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Research Article

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Investigation of the Origin of Common *LDLR* Mutation Alleles in New Zealand Familial Hypercholesterolemia Patients

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Abstract

Objective

Amongst New Zealand patients with familial hypercholesterolaemia (FH) some *LDLR* mutations have been identified in multiple unrelated individuals. This could be because these variants occur at sites prone to recurrent mutation, or because ancestral mutation alleles are present at an increased frequency in the population. The aim of this study was to investigate the contribution of these mechanisms to the aetiology of FH in New Zealand.

Methods

To assess which of these scenarios underlies the prevalence of these common *LDLR* mutations, haplotype analysis was performed using five short tandem repeat (STR) markers which flank *LDLR*. Haplotype data was used to identify whether mutation alleles were identical-by-descent (IBD), indicating an origin from a common ancestor. Absence of a common complete or partial haplotype would suggest mutations had arisen independently in separate events.

Results

Of the 26 *LDLR* mutations included in the study which have been detected in two or more index patients, most (65%) showed strong evidence of IBD. The data also revealed further complexities, such as the presence of two ancestral alleles for some mutations, and evidence of historic recombination events. The South African Afrikaner mutations present in the cohort were confirmed to have common ancestral haplotypes, although for FH Afrikaner-1 another distinct ancestral allele was also identified.

Conclusion

The high prevalence of some *LDLR* gene mutations in New Zealand FH patients reflects the presence of ancestral mutation alleles in the population. This is likely to be either a founder effect whereby early settlers introduced mutation alleles to New Zealand or due to the prevalence of the mutation in other populations from where ongoing migration is occurring, such as South Africa and parts of Europe.

Keywords

LDLR; Mutation; Hypercholesterolemia; Hyperlipidaemia; Identity-by-descent; Haplotype

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Introduction

Familial hypercholesterolaemia (Frederickson Type IIa) is caused by mutations in the low density lipoprotein receptor gene (*LDLR*). In excess of 1200 mutations have been described in *LDLR*, and these include the full spectrum of mutation types (missense, nonsense, splicing variants, and both small and multi-exonic insertions and deletions) and affect all functional domains of the receptor [1].

Some mutations are observed solely, or at a higher incidence, in certain geographic regions or in isolated populations, for example the three common Afrikaner mutations (*LDLR*:c.523G>A, c.681C>G, c.1285G>A) and the Ashkenazi Jewish mutation c.654_656del [2-4]. In such cases it may be assumed that multiple instances of an identical *LDLR* mutation present in apparently unrelated families reflects identity-by-descent (IBD); that is, individuals with the same mutation share a common ancestor, and all instances of the mutation are derived from a single mutation event [5]. An alternative scenario in which multiple families in separate geographic regions carry the same *LDLR* mutation but do not have IBD is termed identity-by-state (IBS), whereby the origin of each instance of the mutation is from a separate mutation event.

To identify instances where IBD explains multiple occurrences of the same gene mutation requires haplotype analysis of the segment of DNA containing the gene of interest, using either short tandem repeat markers (STRs), often referred to as microsatellites, or single nucleotide polymorphism (SNP) markers [5-8]. Such analysis though, may be complicated by recombination and mutation events within the segment that may mask IBD by altering the haplotype.

Since 2003 the FH screening programme in Christchurch, New Zealand, has identified 234 index patients who have an *LDLR* mutation in patients attending the Christchurch Hospital Lipid Disorders Clinic [9,10]. More than 120 different mutations have been characterised in this cohort, illustrative of the mutational heterogeneity of the *LDLR* gene. A key feature of this group of patients is that some mutations have been detected in multiple index cases, for example, *LDLR*:c.1444G>A has been identified in 12 apparently unrelated families, and c.313+1G>A was identified in 7 different families, with numerous other mutations observed in two or more families.

