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ARTICLE

Abundance of the POLG disease mutations in Europe, Australia, New Zealand, and the United States explained by single ancient European founders

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We reported previously that the DNA polymerase γ (POLG) W748S mutation, a common cause of mitochondrial recessive ataxia syndrome (MIRAS), has a common ancient founder for all the disease chromosomes in Finland, Norway, United Kingdom, and Belgium. Here, we present results showing that the same ancestral chromosome underlies MIRAS and Alpers syndrome in Australia and New Zealand. Furthermore, we show that a second common POLG mutation, A467T, also shows common European ancestry: patients from Australia, New Zealand, and the United States share a common haplotype with the previously reported European patients. These data of ancestral haplotypes indicate that the *POLG* locus is quite stable and that the recessive W748S and A467T mutations, and probably also G848S, have occurred once in history. They have effectively spread to populations of European descent with carrier frequencies up to 1% in several populations. Our data predict that these mutations are common causes of ataxia and Alpers disease in the Western world.
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Introduction

Polymerase γ (POLG [MIM 174763]) is the only known DNA polymerase responsible for mitochondrial DNA (mtDNA) replication and repair.[1,2] The W748S, A467T, and the G848S mutations in the catalytic subunit of this polymerase underlie various severe central nervous system phenotypes, ranging from infantile Alpers syndrome (MIM 203700)[3–9] to mitochondrial recessive ataxia syndrome (MIRAS) with juvenile or adult onset.[10–14] These three autosomal recessive mutations cause disease either in compound heterozygous or homozygous states. In the case of Alpers syndrome, most patients with a defined genetic background carry either the W748S or the A467T mutation in combination with another POLG mutation, most commonly G848S.[3–9]

We and collaborators have previously reported the W748S mutation as a common cause of ataxia with ancient

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European origin.[12] The carrier frequency of the W748S mutation was 1:125 in Finland, and the combined frequency of W748S and A467T mutations in the Norwegian population was estimated to be as high as 1:50,[12,14] making it the most common pathogenic POLG mutation. We studied the European W748S disease chromosomes in Finnish, British, Belgian, and Norwegian patients and showed that they all originate from a single common ancient founder.[12] In all these patients, we identified a common intragenic single-nucleotide polymorphism (SNP) haplotype and at least remnants of a common haplotype in the immediately adjacent chromosomal region. In addition to European countries, the W748S mutation has been reported in Australia[6] and in one patient with undefined nationality.[7] In all patients, the mutation has been found in *cis* with E1143G, a common polymorphism with ~3% frequency in the normal population (dbSNP). However, a modifying role for E1143G in POLG diseases remains possible.

The other frequently found disease mutation in POLG, A467T, is common in Europe (for references, see the Human DNA Polymerase Gamma Mutation Database: http://dir-apps.niehs.nih.gov/polg/), with a carrier frequency as high as 0.6% in Belgium and 1% in Norway.[13,15] In our previous haplotype analysis of the European A467T disease chromosomes, a long common haplotype was seen in the British and Belgian patients and remnants of this haplotype were also seen in Norwegian patients, raising the possibility of a common founder also for the A467T mutation.[12]

Here, we studied the haplotypes of patients with W748S and A467T mutations from Australia, New Zealand, and the United States to determine whether these mutations would originate from European founders or rather result from recurrent mutation events.

Materials and methods

DNA samples were collected with informed consent and the study was approved by the local ethical boards. We analyzed the *POLG* genomic region haplotypes of 17 unrelated patients from Australia or New Zealand (14 from Australia and three from New Zealand), who all carried at least one W748S+E1143G or A467T allele, as our previously published European samples.[12] The corresponding nucleotide changes are the following (GenBank NM_002693; sequence numbering starts from ATG): c.2243G>C (p.W748S), c.3428A>G (p.E1143G), and c.1399G>A (p.A467T). The other mutations, including the chromosomes carrying the G848S mutation (c.2542G>A), are shown in Figure 1. Four of the patients have been reported previously.[6] Most patients were known to have European ancestry in the past eight generations. In addition, we analyzed the haplotype of one patient, originating from the United States, who was homozygous for A467T. All patients had clinical findings consistent with Alpers syndrome. From now on, we will use the protein nomenclature (A467T, W748S, and G848S) for the POLG mutations, since these are widely known and used.

