-linear association test and ordinal logistic regression (OLR) analysis assessed the association between *IL7RA* SNPs and the spontaneous control of HIV infection (with the reference category as RPs). OLR models were adjusted by gender, injecting drug use (IDU, risk for HIV acquisition), and age at the time of HIV diagnosis. Significant results were validated using the BCa Bootstrap, including Jackknife replications (665) and Bootstrap replications (10,000), to assess the fit of OLR models to a hypothetical test set. The Stata's *Haplologit* package was used to evaluate haplotype associations. The linkage disequilibrium among SNPs was evaluated using Haploview 4.2 software (MIT/Harvard Broad Institute, Cambridge, MA, USA), which provided standardized D' and r^2 values.

The role of *IL7RA* SNPs in *IL7RA* gene expression was analyzed using two resources: the GTEx (Genotype-Tissue Expression) PORTAL Release V8 (https://gtexportal.org/home/) and the rSNPBase 3.1 software (http://rsnp3.psych.ac.cn/). All resources were accessed on July 12, 2023.

Results

There was a decreasing percentage of men and an increasing time since HIV diagnosis, rate of IDUs, age at inclusion, and age at HIV diagnosis as the groups progressed from RPs to LTNPs-EC (**Table 1**; $p<0.001$).

Table 1. Clinical and epidemiological characteristics of PLWH

Characteristics	RPs	MPs	LTNPs-EC	LTNPs-non-EC	*p*-value
No.	150	334	86	97	-
Male	142 (94.6)	283 (84.7)	49 (57.6)	68 (70.1)	**<0.001**
Age at study inclusion, years	38 (33 - 44)	38 (33 - 45)	49 (47 - 52)	48 (46 - 52)	**<0.001**
Age at HIV diagnosis, years	34 (30 - 38)	32 (27 - 38)	40 (34 - 43)	39 (35 - 44)	**<0.001**
Year at HIV diagnosis	2009 (2007 - 2010)	2006 (2005 - 2008)	1992 (1989 - 1996)	1993 (1991 - 1998)	**<0.001**
Risk group for HIV acquisition					**<0.001**
IDU	7 (4.7)	29 (8.7)	63 (74.1)	67 (69.1)	-
Homosexual	126 (84)	220 (65.8)	3 (3.5)	10 (10.3)	-
Heterosexual	15 (10)	76 (22.7)	15 (17.6)	12 (12.4)	-
Others	2 (1.3)	9 (2.7)	4 (4.7)	8 (8.2)	-

Statistics: Values were expressed as absolute numbers (percentages) and medians (percentile 25; percentile 75). *P*-values were calculated by Chi-square and Kruskal-Wallis test. Statistically significant differences are shown in bold. **Abbreviations**: IDU = intravenous drug users; LTNP = long-term nonprogressors; LTNP-EC = LTNPs who were elite controllers; LTNP-non-EC = LTNPs who were not HIV elite controllers; MPs = moderate progressors; PLWH = people living with HIV; RPs = rapid progressors

All *IL7RA* SNPs had a minor allele frequency higher than 5% (**Supplementary Table 2**), indicating that these genetic variants were relatively common in the studied population. The *IL7RA* SNPs were in HWE, meaning that the observed genotype frequencies of these SNPs did not deviate significantly from the frequencies expected under the equilibrium assumption.

The allelic distributions of *IL7RA* SNPs in the studied population were similar to those found in the European population from the Ensembl website (https://www.ensembl.org/). The linkage disequilibrium analysis among the *IL7RA* SNPs (**Supplementary Figure 1**) showed D' values were >0.90, suggesting that these SNPs tend to be inherited together. However, the r^2 values were <0.60, indicating that each SNP provides different information and is not strongly correlated.

We found a significant genetic association between the rs10491434 G allele and a higher likelihood of spontaneous control of HIV infection (**Figure 1**; $p=0.021$). In the adjusted OLR, carriers of the rs10491434 G were more likely to have spontaneous HIV infection control (adjusted odd ratio (aOR)=1.33; $p=0.023$) (**Table 2**). This finding was further validated through BCa Bootstrap validation ($p=0.024$).

