



# Was the C282Y mutation an Irish Gaelic mutation that the Vikings help disseminate?

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**Summary** The C282Y mutation is held to have arisen in either a Celtic or a Viking ancestor some 60 generations ago. While the Scandinavians have a high frequency of C282Y, the Irish have the highest frequency of the C282Y mutation in the world. However testing of the Irish people for C282Y has been patchy. The true frequency of the C282Y mutation in Ireland and specifically in the relatively isolated western province of Connaught is unknown. Establishment of the C282Y frequency in the Irish male population of Connaught with traditional Irish surnames, a group which has a virtual fixation for Y chromosome R1b3, could help establish C282Y as an Irish mutation. Elucidation of greater C282Y haplotype diversity for the Irish as opposed to the Scandinavians would indicate the Irish as the likely source population for C282Y. Taken together, linking of C282Y to the Irish Gaelic male population of Connaught and establishment of an Irish origin of the C282Y mutation would point to dissemination of the C282Y mutation by Viking raiders and colonizers. © 2006 Elsevier Ltd. All rights reserved.

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## Introduction

C282Y homozygous hemochromatosis is the most common form of hemochromatosis. It is a disorder of northern Europeans. There has been debate as to whether the C282Y mutation originated with the Celts or the Vikings [1]. There is also the previously unconsidered possibility that the mutation originated in Gaelic Ireland and that Viking raids, slave taking and colonizations as well as Gaelic migrations help spread it throughout Europe. Refinements that have occurred in genetic evaluation techniques such as Y chromosome and mito-

chondrial DNA analysis may help elucidate this question. Y chromosomes are passed in the male line while mitochondrial DNA is passed in the female line.

## Origin and distribution of the C282Y mutation

The age of the C282Y mutation has been variously estimated. It may have occurred as a unique event in mainland Europe before 4000 BC [2] or be some 60–70 generations old as estimated by linkage disequilibrium analysis [3]. The 60–70 generation theory is now the favored option. This gives an estimate of approximate age of 1200–2100 years to the C282Y mutation if a generation is assumed

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to be 20–30 years. The first Viking raids of Ireland occurred before 800 AD. This timing opens the possibility of either a Viking or an Irish Gaelic mutation.

The highest allele frequency of C282Y is in Ireland and has been reported at 14% in the Dublin area [4] which was a Viking settlement. However there is testing done outside of the Dublin area which points to the possibility of an even higher frequency in the rest of Ireland [5]. Overall the highest allele frequencies for C282Y are in the Celtic populations of Ireland, France and the United Kingdom [6]. Elevated frequencies are also observed in Scandinavia [6] and in the Faroe Islands [7] and Iceland [8]. The inhabitants of the Faroe Islands and Iceland are of mixed Celtic and Viking descent. The Basques provide a clue as to the origin of C282Y, for the French Basques especially have a low frequency of the C282Y mutation [6,8–11].

A line of increasing allele frequency for C282Y can be drawn from Turkey to the north west of Europe peaking in the west of Ireland [12]. Also the allele frequency of C282Y decreases from northern to southern Europe. While the highest frequencies are in northern Europe the lowest frequencies are in populations in southern Europe and the Mediterranean [6]. An intermediate frequency is recognized in central Europe [3]. The highest allele frequencies for C282Y are reported in populations living along the European coastlines. These figures imply that not one single migration spread the C282Y mutation in Europe.

### The C282Y mutation in the North Atlantic Islands

The Islands of the north Atlantic were settled by Scandinavians or Scandinavians with Celtic women. The Orkney and Shetland Islands were Viking age settlements. Recent genetic evidence using Y chromosomal and mitochondrial DNA variation points to an equal contribution from Scandinavian males and females to the settlement of Orkney and Shetland. Overall Scandinavian ancestry was estimated at 44% of Shetland and 30% for Orkney. Family based Scandinavian settlement of Orkney and Shetland during the Viking period has been proposed [13]. No allelic frequency for C282Y is currently available for Orkney and Shetland.

While Scandinavian families settled Orkney and Shetland, Vikings venturing further a field were more likely to interbreed with non-Scandinavian women. Icelandic lore holds that Iceland was settled by Scandinavian men and Celtic women. Y chromosome analysis and comparison of Icelandic,

Scandinavian and Gaelic Irish and Scots suggests that 75–80% of Icelandic founding males had Scandinavian ancestry [14]. The allelic frequency of C282Y has been estimated at 4.5% in Iceland [8].

The population of the Faroe Islands is among the most homogenous and isolated in the north Atlantic. Genetic studies have suggested an excess of Scandinavian males and Celtic (British Isles) females in the founding population [15]. The allelic frequency of C282Y in the Faroe Islands has been estimated at 5.1% [8] or 8.0% [7].

### The C282Y mutation in Ireland

Ireland at the western edge of Europe has a relatively isolated genetic heritage. Analysis of Irish Y chromosome haplotypes has highlighted a predominance of a single nucleotide polymorphism (SNP) delineated haplotype R1b3. R1b3 is roughly equivalent to the old haplogroup 1. R1b3 displays a cline of increasing frequency from the Middle East to northwestern Europe and peaks with near fixation (98%) in men with traditional Irish surnames in Connaught [16]. Connaught is the most western province of Ireland. The distinctive Y chromosome cline for R1b3 provides an opportunity to assess the population of the western parts of Ireland, for this population has been relatively undisturbed by migration. Y chromosome haplogroup 1 likely came to Europe with a Palaeolithic migration [17]. The other European peak for haplogroup 1 is the Basques (89%) [18]. Because the Basques do not have a high frequency of C282Y this argues against the C282Y mutation having come to Europe with a Palaeolithic migration. This raises the possibility of C282Y having arisen in the Irish population.

