

Celtic Origin of the C282Y Mutation of Hemochromatosis

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ABSTRACT : The C282Y mutation in the *HFE* gene is the main mutation causing hemochromatosis, and C282Y frequencies have been reported for various European populations. The aim of this review is to compile the Y allele frequencies of the C282Y mutation for twenty European populations. The most elevated value (6.88%) is observed in residual Celtic populations in UK and France, in accordance to the hypothesis of Simon et al. concerning a Celtic origin of the hereditary hemochromatosis mutation.

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Genetic hemochromatosis is an autosomal recessive disorder characterized by iron overload and a variety of clinical manifestations, such as arthropathy and liver cirrhosis. In Northern European populations, as many as 1 in 300 individuals are affected. Simon et al. (1) showed that the gene responsible for genetic hemochromatosis mapped close to the major histocompatibility complex locus HLA-A on chromosome 6p. Most of genetic hemochromatosis chromosomes carry an extended "ancestral" haplotype of chromosome 6 microsatellite marker alleles (including HLA-A3), reflecting the haplotype of the founder mutation (2). Feder et al. (3) reported a candidate gene for hereditary hemochromatosis, now designated as *HFE*. The role of this gene in hemochromatosis is supported by the high frequency of a G→A transition at nucleotide 845 in the open reading frame of the gene in patients (3), a mutation that predicts substitution of the cysteine residue 282 by a tyrosine (C282Y) in the

α3 domain of the molecule. This main mutation has been found in a very high proportion of the patients tested so far in the United States (3,4), in Australia (5) and in France (6).

Merryweather-Clarke et al. (7) reported C282Y allele frequencies in a world-wide study of 2978 people (5956 chromosomes 6); they found a mean allele frequency of 1.9%, the highest frequency being 10% in Irish chromosomes. In that study C282Y was most frequent in Northern European populations, and absent in African, Asian and native Australian chromosomes. We report here a compilation of recently published studies concerning the *HFE* codon 282 (C/Y) in European populations in control individuals. In most of these studies, including our own (8), extraction of DNA and PCR amplification was performed as previously described in (6): the PCR product has a constant *RsaI* site producing two fragments of 247 and 140 bp in the normal C allele, and another *RsaI* site in

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the mutant Y allele generates two fragments as 111 and 29 bp cleavage of the 140 bp fragment.

The country of origin of the DNA samples is shown in Table 1. Twenty European populations were reported (one Algerian population was added), comprising a total of 2823 unrelated individuals (5646 chromosomes 6). The C282Y allele was absent in Algeria (21), and the highest European frequency was 8.50% in chromosomes from UK towns of Norfolk and Norwich (11). The lower values were 1.00% for the Italian

population (19), 1.31% for the Ashkenazi Jews (13) and 1.63% for the French Basques in Biarritz (8). Low values (1.99% and 1.76%, respectively) of the Y allele were also observed for Saamis in Sweden and for Mordvinians in Russia (9). All the 20 European populations reported are in Hardy-Weinberg equilibrium. In the whole, allelic Y frequency = 4.36%, a global value also in Hardy-Weinberg equilibrium ($\chi^2 = 3.477$ at $\alpha = 5\%$).

Table 1. HFE (*RsaI*) Genotypes and Y Allele Frequencies in 20 European Populations and in Algeria (*N* are the numbers of individuals tested in each population).

Country	Town (region/ethnic group)	Degree Latitude North	<i>N</i>	HFE Genotypes			Y Frequency	References
				CC	CY	YY		
Sweden	Saamis		151	145	6	0	0.019	Beckman et al. (9)
	Umea	64	206	178	25	3	0.075	"
Finland	North-East	66	173	157	14	2	0.052	"
Russia	Mordvinians	58	85	82	3	0	0.017	"
Britain	South Wales	51.5	101	90	10	1	0.059	The UK Haemochromatosis Consortium (10)
	Norfolk and Norwich	52.5	200	167	32	1	0.085	Willis et al. (11)
Germany	Frankfurt	50	153	145	8	0	0.026	Gottschalk et al. (12)
	Ashkenazi Jews		381	371	10	0	0.013	Beutler and Gelbart (13)
France	Rennes	48	139	131	8	0	0.028	Jouanolle et al. (14)
	Brest	48.5	163	139	24	0	0.073	Mura et al. (15)
	Finistère sud	48	254	208	44	2	0.094	Jézéquel et al. (16)
	Brittany	48.5	62	55	7	0	0.056	Mercier et al. (8)
	Paris	49	126	116	10	0	0.039	"
	Biarritz	43.5	92	89	3	0	0.016	"
	Perpignan	42.5	76	73	3	0	0.019	"
	Grasse	43.5	90	86	4	0	0.022	"
	Toulouse	43.5	95	87	8	0	0.042	Borot et al. (17)
Montpellier	43.5	60	56	4	0	0.033	Martinez et al. (18)	
Portugal	North	41	71	67	4	0	0.028	Porto et al. (19)
Italy	North	45.5	50	49	1	0	0.010	Carella et al. (20)
Algeria	Mozabites	35	95	95	0	0	0.000	Roth et al. (21)
Total			2823	2586	228	9	0.043	