Furthermore, as each SNP seems to provide different information, we analyze whether the combined effect of the tree SNP improved this association. Similarly, we observed that the *IL7RA* GCT haplotype, composed of the three SNPs (rs6897932, rs987106, and rs10491434), was associated with the control of untreated HIV infection (aOR=1.34; $p=0.050$) (**Table 2**). This association was also validated through BCa Bootstrap validation ($p=0.049$). The rs10491434 polymorphism and *IL7RA* GCT haplotype showed similar aOR values, with rs10491434 probably being responsible for the observed effect of the haplotype.

In silico analysis showed, using rSNPBase 3.1 software, the rs10491434 SNP was found to be located at hsa-circ-IL7R-antisense.3, a circular RNA (circRNA) regulatory element. Besides, the rs10491434 SNP has been annotated as a splicing quantitative trait locus (sQTL) in the GTEx Portal.

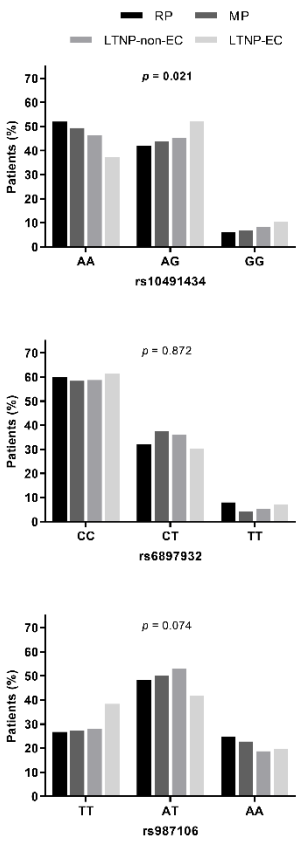

Figure 1. Distribution of *IL7RA* genotypes and spontaneous control of HIV infection. **Statistic:** The linear-by-linear association test among *IL7RA* genotypes and spontaneous control of HIV infection groups. **Abbreviations**: LTNP = long-term nonprogressors; LTNP-EC = LTNPs who were elite controllers; LTNP-non-EC = LTNPs who were not HIV elite controllers; MP = moderate progressors; PLWH = people living with HIV; RP = rapid progressors.

Table 2. Genetic association of *IL7RA* polymorphisms with spontaneous control of HIV infection in treatment-naïve PLWH.

		Unadjusted		**Adjusted**	
SNPs	**Freq.**	**OR (95%CI)**	***p*-value**	**aOR (95%CI)**	***p*-value**
Alleles					
rs10491434 G	30.5%	1.28 (1.02 - 1.61)	**0.032**	1.33 (1.04 - 1.69)	**0.023**
rs6897932 T	23.1%	0.98 (0.77 - 1240)	0.837	0.89 (0.69 – 1.13)	0.334
rs987106 A	46.2%	0.84 (0.69 - 1031)	0.095	0.89 (0.72 – 1.10)	0.279
Haplotypes					
ACA	45.9%	0.91 (0.78; 1.05)	0.193	0.97 (0.73; 1.28)	0.821
ATT	23.7%	0.97 (0.83; 1.13)	0.701	0.97 (0.73; 1.32)	0.887
GCT	29.0%	1.23 (1.06; 1.42)	**0.006**	1.34 (1.00; 1.79)	**0.050**

Statistics: Data were calculated by ordinal logistic regressions, which were adjusted by gender, age at HIV diagnosis, and injecting drug use (IDU) as the risk factor for HIV acquisition. *IL7RA* haplotypes comprised three SNPs (rs10491434, rs6897932, and rs987106). Significant differences are shown in bold.

Abbreviations: 95%CI = 95% confidence interval; aOR = adjusted odds ratio; HIV = human immunodeficiency virus; IL7RA = Interleukin 7 receptor alpha; OR = odds ratio; PLWH = people living with HIV.

Discussion

In this study, the *IL7RA* rs10491434 G allele was associated with spontaneous HIV infection control in a large cohort of ART-naïve PLWH. Besides, the *IL7RA* haplotype GCT, formed by the minor allele of the *IL7RA* rs10491434 and the major alleles of rs6897932 and rs987106, was associated with a higher likelihood of spontaneous HIV infection control.