DNA marker / intragenic SNP	Distance from POLG / intron for SNP	W748S						W748S/G848S										A467T/G848S						A467T / other mutation																A467T/ A467T				A467T				
		FIN / N			UK	BEL		NZ1		A1		A2		A3		A4		A5		A6		NZ2		A7[a]		A8[b]		NZ3[c]		A9[d]		A10[e]		A11[f]		A12[g]		A13[h]		A14		USA		EU	N			
		A	B	C																																												
D15S1045	263kb	3	4	3	3	5	5	3	5	3	5	6	5	3	5	3	5	3	3	3	5	3	3	3	5	3	3	1	5	3	5	5	5	3	5	3	3	3	5	3	3	3	3	3	4	5	3	5
D15S276	202kb	3	3	3	3	5	6	3	7	3	7	4	7	3	5	3	5	3	3	3	7	3	6	3	3	3	3	3	3	3	5	3	5	3	4	3	3	3	5	3	3	3	3	3	3	4	6	3
D15S299	171kb	3	3	3	1	3	2	3	6	3	6	3	6	3	5	3	6	5	6	5	6	5	6	5	3	5	7	5	6	5	8	5	7	5	3	5	6	5	2	5	5	5	5	5	6	6	5	5
rs2307438	int 21	G			G	G	G	G	T	G	T	G	T	G	T	G	T	T	T	T	T	T	T	T	G	T	G	T	G	T	T	T	G	T	G	T	T	T	T	T	T	T	T	T				
rs2302084	int 19	C			C	C	C	C	T	C	T	C	T	C	T	C	T	T	T	T	T	T	T	T	C	T	C	T	C	T	T	T	C	T	C	T		T	T	T	T	T	T	T	T	T	T	T
rs2246900	int 19	G			G	G	G	G	A	G	A	G	A	G	A	G	A	A	A	A	A	A	A	A	G	A	G	A	G	A	A	A	G	A	G	A	A	A	A	A	A	A	A	A	A	A	A	A
rs2307449	int 18	C			C	C	C	C	A	C	A	C	A	C	A	C	A	A	A	A	A	A	A	A	C	A	C	A	C	A	A	A	C	A	C	A	A	A	A	A	A	A	A	A				
rs2307433	int 17	I			I	I	I	I	D	I	D	I	D	I	D	I	D	D	D	D	D	D	D	D	I	D	I	D	I	D	D	D	I	D	I	D	D	D	D	D	D	D	D	D	D	D	D	D
rs2072267	int 11	C			C	C	C	C	T	C	T	C	T	C	T	C	T	T	T	T	T	T	T	T	C	T	C	T	C	T	T	T	C	T	C	T	T	T	T	T	T	T	T	T	T	T	T	T
rs3176183	int 9	I			I	I	I	I	D	I	D	I	D	I	D	I	D	D	D	D	D	D	D	D	I	D	D	D	I	D	D	D	D	D	I	D	D	D	D	D	D	D	D	D	D	D	D	D
rs2247233	int 2	A			A	A		A	G	A	G	A	G	A	G	A	G	G	G	G	G	G	G	G	A	G	A	G	A	G	G	G	A	G	A			G	G	G	G	G	G	G				
rs2239286	int 2	C			C	C		C	G	C	G	C	G	C	G	C	G	G	G	G	G	G	G	G	C	G	C	G	C	G	G	G	C	G	C	G	G	G	G	G	G	G	G	G				
rs2283430	int 2	T			T	T		T	G	T	G	T	G	T	G	T	G	G	G	G	G	G	G	G	T	G	T	G	T	G	G	G	T	G	T	G	G	G	G	G	G	G	G	G				
D15S510	43kb	2	2	2	2	1	2	2	8	4	8	10	8	4	2	4	2	4	6	4	8	4	8	4	2	1	8	4	11	4	6			4	3	4	9	4	4	4	4	4	4	4	4	4	4	4
D15S542	83kb	2	2	2	2	2	1	2	3	3	3	5	3	3	7	3	6	3	3	3	6	3	3	3	4	4	5	3	6	3	5	3	3	3	4	3	9	3	8	3	6	3	3	3	3		3	3
D15S202	142kb	2	3	4	4	4	4	1	4	1	1	1	4	4	2	4	7	1	1	1	1	1	4	8	3	1	4	1	1	2	7	1	7	1	2	1	4	1	2	1	1	1	1	1	2	2	2	2