Table 2. Genotype and Y allele Frequencies (in %) for Celts, Nordics, Anglo-Saxons, peoples from South of Europe, and Russia (for each genotype expected values are indicated in parenthesis).

	Genotypes						χ^2	Significance
	Populations*	N	CC	CY	YY	Y frequency (%)		
Celts	5 + 9 – 12	719	623 (658)	93 (60)	3 (1)	6.88	24.01	$P < 0.001$
Nordics	2 + 3	379	335 (347)	39 (31)	5 (1)	6.46	18.48	$P < 0.001$
Anglo-Saxons	6 + 7	353	312 (323)	40 (29)	1 (1)	5.95	4.55	NS
South of Europe	14 – 20	534	507 (488)	27 (45)	0 (1)	2.53	8.94	$P < 0.02$
Russia	4	85	82 (78)	3 (7)	0 (0)	1.76	2.49	NS

* see Figure 2

To ascertain a trend in variation of allele frequencies from north to south Europe, we plotted C282Y allele frequencies against degrees of latitude north (reported in Table 1 for each population, Saamis and Ashkenazi Jews excepted). The equation of correlation is $y = 1.73 \cdot 10^{-3}x - 0.043$ (Figure 1), with a North-South decreasing cline for C282Y frequencies and a significant ($p < 0.05$) correlation coefficient ($r = 0.49$).

It was initially hypothesized that the genetic mutation leading to hemochromatosis originally occurred in the Celtic people (22). The Celts emerged at around 1000 B.C. in Europe north of the Alps (23) and they colonized Central, South-Western and South-Central Europe. Culture, language and technology spread rapidly over most of the continent, reaching Ireland before 100 B.C. The term "Celtic" is used here to describe Irish, Scottish, Welsh or Bretons' genes (24,25,26), but without genetic substantiation.

If we add together all the populations reported here and of Celtic origin (population 5 from South Wales, and French populations 9, 10, 11 and 12 from Rennes, Brest, Finistère sud and Brittany, see Figure 2), the global frequency of the C282Y mutation in Celtic populations is 6.88%, the highest value obtained from ethnically homogeneous areas reported in Figure 2 and in

Table 2. The mean Y frequency in celtic populations is significantly greater ($p < 0.001$) than the mean value for all the populations reported in Table 1 ($\chi^2 = 24.01$, > the 5.99 limit value). Table 2 shows that Nordics have also a significantly higher value of C282Y frequency ($\chi^2 = 18.48$, $p < 0.001$). Anglo-Saxons and Russians do not differ significantly from the mean value of Y frequencies. In the populations from the south of Europe the Y allele frequency is significantly lower ($p < 0.02$) than the mean value. The Y allele frequency is significantly higher ($\chi^2 = 5.385 > 3.841$; $p < 0.03$) in Celts compared to Anglo-Saxons, but the frequencies are not significantly different ($\chi^2 = 0.67$) between Nordics and Celts.

In the French Basque population studied (8), the 1.6% frequency for the C282Y allele detected falls into the Southern European range. Historically it was suggested that the mesolithic settlers of western Europe could have mixed with Neolithics to give rise to present day Europeans, and that a few groups of mesolithic people in the Pyrenean region could have remained sheltered from subsequent invasions, giving rise to the present day Basques (27). The low frequency of the C282Y allele in Basques confirms that it is highly improbable that this mutation is of ancient European origin.