Our findings are consistent with previous studies that found associations between *IL7RA* SNPs and the progression of AIDS in ART-naïve PLWH and $CD4^+$ T-cell recovery in patients receiving ART [6-12]. However, a previous study conducted by our group in the same cohort, Medrano *et al.* [13], did not find any significant associations between *IL7RA* SNPs and the clinical progression of AIDS (referring to RPs, MPs, and LTNPs) in ART-naïve PLWH. The key difference between the current and previous studies is the stratification of LTNPs into two groups according to elite control of HIV infection. This new analysis is based on the division of LTNPs into LTNP-EC and LTNP-non-EC, a fact that previously could not be done due to the lack of information. In the present study, we have obtained sufficient clinical information to classify LTNP individuals into two subgroups: LTNP-non-ECs and LTNP-ECs. This improved stratification provided valuable insights into this population's diversity, augmenting our analysis's significance.

Our data reveal that the *IL7RA* rs10491434 G allele impacts the control of untreated HIV infection, suggesting its functional role in HIV pathogenesis. A previous study has linked this allele to preventing rapid progression during HIV infection [14]. *In silico* analysis using rSNPBase 3.1 software revealed that rs10491434 is located in hsa-circ-IL7R-antisense.3, a circRNA known to be involved in controlling various biological and molecular processes, particularly gene regulation [15]. This suggests that the rs10491434 SNP might have a role in gene regulation through circRNA modifications. Our GTEx analysis found that the G allele of rs10491434 exhibits a lower intron-excision ratio than other alleles. This splicing alteration could result in higher levels of specific splicing isoforms and lower levels of others, potentially impacting the balance between transmembrane and soluble forms of *IL7RA* [16]. The G allele of rs10491434 has been associated with lower plasma levels of the soluble form of IL7RA (sIL7RA) in HIV-infected patients who have experienced immunological recovery after undergoing ART [17].

Moreover, *IL7RA* rs10491434 SNP in the 3' UTR can potentially influence methylation at nearby methylation-sensitive restriction enzyme-CpG sites. In this setting, Hutchinson *et al.* [18] showed that the rs10491434 G allele alters the methylation patterns at CpG sites near this SNP, resulting in changes in the expression levels of *IL7RA*. Thus, the rs10491434 G allele could increase *CD127 (IL7RA)* expression on T-cells. This alteration in *CD127* expression could potentially modify the natural progression of HIV infection and contribute to the spontaneous control of viral replication.

The increased *CD127 (IL7RA)* expression on T-cells plays a role in the host's defense against HIV [5]. In HIV-viremic patients, immune activation and depletion of $CD4^+$ T-cells contribute to a lower frequency of long-lived memory $CD4^+$ T-cells. Several studies have reported lower frequencies of $CD4^+CD127^+$ cells and downregulation of *CD127* expression on $CD4^+$ T-cells in ART-naïve patients who progress to AIDS [5]. This loss of $CD4^+CD127^+$ memory T-cells leads to decreased antigen-specific responses of $CD4^+$ T-cells against HIV and other chronic infections like cytomegalovirus and *Mycobacterium tuberculosis*. In contrast, LTNPs demonstrate higher frequencies of $CD4^+CD127^+$ cells and higher *CD127* expression levels on $CD4^+$ T-cells compared to MPs. Moreover, a decrease in *CD127* expression on $CD4^+$ T-cells is observed before the loss of HIV control in LTNPs [5]. Therefore, the data from our study suggest that the rs10491434 G allele may promote increased *IL7RA* expression, which is crucial for controlling untreated HIV infection.

Finally, it is essential to note that the *IL7RA* haplotype GCT, composed of *IL7RA* rs10491434, rs6897932, and rs987106, was associated with a higher likelihood of spontaneous HIV infection control. However, the GCT haplotype did not improve the association observed with the rs10491434 allele alone.

Our study has some limitations that must be considered when interpreting the obtained results. First, our study had a limited sample of participants in each group, which could have affected the statistical power and increased the potential for false positives. Second, the research was conducted using a

retrospective design, which may introduce biases and lack relevant data, such as the HIV genotype. Third, plasma *sIL7RA* and *CD127* expression on T-cells data were not available for assessing the concordance between them and the *IL7RA* rs10491434 genotype.

In conclusion, *IL7RA* rs10491434 G allele was associated with a higher likelihood of spontaneous HIV infection control, suggesting that *IL7RA* plays a role in pathogenesis, potentially influencing the natural course of infection and the ability to control viral replication.

Declarations

Ethics approval and consent to participate

This study was approved by the Research Ethics Committee of the Instituto de Salud Carlos III (CEI PI_2010-v3).

Consent for publication

Not applicable.

