HCV-GT1a Spatiotemporal Distribution, Epidemic History and NS5A Resistance in Spain

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Background

- Any successful strategy to prevent and control HCV infection requires an understanding of the epidemic behavior of the virus.
- The presence of NS5A resistance-associated substitutions (RASs) may compromise the efficacy of NS5A inhibitors[1].
- In Spain, the HCV seroprevalence is 1.1%[2] and GT1a represents almost 40% of the GT1 infections. Until October 2018, 117,452 patients had access to DAAs through the national plan of universal treatment[3].

Objective

- To characterize the origin, epidemic history, transmission dynamics and diversity of HCV-GT1a in Spain.

Patients & Methods

- Nationwide cross-sectional survey of DAAs-naïve patients chronically-infected with G1a attended in 84 hospitals during 2014-2015.
- HCV population sequencing was used to identify relevant RASs to NS5A inhibitors.
- Phylogenetic analysis was used for subtyping and transmission cluster identification. GT1a lineages (clade I and II) were confirmed by geno2pheno[HCV]. Bayesian methods were used to reconstruct the epidemic history of GT1a.

Results

- 588 patients were included, 80.8% men, 51.0% HCV-monoinfected and 49.0% HIV/HCV-coinfected (Tab.1).
- Clade II was more prevalent than clade I (82.7% vs. 17.3%; P<0.0001) and was more represented in HCV-monoinfected than in HIV/HCV-coinfected patients (87.0% vs. 78.1%; P=0.004).
- Twenty-three transmission pairs and 3 transmission clusters (including >2 individuals) were identified (Fig.1A), representing 9.5% (n=56/588) of the study population

Table 1. Baseline characteristics of the patients.

Characteristics	All patients	HIV status		*P*-values
		HCV-monoinfected	HIV/HCV-coinfected	
N. (%)	588	300 (51.0%)	288 (49.0%)	
Age, years (median, IQR)	50 (47;53)	51 (47;55)	49 (46;53)	<0.001
Sex, men (n, %)	475 (80.8)	236 (78.7)	239 (83.0)	0.184
HCV clade (n, %)				
I	102 (17.3)	39 (13.0)	63 (21.9)	0.004
II	486 (82.7)	261 (87.0)	225 (78.1)	
RASs (n, %)	N = 58	N=28	N=30	
K24R	4 (0.7)	2 (0.7)	2 (0.7)	--
M28A/T/V	22 (3.7)	11 (3.7)	11 (3.8)	--
Q30E/H/R	12 (2.0)	7 (2.3)	5 (1.7)	--
L31M	4 (0.7)	1 (0.3)	3 (1.0)	--
H58D	2 (0.3)	--	2 (0.7)	--
Y93C/F/H/N	14 (2.4)	7 (2.3)	7 (2.4)	--
Double mutations (n, %)	7 (1.2)	5 (1.7)	2 (0.7)	--
Patients with reduced susceptibility to DAAs, (n, %)	50 (8.5)	22 (7.3)	28 (9.7)	0.299
Resistance to DAAs (n, %)				
DACLATASVIR	32 (5.4)	12 (4.0)	20 (6.9)	0.116
ELBASVIR	31 (5.3)	11 (3.7)	20 (6.9)	0.075
LEDIPASVIR	35 (6.0)	13 (4.3)	22 (7.6)	0.090
OMBITASVIR	41 (7.0)	20 (6.7)	21 (7.3)	0.766
PIBRENTASVIR	8 (1.4)	5 (1.7)	3 (1.0)	0.725
VELPATASVIR	20 (3.4)	6 (2.0)	14 (4.9)	0.069
1 DAAs	18 (3.1)	10 (3.3)	8 (2.8)	--
2 DAAs	--	--	--	--
3 DAAs	2 (0.3)	1 (0.3)	1 (0.3)	--
4 DAAs	15 (2.6)	6 (2.0)	9 (3.1)	--
5 DAAs	7 (1.2)	--	7 (2.4)	--
6 DAAs	8 (1.4)	5 (1.7)	3 (1.0)	--
Possibly resistant	12 (2.0)	5 (1.7)	7 (2.4)	--

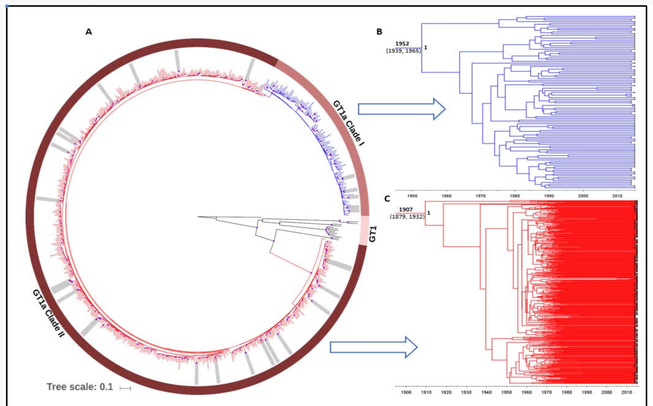

Figure 1: Phylogenetic tree reconstruction of GT1a strains circulating in Spain. A) A maximum likelihood tree produced under the GTR+Γ with 1000 bootstrap replicates segregates the GT1a into two clades, clade I (blue) and clade II (red). Bootstrap supports ≥70% are depicted as purple filled circles at the nodes. B) and C) Maximum clade credibility trees for each of the clades, clade I (blue) and clade II (red) are presented with the mean tMRCA (95% HPD interval) estimates in calendar years.