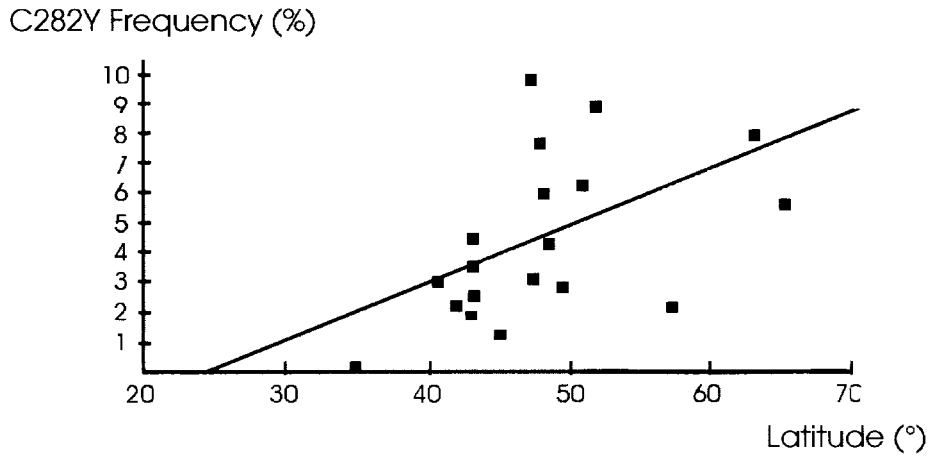


Figure 1. Correlation between C282Y Frequencies (in %) and Degrees of Latitude North for the 19 European Populations Reported in Table 1 ($r = 0.49, p < 0.05$).

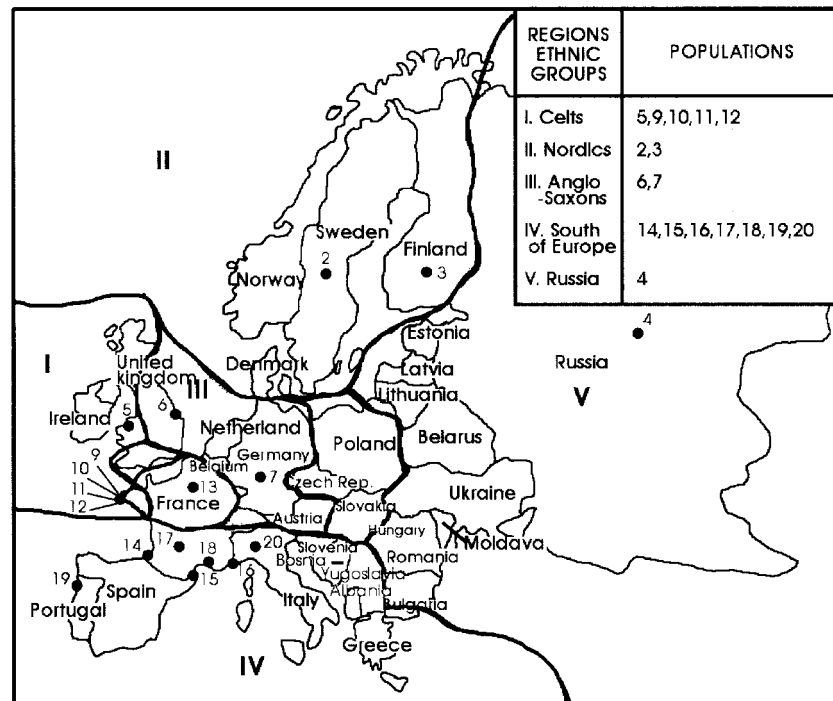


Figure 2. Map of Europe Arbitrary Subdivided into Five Geographic Regions (the nomenclature used in this figure is not the same that the nomenclature used in Smith et al. (28))

Since Simon et al. originally postulated a celtic origin for hemochromatosis in 1980 (22), this hypothesis was reported as verified at least once in the literature (28). The recent availability of the candidate gene for hereditary hemochromatosis by Feder et al. (3) and the description of the C282Y mutation, the main mutation involved, might help to confirm the Celtic origin of the disease. The Merryweather-Clarke et al. publication (7) established that the C282Y mutation was most prevalent in Northern European populations, the highest allele frequencies being found in the UK and Danes. We extend these findings in the present study, based on reports more recently published concerning a total of 2823 European controls, and show that C282Y allele frequencies are distributed among a decreasing cline from north to south of Europe. A peak of allele Y frequencies is effectively observed in residual populations of Celtic origin that actually live in UK and France. That sort of geographical distribution indicates the possible existence in the past of a Celtic "gene center". Further dissemination during historical times of the corresponding mutation from this centre of origin probably occurs with the celtic migrations in Europe (23) during the Iron age.

By constructing a haplotype phylogeny for chromosomes carrying the hemochromatosis gene (29,30), it was recently estimated that the C282Y mutation first appeared about 60-70 generations ago; assuming a mean generation time of 20 years, this time equates to 600-800 years AD.

The high prevalence of hemochromatosis may be the result of selective forces. Whereas hemochromatosis is a disorder of iron excess, it may confer a selective advantage in time of nutritional deficit. If iron were a limiting resource due to diet, hemochromatosis may be considered to confer an heterozygous advantage (protecting females of child-bearing age from iron deficiency), which can result from the physiologic blood loss of menstruation and pregnancy (30).

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