Availability of data and materials

The datasets analyzed during the current study may be available upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Supervision and visualization: SR, NR, and JMB.
Writing – original draft preparation: MAJS, DSC, and SR.
Writing – Review & Editing: AFR, IM, NR, and JMB.
All authors read and approved the final manuscript.

Authors' information (optional)

Not applicable.

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Appendix 1

Appendix 1. Centers and investigators involved in CoRIS:

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Hospital Universitari Mutua Terrassa (Terrassa)
David Dalmau, Marina Martinez, Angels Jaén, Mireia Cairó, Javier Martinez-Lacasa, Roser Font, Laura Gisbert.

Hospital Universitario de La Princesa (Madrid)
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Enrique Bernal, Antonia Alcaraz, Joaquín Bravo, Ángeles Muñoz, Cristina Tomás, Mónica Martínez, María del Carmen Villalba.

Hospital Nuevo San Cecilio (Granada)
Federico García, Clara Martínez, José Hernández, Leopoldo Muñoz Medina, Marta Álvarez, Natalia Chueca, David Vinuesa, Adolfo de Salazar, Ana Fuentes, Emilio Guirao, Laura Viñuela, Andrés Ruiz-Sancho, Francisco Anguita.

Centro Sanitario Sandoval (Madrid)
Jorge Del Romero, Montserrat Raposo, Carmen Rodríguez, Teresa Puerta, Juan Carlos Carrió, Mar Vera, Juan Ballesteros, Oskar Ayerdi, Begoña Baza, Eva Orviz.

Hospital Universitario Son Espases (Palma de Mallorca)
Melchor Riera, María Peñaranda, Mª Àngels Ribas, Antoni A. Campins, Mercedes Garcia-Gazalla, Francisco J Fanjul, Javier Murillas, Francisco Homar, Helem H Vilchez, Luisa Martin, Antoni Payeras.

Hospital Universitario Virgen de la Victoria (Málaga)
Jesús Santos, María López, Cristina Gómez, Isabel Viciana, Rosario Palacios.

Hospital Universitario Virgen del Rocío (Sevilla)
Luis Fernando López-Cortés, Nuria Espinosa, Cristina Roca, Silvia Llaves.

Hospital Universitario de Bellvitge (Hospitalet de Llobregat)
Juan Manuel Tiraboschi, Arkaitz Imaz, Ana Karina Silva, María Saumoy, Sofía Catalina Scévola.

Hospital Costa del Sol (Marbella)
Julián Olalla, María José Sánchez, Javier Pérez, Alfonso del Arco, Javier de la Torre, José Luis Prada.

Hospital General Universitario Santa Lucía (Cartagena)
Onofre Juan Martínez, Lorena Martínez, Francisco Jesús Vera, Josefina García, Begoña Alcaraz, Antonio Jesús Sánchez Guirao.

Complejo Hospitalario Universitario a Coruña (CHUAC) (A Coruña)
Álvaro Mena, Ángeles Castro, Berta Pernas, Pilar Vázquez, Soledad López.

Hospital Universitario Virgen de la Arrixaca (El Palmar)
Carlos Galera, Marian Fernández, Helena Albendin, Antonia Castillo, Asunción Iborra, Antonio Moreno, M Angustias Merlos, Asunción Vidal.

Hospital Universitario Infanta Sofía (San Sebastián de los Reyes)
Inés Suarez-García, Eduardo Malmierca, Patricia González-Ruano, Mª Pilar Ruiz, José Francisco Pascual, Luz Balsalobre, Ángela Somodevilla.

Hospital Universitario Príncipe de Asturias (Alcalá de Henares)
José Sanz, Alberto Arranz, Cristina Hernández, María Novella.

Hospital Clínico Universitario de Valencia (Valencia)
María José Galindo, Sandra Pérez Gómez, Ana Ferrer.

Hospital Reina Sofía (Córdoba)
Antonio Rivero Román, Inma Ruíz, Antonio Rivero Juárez, Pedro López, Isabel Machuca, Mario Frías, Ángela Camacho, Ignacio Pérez, Diana Corona.

Hospital Universitario Severo Ochoa (Leganés)
Miguel Cervero, Rafael Torres.

Nuestra Señora de Valme (Sevilla)
Juan Macías Sánchez, Pilar Rincón, Luis Miguel Real, Anais Corma, Marta Fernández, Alejandro González-Serna.