Figure 1 Haplotypes and intragenic SNPs of the Australian (A), New Zealand (NZ), and American (USA) patients. Data of some of the previously published Finnish (FIN), Norwegian (N), British, and Belgian (EU = British and Belgian) patients are also shown for comparison.[12] The following colors indicate the common haplotypes for each of the disease chromosomes: pink for W748S, green for A467T, and yellow for G848S. For Australian and New Zealand patients compound heterozygous for A467T and another mutation, the mutations not shown in the figure are the following: (a) IVS14+1G>A, (b) IVS17+1G>A, (c) C418R, (d) R852C, (e) S305R, (f) L966R, (g) E358(A)Del-364X, and (h) T914P. I = insertion and D = deletion.

To determine the haplotypes of our patients with the W748S, A467T, or G848S mutations, we analyzed the following six polymorphic dinucleotide markers flanking the *POLG* gene: *D15S1045*, *D15S276*, *D15S299*, *D15S510*, *D15S542*, *and D15S202*. Figure 1 shows their distances from *POLG*. The marker amplification conditions were as described previously[12] or modified as follows: one of the PCR primers of a reaction was 5′-phosphorylated with [γ^{32}P]dATP before the PCR reaction and the PCR was performed with AmpliTaq Gold DNA polymerase in its buffer (Applied Biosystems).

In addition, we analyzed 10 intronic SNPs using standard PCR amplification and sequencing methods. To determine SNPs rs2247233, rs2239286, and rs2283430, we designed new sequencing primers, whereas for the remaining SNPs, we used primers that have previously been described,[16] except for primers amplifying exon 22 (rs2307438). The previously published primer sequence[16] overlaps with a common SNP, leading to allele-specific PCR if the nucleotide variant is present. The haplotypes were constructed manually from the marker data, assuming minimal number of different segregating haplotypes in a given population.

Results

We performed a dense DNA marker analysis of an over 400 kb genomic region containing the POLG gene, utilizing information from both SNPs and polymorphic dinucleotide repeat markers. Figure 1 shows the constructed haplotypes of disease chromosomes carrying mutations p.W748S, A467T, or G848S.

The W748S disease chromosomes from Australia and New Zealand shared a common dinucleotide and SNP haplotype with each other, and a telomeric Australian-specific haplotype signature 4-3-4 could be recognized. Further, all but one of these Australian and New Zealand W748S haplotypes shared a region of $>260-350$ kb with the major Scandinavian haplotypes of our Finnish and Norwegian patients,[12] and also the least resembling chromosome showed remnants of the Scandinavian haplotype (Figure 1). However, the W748S haplotypes from Australia and New Zealand shared only the short intragenic SNP haplotype and its immediate vicinity with our Belgian and British patients.[12]

The A467T disease chromosomes from Australia, New Zealand, and the United States shared a long common haplotype with each other, often extending beyond the entire analyzed genomic region of 400 kb. This long haplotype was identical with that previously reported in our British and Belgian patients:[12] over a region of more than 350–400 kb in 13 out of the 15 non-European A467T disease chromosomes, and a region of at least 260 kb in two chromosomes. The Scandinavian A467T chromosomes shared only the SNP haplotype and its immediate vicinity with the Anglo-Australian samples.