In contrast to the near fixation of Y chromosome R1b3 in the true Irishmen of Connaught, the overall Y chromosome pattern in Ireland has significantly different eastern and western complements. This has been attributed to preferential migration to the more accessible east coast after initial colonization. Some of this Y chromosome variation could be a mark of raiding Scandinavian males, for the coastal areas of Dublin, Waterford, Howth and Wexford were all originally Viking encampments. In contrast mitochondrial DNA samples from eastern and western Ireland do not show these significant differences. The movement of settling women is different from men in the history of Ireland.

A true estimate of the rate of the C282Y mutation in the areas of western Ireland where Y chromosome R1b3 is virtually fixated could provide

the strongest evidence to date for an Irish origin of C282Y. This work remains to be done.

## Gaelic versus Viking origin of C282Y

Lucotte and Dieterlen [1] eloquently calculated a significantly higher contribution of Celtic genes versus Viking genes to explain the observed European distribution of C282Y mutation frequencies. It was however noted that high values of C282Y were observed in Scandinavia, Iceland and the Faroe Islands. What was not factored in was the information that the Vikings and Celts interbred. The Vikings raided Ireland and took slaves in large numbers and Viking men and Celtic women were instrumental in settling Iceland and the Faroe Islands.

The Celtic world had population flow between different Celtic peoples and if the C282Y mutation arose in one branch of the Celtic world it could have been relatively easily transmitted to other areas. It is possible that the C282Y mutation arose in Ireland and was transmitted through Celtic migration to other areas of Europe. This "Insular Celtic" hypothesis for the origin and spread of C282Y is a new theory [12]. Celtic migration to Europe not only happened in remote history. It occurred 350 years ago after the Battle of the Boyne when many Irish soldiers left to fight in European armies and never returned to Ireland. Another massive migration from Ireland happened with the potato famines of the 1800s. Though many Irish left for the New World others settled in closer European countries.

If the C282Y mutation entered the Scandinavian population when the Vikings took slaves who were integrated into the Scandinavian population and also selected Celtic women to colonize Iceland and the Faroe Islands, the C282Y mutation should have been present longer in the Irish population. Thus the C282Y mutation should be present on a more diverse background in Ireland and especially in the west of Ireland. Comparison of haplotypes in Irish and Scandinavian populations should display more variation in the Irish. Haplotype diversity indirectly measures allele age. If a disease mutation is extremely old it will have been present in a population for many generations. This allows a lot of time for mutations to occur on chromosomes carrying the disease mutation. Analyzing haplotypes made up of neutral DNA markers (microsatellites and SNPs) within and flanking the gene allows sampling of how much mutation has occurred. More mutation (longer time) is reflected in a greater number

of haplotypes associated with the disease mutation. If the same disease is associated with different numbers of haplotypes in two different populations, the population with the greater number is likely to have been the source population [12,19].

Significant information with respect to the origin and dissemination of C282Y is unlikely to come from the analysis of the North Atlantic Islands. The people of Iceland and the Faroe Islands are of mixed Scandinavian and Celtic descent. Because of the small isolated populations, founder effects occur and the analysis is difficult. However Iceland and the Faroe Islands should have a C282Y frequency intermediate between Ireland and Scandinavia and this is the case.

Testing for the C282Y allelic frequency and extended haplotype analysis in Orkney and Shetland is unlikely to add much to understanding of the origin of C282Y. This is because settlement did not end with Scandinavian families.

## The hypotheses

1. C282Y was an Irish Gaelic mutation.
2. The Vikings help disseminate C282Y by interbreeding with the Gaelic Irish.

## Testing of the hypotheses

1. *C282Y was an Irish Gaelic mutation.*  
Analysis of populations in Ireland outside of the Dublin area for frequency of the C282Y mutation is probably the easiest and most productive route to supporting the hypothesis of an Irish Gaelic origin for C282Y. As Dublin was a Viking settlement and many peoples have moved in and out of Dublin over the centuries the frequency of C282Y in Dublin should be lower than many other parts of Ireland. If the relatively isolated western areas of Ireland, who have an almost complete fixation of Y chromosome R1b3, have the highest incidence of C282Y in the world then the C282Y mutation is extremely likely to have originated in this population. Selective testing of Irish men in Connaught with traditional Irish surnames would be even more specific. If the highest frequency ever recorded occurs in the Gaelic men of Connaught, this is strong evidence of an Irish Gaelic origin for C282Y.
2. *The Vikings help disseminate C282Y by interbreeding with the Gaelic Irish.*  
Ideally both Irish and Scandinavian populations should be tested for haplotype diversity. If the

Irish have the greater haplotype diversity then they are the likely source population for C282Y. It then follows that the Vikings spread C282Y after the mutation entered the Scandinavian population for the age of the mutation and its distribution fits with the contacts of the Viking Age. If testing of both Irish and Scandinavian populations is not possible haplotype comparison within different areas of Ireland could be carried out. Within Ireland comparison is important between Connaught and areas with significant Viking or Viking related (Norman, British) gene pools.

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