Hospital Álvaro Cunqueiro (Vigo)
Eva Poveda, Alexandre Pérez, Luis Morano, Celia Miralles, Antonio Ocampo, Guillermo Pousada, Lucía Patiño.

Appendix 2

Appendix 2. Centers involved in Long Term Nonprogressors (LTNPs) cohort

C. Sandoval - Madrid
H. 12 de Octubre - Madrid
H. Arnau de Vilanova - Lleida
H. Asturias
H. Bellvitge - Barcelona
H. Castellón
H. Clínic - Barcelona
H. Donostia - San Sebastián
H. Elche - Alicante
H. Germans Trias i Pujol - Badalona
H. Gregorio Marañón - Madrid
H. Joan XXIII - Tarragona
H. La Fe - Valencia
H. La Paz/Carlos III - Madrid
H. La Princesa - Madrid
H. Navarra - Pamplona
H. Parc Taulí- Sabadell
H. Ramón y Cajal - Madrid
H. San Cecilio - Granada
H. San Pedro - Logroño
H. Son Dureta - Mallorca
H. Virgen del Rocío – Sevilla

Supplementary Materials

Supplementary Table 1. STrengthening the REporting of Genetic Association studies (STREGA) reporting recommendations, extended from STROBE Statement

Item	Item no	STROBE Guideline	Extension for Genetic Association Studies (STREGA)	Page no
Title and Abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract.		1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found.		3
Introduction				
Background rationale	2	Explain the scientific background and rationale for the investigation being reported.		4-5
Objectives	3	State specific objectives, including any pre-specified hypotheses	***State if the study is the first report of a genetic association, a replication effort, or both.***	4-5
Methods				
Study design	4	Present key elements of study design early in the paper.		6
Setting	5	Describe the setting, locations and relevant dates, including periods of recruitment, exposure, follow-up and data collection.		6
Participants	6	(a) **Cohort study –** Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up. **Case–control study –** Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls. **Cross-sectional study –** Give the eligibility criteria, and the sources and methods of selection of participants.	***Give information on the criteria and methods for selection of subsets of participants from a larger study, when relevant.***	6
		(b) Cohort study – For matched studies, give matching criteria and number of exposed and unexposed. **Case–control study –** For matched studies, give matching criteria and the number of controls per case.		
Variables	7	(a) Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	***(b) Clearly define genetic exposures (genetic variants) using a widely –used nomenclature system. Identify variables likely to be associated with population stratification (confounding by ethnic origin).***	6-7
Data sources measurement	8*	(a) For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group.	***(b) Describe laboratory methods, including source and storage of DNA, genotyping methods and platforms (including the allele calling algorithm used, and its version), error rates and call rates. State the laboratory /centre where genotyping was done. Describe comparability of laboratory methods if there is more than one group. Specify whether genotypes were assigned using all of the data from the study simultaneously or in***	6-7

			smaller batches.	
Bias	9	(a) Describe any efforts to address potential sources of bias.	***(b) For quantitative outcome variables, specify if any investigation of potential bias resulting from pharmacotherapy was undertaken. If relevant, describe the nature and magnitude of the potential bias, and explain what approach was used to deal with this.***	7
Study size	10	Explain how the study size was arrived at.		6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why.	***If applicable, describe how effects of treatment were dealt with.***	6-7
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding.	***State software version used and options (or settings) chosen.***	7
		(b) Describe any methods used to examine subgroups and interactions.		7
		(c) Explain how missing data were addressed.		
		(d) **Cohort study –** If applicable, explain how loss to follow-up was addressed. **Case–control study –** If applicable, explain how matching of cases and controls was addressed. **Cross-sectional study –** If applicable, describe analytical methods taking account of sampling strategy.		
		(e) Describe any sensitivity analyses.		
			(f) State whether Hardy-Weinberg equilibrium was considered and, if so, how.	7
			(g) Describe any methods used for inferring genotypes or haplotypes.	7
			(h) Describe any methods used to assess or address population stratification.	7
			(i) Describe any methods used to address multiple comparisons or to control risk of false positive findings.	7
			(j) Describe any methods used to address and correct for relatedness among subjects.	7
Results				
Participants	13*	(a) Report the numbers of individuals at each stage of the study – e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up and analysed.	***Report numbers of individuals in whom genotyping was attempted and numbers of individuals in whom genotyping was successful.***	8
		(b) Give reasons for non-participation at each stage.		
		(c) Consider use of a flow diagram.		
Descriptive data	14*	(a) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders.	***Consider giving information by genotype.***	8
		(b) Indicate the number of participants with missing data for each variable of interest.		
		(c) **Cohort study –** Summarize follow-up time, e.g. average and total amount.		