The G848S disease chromosomes of patients from Australia and New Zealand shared a common SNP haplotype. Furthermore, in five out of the eight patients, the common haplotype extended over a region of at least 300–400 kb, and two patients had remnants of the common haplotype.

Discussion

We extend here our previous studies on POLG haplotypes[12] associated with mutations causing MIRAS, Alpers syndrome, and related neurological phenotypes. The patients originated from Australia, New Zealand, and the United States, and their results were compared with our previous results from Finnish, Belgian, British, and Norwegian patients carrying the same mutations.[12] Long identical genomic regions around the *POLG1* locus, in patients from different countries, strongly support the existence of single ancestral European founders for these patients. We show here that all the patients with A467T, W748S, and likely also G848S mutations of POLG derive from single ancient ancestors, and that these mutations are spread to all populations of European origin. Furthermore, the mutation carrier status varies in different countries in which subisolates have formed, varying from $\sim 1\%$ in Norway and $<0.2\%$ in Finland for A467T, to 1% of Norwegians and 0.8% of Finns for W748S.[12,13,17]

We show here that all the POLG A467T disease chromosomes from Australia, New Zealand, and the United States share a common haplotype with the European patients. This indicates that all these patients originate from a common European founder. When comparing with the British and Belgian patients, the shared haplotype extended over a region of at least 350–400 kb in most of the patients, in contrast to a region of less than 285 kb when comparing with the Norwegian patients. Consequently, the Norwegian haplotype diverged earlier to form a subisolate than the Australian, New Zealand, and the American haplotypes. Furthermore, these findings indicate that the abundance of the A467T mutation in different populations does not result from recurrent mutation events, but is caused by the spreading of one recessive founder chromosome in populations of European origin.

Similarly to A467T, the haplotype and SNP data on the W748S disease chromosome indicate that patients from Australia and New Zealand have common ancestry with the European patients. Based on the shorter area of linkage disequilibrium, the W748S disease chromosome appears to be older than the A467T disease chromosome. The major W748S haplotype of Australians and New Zealanders shares a long region with the Finnish and Norwegian patients – up to 350 kb – but only the intragenic SNP haplotype and the immediate *POLG1* vicinity with our previously reported Belgian and British patients. This suggests, perhaps surprisingly, that the founder(s) who formed the subisolate for the W748S chromosome in Australia and New Zealand

was possibly of Scandinavian, rather than British, ancestry. Scandinavian chromosomes were spread effectively during Viking times, eighth to tenth century, to the British Isles, and if a descendant was deported later to Australia, the Scandinavian ancestry would be explained. Direct Scandinavian contribution to Australian population through immigration occurred only during early 1900s, and would not explain the wide spreading of the W748S chromosome. This disease chromosome could be, to our knowledge, the first Scandinavian founder chromosome to have migrated and spread effectively to Australia and New Zealand.

As for the W748S and A467T mutations, our data indicate that most, if not all, of the Australian and New Zealand G848S disease chromosomes originate from a common ancestor. This is based on a common SNP haplotype and on dinucleotide marker data showing at least remnants of a common haplotype in all except one patient. The fact that the intragenic SNPs were identical in the G848S and A467T disease chromosomes could either be the result of the A467T and G848S mutations arising independently on a similar ancestral chromosome or due to an inadequate information content of the SNPs. However, the microsatellite analysis allowed us to distinguish between the A467T and G848S disease chromosomes. The origin of the G848S chromosomes remains an open issue due to the lack of European G848S disease chromosomes in this study. However, a European origin is most likely, since the G848S mutation has also been reported in one Italian,[18] one Belgian,[19] one Swedish,[20] and one German patient.[5]