About 75% of the New Zealand population of 4.8 million has European ancestry, stemming from colonisation which began in the early nineteenth century. Therefore, the *LDLR* mutation spectrum would be expected to reflect those populations from which the settlers were derived. Additionally, there may be founder effects if very early settlers to New Zealand carried mutations which have been passed through subsequent generations in the local population.

We were interested to know whether IBD could explain the multiple instances of the same *LDLR* mutations being identified in unrelated index patients in our cohort, and thereby assess the role of founder effect in the aetiology of FH in New Zealand. Haplotypes for each mutation allele were examined to assess whether patients with identical mutations have the same haplotype, indicative of IBD. Patients with the same mutation but without a common haplotype would have IBS, and their mutations could be assumed to have arisen from independent mutation events.

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Methods

The DNA samples used in this study had been previously extracted from patient blood and analysed as part of the FH genetic screening programme [9,11]. Informed consent was obtained from all patients for DNA analysis.

Five STR markers flanking *LDLR* were used to obtain haplotypes for individuals with *LDLR* mutations; details of these STRs are given in Table 1. STRs were amplified using Qiagen Multiplex PCR mix (Qiagen, Hilden, Germany) with FAM-labelled primer sets, and analysed using an ABI3130 instrument and Genemapper v5 software (Applied Biosystems (Life Technologies), Foster City, CA., USA).

Allele frequencies were determined for each marker by analysing 50 random patient samples (100 chromosomes) (Table 2). The markers used had a good level of heterozygosity, with a wide range of alleles observed in the control sample of 50 individuals. *D19S394*, *D19S221* and *D19S906* did not have any single allele dominating the distribution of repeat lengths, whereas for both *D19S1165* and *DT17xGT* a single allele was observed at a high frequency (*D19S1165* - allele 238, 0.41; *DT17xGT* - allele 276, 0.47). Therefore, in analysing the haplotype data, the presence of these alleles was taken into account when considering IBD as there is a high chance such alleles are present by chance. Similarly though, the presence of rare alleles in common between index patients with the same *LDLR* mutation provides strong evidence for IBD.

For each *LDLR* mutation included in the study, a five-marker haplotype of the 2.02 megabase (Mb) chromosomal region encompassing *LDLR* (0.53 Mb distal-1.49 Mb proximal) was derived for each index patient. In cases where family members of an index case had been analysed through the cascade screening programme and their DNA samples were available for STR genotyping, the phasing of the marker alleles could be determined to give a certain haplotype on which the *LDLR* mutation is present. When family members were not available the allele phasing could not be determined (except for a homozygous genotype), but a most likely haplotype could be obtained when genotypes were consistent with the conserved haplotype in other index patients with the same mutation; this approach has been previously described [3].

Results

The Christchurch *LDLR* mutation database was analysed to select mutations that had been identified in multiple unrelated index patients. This resulted in selection of 26 mutations that were observed in two or more index patients, and for which archived DNA samples were available for haplotype analysis. Where cascade testing of other family members had been performed, these samples were included in the analysis so that STR marker alleles could be phased with the *LDLR* mutation.

Table 1: Details of the microsatellite STR markers used in this work.

Marker	Heterozygosity[a]	Location relative to *LDLR*	Location on chr. 19[b]	Distance from *LDLR* in Mb[c]
D19S394	0.86	distal	10585042	0.53
LDLR-DT17xGT	-	distal	10794271	0.32
D19S906	0.78	proximal	11815211	0.70
D19S1165	0.78	proximal	12183309	1.07
D19S221	0.85	proximal	12601928	1.49

[a]Heterozygosity scores from Marshfield Comprehensive human genetic maps (Broman et al. [12])

[b]Position on *GRCh38/hg19* Assembly

[c]Distance calculated from midpoint of *LDLR* gene (11,110,763)

Table 2: Frequency of observed alleles for five STR microsatellite loci flanking *LDLR* in 100 chromosomes (50 random individual samples).

