Appendix S1

SUPPLEMENTARY MATERIAL AND METHODS

Linkage disequilibrium analysis and mutation age estimation

The following microsatellite markers were chosen: D6S2446, D6S497, D6S439, D6S1548, D6S943, D6S2427, D6S1607 and D6S400 for TMRCA and mutation age estimations. Forward PCR primers were labelled with either FAM or HEX fluorescent dyes (Sigma-Genosys Ltd. Cambridgeshire, UK), DNA was specifically amplified by PCR with the labelled primers using 5 PRIME MasterMix (5Prime, Eppendorf, Hamburg, Germany).The amplification products were separated by capillary electrophoresis on an ABI3730xL sequencer and analyzed with GeneMapper v4 Software (Applied Biosystems, Foster City, CA, USA). All reactions were performed according to the manufacturer's protocols. The phase of the haplotype was inferred using PHASE software (http://stephenslab.uchicago.edu/phase), and then, these phased haplotypes were used to calculate the age of the mutation and the time to the most recent common ancestor (TMRCA).

The age of TMRCA was calculated by employing two types of Linkage Disequilibrium (LD) methods: (*i*) Three single marker methods proposed by Bergman et al. (S1), Lander & Botstein (S2) and Labuda et al. (S3), respectively, applying the correction proposed by Labuda et al. (S4) for a growth rate of 0.0748. These methods are based on the fact that the mutation will be in LD with nearby marker alleles at polymorphic loci, and decay of this LD over time (through recombination) provides information about the TMRCA age. (*ii*) The gamma method published by Gandolfo et al. (S5) based on the idea that the size of the common haplotype region of the chromosome (genetic length of ancestral haplotypes) can be related to the number of generations that link the patients to their most recent common ancestor.

Single marker estimates were summarized by the mean of the results across 7 out of 8 available markers (D6S439 was not considered because it was not informative for the calculations since the same allele was present in all patients).

The most frequent allele outside the common region was considered as the founder allele, hence the conserved haplotype. The physical distances were converted into centimorgans (cM) assuming a sex averaged recombination rate of 1.3 cM equal to 1 Mb, which was calculated by using the estimates of recombination rates across the studied region according to deCODE genetic map available in the UCSC database (S6). Haldane's mapping function (S7) was used for translation of map distances into recombination frequencies. For further details see **STable I**.

The time at which the c.417_418delinsTC mutation first occurred was also estimated by using DMLE+ (http://www.dmle.org). This program takes into consideration map distances between the markers and the mutation site, haplotype data from affected patients and controls, the proportion of population sampled (f=2.95E-04. f=2.08E-04. f=2.49E-04) and the population growth rate (r=0.0748).

There are few data on the epidemiology of ARCI in Spain due to the lack of official reference centers for the disease and complete data from an official patient registry; consequently, it is not possible to know the exact number of patients diagnosed with ARCI. Therefore, we considered 3 different values of *n* (total number of patients) to calculate the proportion of population sampled (f): 144 which is the actual number of ARCI cases identified in Spain by Hernández-Martín et al. (S8) in 2011, 294 which is the estimated number of patients they have estimated in this same study, and the mean of both, 219.

STable SI. Linkage disequilibrium analysis

Markers	Haldane (θ)	Founder allele	PD	PN	TMRCA in generations		
					Bergman et al. (S1)	Lander & Botstein (S2)	Labuda et al. (S4)
D6S2446	0.0452	11	0.3333	0.1350	38	15	31
D6S497	0.0352	5	0.6666	0.3681	30	41	21
D6S1548	0.0164	5	0.6666	0.4724	80	87	44
D6S943	0.0239	2	0.6666	0.4540	54	61	32
D6S2427	0.0401	5	0.4444	0.2699	43	22	28
D6S1607	0.0525	6	0.4444	0.2086	27	15	20
D6S400	0.0711	1	0.6666	0.6135	27	16	6
				Mean	43 (29–57)	37 (16–57)	26 (17–35)

θ: recombination fraction according to Haldane mapping function; PD: frequency of the founder allele in the normal population; PN: frequency of the founder allele in the disease population; TMRCA: time to the most recent common ancestor.

SUPPLEMENTARY REFERENCES

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