A conservative estimation of the age of the mutations suggests that the common ancestor for the A467T haplotype lived more than 15–30 generations ago (ie before 1700 – 1400 A.D.), and for the shorter W748S haplotype, more than 40–60 generations ago (ie before 1200 – 800 A.D.), based on the length of the shared haplotype regions.[21] These estimations and the spreading of the disease chromosome in the Western world are in agreement with the Australian and New Zealand population history, and the W748S estimation overlaps with Viking times. The early settlement of Australia by Caucasians began when the first English, Irish, and Scottish convicts were transported to Australia in 1788. In 1938, 90% of Australians were of Anglo-Celtic descent.[22] In the census of 2001, with 18.8 million people living in Australia, 6.7 million reported their ancestry as Australian, 6.4 million as English, and 1.9 million as Irish, followed by a multitude of other European and other nationalities.[23] The Australian disease chromosomes often seem to reflect this ethnic composition, as seen in phenylketonuria patients with disease alleles originating from the British Isles.[24] At the national New Zealand census in 1921, the European population of 1.2 million outnumbered the Maori population of 57 000.[25] The colonizers of the United States were predominantly English, Scottish, or Irish before the mid 19th century, whereas during the following decades (between the mid 19th century and the 1920s) considerable numbers of immigrants arrived from Italy, Scandinavia, Germany, and Eastern Europe.[26]

The A467T and W748S mutations have effectively spread to many populations of European descent not only through heterozygous carriers of the mutation, but also through homozygous patients with adult-onset ataxia. Similarly, a global ancient founder chromosome has been found in Friedreich ataxia (MIM 229300),[27] which resembles MIRAS in its phenotype and pathogenesis, as a mitochondrial ataxia. An ancient world-wide ancestry of a founder allele is not, however, common among recessive diseases. One cause of effective spreading of a recessive allele could be selective advantage for heterozygote carriers, increasing either reproductive fitness or survival of the offspring. Available functional evidence on the consequences of A467T and W748S mutations for POLG, however, does not support selective advantage for them, since the mutant enzymes are catalytically defective,[17,28] and would lead to mtDNA depletion and/or increased mutagenesis. Furthermore, the frequency of the A467T mutation in Australia (Thorburn *et al*, manuscript in preparation) seems to parallel the observed frequencies in European countries (0.6% in Belgium and 1% in Norway[13,15]), reflecting the European origin of the Australians. The occurrence of A467T mutation, therefore, seems to support random segregation over many centuries. The high frequency of W748S mutation in Norway, Finland, and Australia may be a general phenomenon in populations of European origin, as population carrier data are not available from other countries. Potential enrichment can also be explained by several separate introductions of the mutant chromosome in the population, followed by regional enrichment in subisolates, as we have previously speculated for Finland.[12]

The common and widespread occurrence of heterozygous carriers – up to 1% of several Western populations – of pathogenic recessive POLG mutations raises the concern whether carrier status is neutral or potentially harmful for the individual. Previously, we have shown that heterozygosity for the A467T mutation may manifest as mild ocular myopathy in some families.[17] If W748S mutation carriers manifested even a mild disease, tens of thousands of individuals would be at risk solely in Finland. Detailed studies of heterozygous carrier phenotype are required to evaluate whether the carriers are more prone to for example, neuropathy or balance disturbances, or susceptible for environmental challenge.

In conclusion, we present here results on Australian and New Zealand patients showing that the A467T and W748S mutations were of ancient European origin, and that patients with the G848S mutation had a common ancestor, possibly also of European origin. In addition, the haplotype data indicated that also the American A467T disease

chromosome originated from the common European founder. A great number of different mutations in human diseases have recently been described in the *POLG* gene (Human DNA Polymerase Gamma Mutation Database). Our data indicate that the most common mutations in *POLG* are not a result of recurrent mutation events but occurred once in the history of humankind – also indicating that *POLG* may not be a mutation hot spot. These recessive mutations are old enough to have spread effectively through heterozygous carriers and through homozygous patients with adult or juvenile onset of the disease. Our results strongly suggest that A467T, W748S, and G848S mutations of POLG are common causes of severe central nervous system diseases in populations of European descent and should be considered in the first-line diagnosis of hereditary ataxias, hepatopathies, and children's encephalopathies in these populations.

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