D19S394		*D19S221*		*D19S906*		*D19S1165*		*LDLR-DT17xGT*	
Allele	Frequency	Allele	Frequency	Allele	Frequency	Allele	Frequency	Allele	Frequency
280	0.01	186	0	140	0	226	0.03	272	0
284	0.04	192	0.05	142	0	230	0.03	274	0.02
288	0	194	0.01	144	0.02	234	0.19	276	0.47
292	0.04	196	0.01	146	0.07	238	0.41	278	0.05
296	0.07	198	0.11	148	0.19	242	0.23	280	0
300	0.09	200	0.16	150	0.15	246	0.09	282	0.05
304	0.07	202	0.08	152	0.1	250	0.01	284	0.05
308	0.1	204	0.07	154	0.05	254	0.01	286	0.16
312	0.14	206	0.11	156	0.14			288	0.18
316	0.09	208	0.24	158	0.06			290	0.02
320	0.13	210	0.12	160	0.07			292	0
324	0.14	212	0.03	162	0.04				
328	0.08	214	0.01	164	0.05				
332	0			166	0.02				
				168	0.01				
				170	0.01				
				172	0.01				
				174	0				
				176	0.01				
Total	1.0		1.0		1.0		1.0		1.0

Five STR markers which flank *LDLR* (spanning a 2.02 Mb region) were used to obtain haplotypes for each mutation allele to assess whether patients with identical mutations have the same haplotype, indicative of IBD.

Table 3 summarises the results of the study of 92 index patients. This shows that, as might have been expected *a priori*, some of the mutations show clear evidence of IBD (17 mutations), whilst other mutations show no evidence of IBD (7 mutations); two of the mutations were ambiguous. However, further interesting complexities are revealed by the data, which are discussed further below.

The most commonly occurring mutation in our group of FH patients is *LDLR*:c.681C>G (legacy naming - D206E/FH Afrikaner-1) which is the most common FH-causing *LDLR* mutation in the Afrikaner population in South Africa [4]. We analysed 12 index patients with this mutation (including one homozygote), and nine of these share a common haplotype assumed to be the Afrikaner-1 allele;

Table 3: Summary of haplotype analysis of unrelated index patients with identified *LDLR* mutations. In this study 92 index patients, plus their relatives if available, were included in the analysis, representing 26 different *LDLR* mutations.