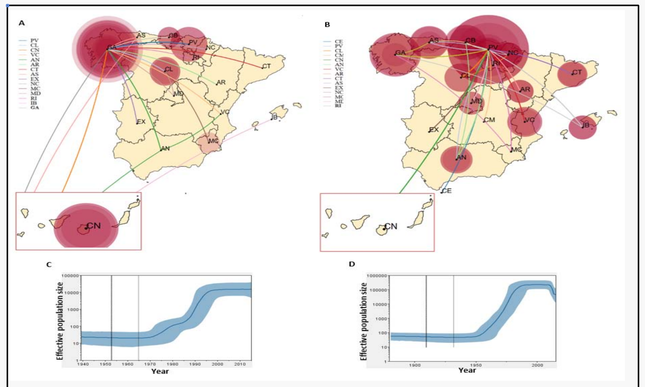

Figure 2: Spatiotemporal distribution of the GT1a epidemic in Spain. The geographic migrations of GT1a strains for clade I (A.) and clade II (B.) amongst the different autonomous regions of Spain (AN - Andalusia; AR - Aragon; AS - Asturias; BC - Basque Country; BI - Balearic Islands; CB - Cantabria; CE - Ceuta; CL - Castile Leon; CM - Castile La Mancha; CN - Canary Islands; CT - Cataluña; EX - Extremadura; GA - Galicia; MC - Murcia; MD - Madrid; NC - Navarra; RI - La Rioja; VC - Valencia). Inward migrations are indicated with colored lines and increment in migration counts are colored in red circles. The Bayesian skyline plots (BSP) for GT1a clade I (C) and GT1a clade II (D) showing the epidemic growth over time are presented.

- The transmission pairs and clusters predominantly comprised clade II viruses (80.8%, n=21/26) and occurred intra-regionally (61.5%, n=16/26). Fifteen transmission pairs and three clusters were made up of men only.
- Clade II was older than clade I (estimated origin in 1907 vs. 1952) and its exponential epidemic growth started earlier (1950s vs. 1970's) (Fig.1B-C, Fig.2C-D).
- Clade II epidemic dissemination was more successful than clade I. However, clade II epidemic is now waning whereas clade I epidemic is still ongoing and is still mostly concentrated in the North of Spain and Canary Islands (Fig.2C-D).
- 58 single RASs were identified, being the most common M28A/T/V (37.9%), Y93C/F/H/N (24.1%) and Q30E/H/R (20.7%). A moderate level (10%) of baseline RASs was observed, with thirteen regions showing an intermediate level (5-15%) and one a high level (20%) (Fig.3).

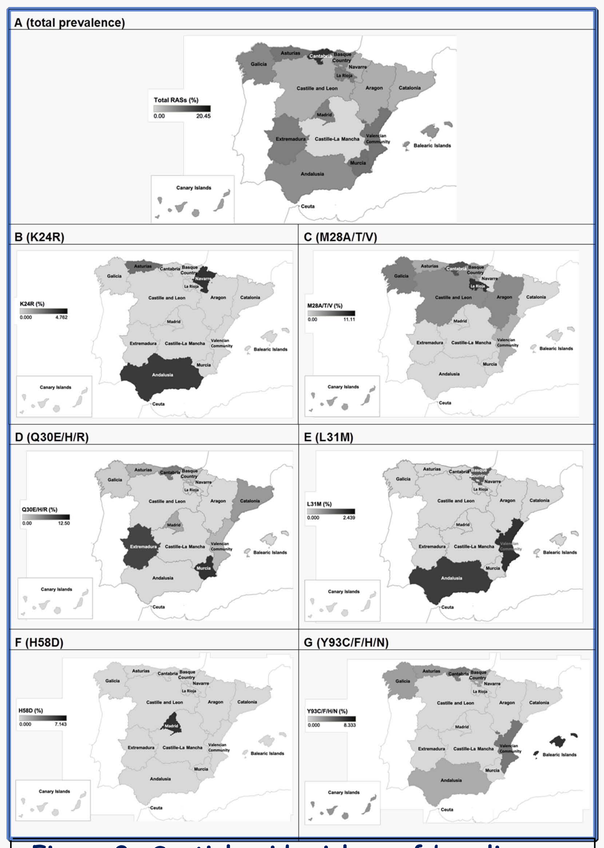

Figure 3. Spatial epidemiology of baseline RASs at the HCV NS5A gene.

Conclusions Current GT1a epidemic in Spain is mainly driven by clade I viruses which seem to have different spreading routes relative to clade II. With the exception of Cantabria, viruses bearing RASs to NS5A-DAAs were present at low to intermediate level in HCV infected patients at baseline.

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References

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