Outcome data	15*	**Cohort study –** Report numbers of outcome events or summary measures over time.	***Report outcomes (phenotypes) for each genotype category over time***	8
		Case–control study – Report numbers in each exposure category, or summary measures of exposure.	***Report numbers in each genotype category***	
		Cross-sectional study – Report numbers of outcome events or summary measures.	***Report outcomes (phenotypes) for each genotype category***	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g. 95% confidence intervals). Make clear which confounders were adjusted for and why they were included.		8
		(b) Report category boundaries when continuous variables were categorized.		
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period.		
			(d) Report results of any adjustments for multiple comparisons.	
Other analyses	17	(a) Report other analyses done – e.g. analyses of subgroups and interactions, and sensitivity analyses.		8
			(b) If numerous genetic exposures (genetic variants) were examined, summarize results from all analyses undertaken.	
			(c) If detailed results are available elsewhere, state how they can be accessed.	
Discussion				
Key results	18	Summarize key results with reference to study objectives.		9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.		10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.		9-10
Generalizability	21	Discuss the generalizability (external validity) of the study results.		9-10
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based.		11

STROBE: STtrengthening the Reporting of Observational Studies in Epidemiology

*Give information separately for cases and controls in case–control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Supplementary Table 2. Allele counts of *IL7RA* polymorphisms and HWE analysis data in PLWH.

rs10491434	**A**	**G**	**χ^2**	***p*-value**
RP	219 (73.0%)	81 (27.0%)	0.643	0.423
MP	476 (71.3%)	192 (28.7%)	1.506	0.220
LTNP-non-EC	134 (69.1%)	60 (30.9%)	0.369	0.543
LTNP-EC	109 (63.4%)	63 (36.6%)	1.390	0.238
All PLWH	938 (70.3%)	396 (29.7%)	3.289	0.078
rs6897932	**C**	**T**	**χ^2**	***p*-value**
RP	228 (76.0%)	72 (24.0%)	2.262	0.133
MP	515 (77.1%)	153 (22.9%)	1.191	0.275
LTNP-non-EC	149 (76.8%)	45 (23.2%)	0.016	0.901
LTNP-EC	132 (76.7%)	40 (23.3%)	2.014	0.156
All PLWH	1024 (76.8%)	310 (23.2%)	0.185	0.665
rs987106	**T**	**A**	**χ^2**	***p*-value**
RP	152 (51.0%)	146 (49.0%)	0.164	0.686
MP	349 (52.2%)	319 (47.8%)	0.001	0.971
LTNP-non-EC	105 (54.7%)	87 (45.3%)	0.497	0.481
LTNP-EC	102 (59.3%)	70 (40.7%)	1.516	0.218
All PLWH	708 (53.2%)	622 (46.8%)	0.158	0.697

Statistic: *P*-values were calculated by chi-squared.

Abbreviations: HWE = Hardy-Weinberg equilibrium; LTNP = long-term nonprogressors; LTNP-EC = LTNPs who were elite controllers; LTNP-non-EC = LTNPs who were not HIV elite controllers; MP = moderate progressors; PLWH = people living with HIV; RP = rapid progressors.

Supplementary Figure 1. *IL-7RA* linkage disequilibrium (LD) maps. Pairwise D' **(A)** and r^2 **(B)** between 3 SNPs located at three regulatory regions from *IL-7RA* are represented. The location of SNPs is indicated on top. The diagonal represents a SNP and the square represents a pairwise comparison between two SNPs, indicating the magnitude of LD (D' and r^2). D' and r^2 range from 0 (absence) to 100 (complete). The red and grey color intensity decreases with decreasing D´ and r^2 values, respectively. **Abbreviations**: D´ = proportion of the possible LD that was present between two SNPs; HIV = human immunodeficiency virus; IL-7RA = Interleukin-7 receptor subunit alpha; LD = linkage disequilibrium; r^2 = square of the correlation coefficient; SNP = single nucleotide polymorphism.