Nucleotide	Protein	Legacy naming	Number of Index Cases	IBD	Notes
c.241C>T	*p.Arg81Cys*	R60C	3	No	3 index patients, no common haplotype.
c.301G>A	*p.Glu101Lys*	E80K FH Lancashire	2	?	2 index patients share a common haplotype for the 2 central markers only (*DT17xGT, D19S906*) – either no IBD, or recombination events on both distal and proximal sides. Common U.K. mutation.
c.313+1G>A	-	FH Elverum FH Olbia	8	Yes	5 index patients share the same haplotype, (2 of these have a distinct allele for *D19S394* indicating a historical recombination event on the distal side), a further 3 patients have distinct haplotypes.
c.418G>A	*p.Glu140Lys*	E119K FH Philippines	2	Yes	Both index patients share a common haplotype.
c.523G>A	*p.Asp175Asn*	D154N FH Afrikaner-3	4	Yes	2 index patients share the same haplotype across all 5 markers, 2 other patients also share this haplotype within the central 3-marker region but differ at the most distal and proximal markers.
c.681C>G	*p.Asp227Glu*	D206E FH Afrikaner-1	12	Yes	9 index patients (including 1 homozygote) share a common haplotype assumed to be the Afrikaner-1 allele; 3 other index patients have an identical distinct haplotype.
c.718G>A	*p.Glu240Lys*	E219K FH Charlotte	3	Yes	All 3 cases share a common 4-marker haplotype, the most distal marker (*D19S394*) is ambiguous indicating a recombination event.
c.938G>A	*p.Cys313Tyr*	C292Y	2	Yes	Both index patients share a common haplotype.
c.1027G>A	*p.Gly343Ser*	G322S FH Picardie	3	Yes	2 index patients share a common 4-marker haplotype, but have no alleles in common at the most proximal marker (*D19S221*) indicating a recombination event. A third proband has a distinct haplotype.
c.1133A>C	*p.Gln378Pro*	Q357P	2	No	2 index patients, no common haplotype.
c.1206–1207del	*p.Phe403Hisfs*37*	-	2	Yes	Both index patients share a common haplotype.
c.1285G>A	*p.Val429Met*	V408M FH Afrikaner-2	4	Yes	3 index patients share a common haplotype, a fourth patient has the same haplotype but differs at the proximal *D19S221* marker.
c.1444G>A	*p.Asp482Asn*	D461N	8	Yes	4 index patients share the same haplotype across all five markers, a further 3 patients also have this haplotype for 3 of the markers but share a distinct haplotype for the 2 proximal markers indicating a recombination event on the proximal side; an eighth index patient differs only at the central *D19S906* marker. Third most common mutation in U.K.
c.1447T>C	*p.Trp483Arg*	W462R	2	No	2 index patients, no common haplotype.
c.1474G>A	*p.Asp492Asn*	D471N	2	No	2 index patients, no common haplotype.
c.1588T>G	*p.Phe530Val*	F509V	2	Yes	2 index patients share a common 3 marker haplotype, but have distinct alleles for *D19S1165* and *D19S221*, indicating IBD for *LDLR* and the distal region, and a recombination event 0.7-1.07Mb proximal to LDLR.
c.1694G>C	*p.Gly565Ala*	G544A	4	Yes	All 4 index patients have the same haplotype, although there appears ambiguity at the *D19S1165* marker in some cases.
c.1796T>C	*p.Leu599Ser*	L578S FH London-5	4	Yes	4 index patients, all share a common haplotype.
c.1813C>T	-	-	7	Yes	6 index patients share a common haplotype, one other patient has a distinct haplotype.

c.2098G>A	*p.Asp700Asn*	D679N	2	?	Shared haplotype for only the 2 closest markers to *LDLR* (*DT17xGT, D19S906*), but since these are rare alleles IBD is possible, and recombination events have occurred on both sides of *LDLR*.
c.2312-3C>A	-	-	2	Yes	Both index patients share a common haplotype.
c.2479G>A	*p.Val827Ile*	V806I FH New York-5	2	No	2 index patients, no common haplotype.
c.(?_-255)_(67+1_68-1) del		PRO_ EX1DEL	2	No	Probably distinct haplotypes, although some alleles are in common.
c.(190+1_191-1)_(1186+1_1187-1) del		EX2_8DUP FH St Louis	2	No	2 index patients, no common haplotype. May not be the same mutation as the breakpoints were not determined.
c.(190+1_191-1)_(1845+1_1846-1) dup		EX2_12DUP	2	Yes	Both index patients share a common haplotype.
c.(2311+1_2312-1)_(*445_?) del		EX15_18DEL FHLondon-9	4	Yes	2 index patients share a common haplotype, the other 2 probands have distinct haplotypes, although have some alleles in common.

Table 4: a) Haplotype data for four index patients with *LDLR*:c.523G>A (D154N/FH Afrikaner-3), showing allele sizes for five STR markers. Alleles which form the D154N mutation haplotype are underlined. Analysis of other family members for Patient 2 allowed a certain haplotype to be determined for all markers except *D19S394*; for the other patients a most likely haplotype is deduced where allele sizes match the conserved D154N haplotype. All four patients share a common haplotype, except Patients 3 and 4 show recombination on the proximal side and Patient 4 also has recombination on the distal side. **b)** Haplotype data for three patients with *LDLR*:c.241C>T (R60C); in this example there is no evidence of a common haplotype.

(a)

			Patient 1	**Patient 2**	**Patient 3**	**Patient 4**
Distal	*D19S394*	0.53 Mb	316, 328	316, 320	304, 316	320, 328
	DT17xGT	0.32 Mb	272, 276	276	276, 278	276, 288
LDLR			c.523G>A	c.523G>A	c.523G>A	c.523G>A
Proximal	*D19S906*	0.70 Mb	156, 164	156	150, 156	156, 158
	D19S1165	1.07 Mb	238, 246	238	238	238, 242
	D19S221	1.49 Mb	186, 204	186	192	192, 206

(b)

			Patient 1	**Patient 2**	**Patient 3**	
Distal	*D19S394*	0.53 Mb	316	308, 316	320, 324	
	DT17xGT	0.32 Mb	278	276, 286	276	
LDLR			c.241C>T	c.241C>T	c.241C>T	
Proximal	*D19S906*	0.70 Mb	162	148, 158	164, 166	
	D19S1165	1.07 Mb	246	234, 238	234, 238	
	D19S221	1.49 Mb	208	200, 204	208	

three other index patients have an identical but distinct haplotype. All patients with the Afrikaner-1 haplotype had characteristically Afrikaner surnames, whilst the three patients with the distinct haplotype had common Anglo names. This finding suggests that most instances of the FH Afrikaner-1 mutation in New Zealand are derived from migrants from South Africa carrying the founder allele. Interestingly though, another distinct allele for this mutation also exists that possibly has an English origin.

Four index patients have another common South African mutation, *LDLR*:c.523G>A (D154N/FH Afrikaner-3) which is estimated to account for 5–10% of FH in the Afrikaner population [4]. Since all of these patients also have characteristic Afrikaner names, IBD was expected for this mutation. The results showed all four patients shared an identical haplotype in the central 1.39 Mb region, but in two patients it appears that recombination events on both distal and proximal sides has occurred (Table 4a).

The FH Afrikaner-2 mutation (c.1285G>A, V408 M) was previously shown to exist on two different haplotypes, one prevalent in the Afrikaner population and the other in the coloured population [13]. The mutation was shown to have arisen independently in the two populations at potential CpG mutation hotspot. Our analysis shows that the four index patients with this mutation in our cohort share IBD, and are likely of the Afrikaner haplotype.

The splicing variant c.1813C>T has been detected in seven separate New Zealand patients, and this is an interesting case because this mutation appears to be quite rare globally, although has been reported in English and French FH patients [14]. Six patients share a common haplotype, and are very likely to have a common ancestor, while a seventh patient has a unique haplotype.

For the two index patients in the cohort who have the *LDLR*:c.301G>A mutation (legacy naming E80K), a common haplotype across only two markers (*DT17xGT*, *D19S906*) is observed. For *DT17xGT* they share the common 176 allele which has a frequency of 0.47, so could easily both have this allele by chance, rather than IBD. For the *D19S906* marker, 1.02 Mb from *DT17xGT* on the proximal side of *LDLR*, both patients share the 160 allele which has a frequency of 0.07, so it is much less likely they would share this allele by chance. Based on this data it is possible that a 1.02-1.6 Mb region

including *LDLR* does share IBD, and that recombination events on both distal and proximal sides has occurred since the two lineages of *LDLR*-E80K separated. In an alternative scenario, *LDLR*-E80K may have arisen independently in separate mutation events, and therefore the two index patients in the cohort share no common ancestry, and the common haplotypes for *DT17xGT* and *D19S906* exist by chance.

Table 4b shows an example where there is no evidence of a common haplotype between the three index patients with *LDLR*: c.241C>T (R60C), indicating IBD does not explain the presence of the multiple occurrences of this mutation.

Discussion

These results confirm that a significant number of *LDLR* mutation alleles that have been observed in New Zealand FH patients share IBD. Although several other studies have used haplotype analysis to confirm IBD for *LDLR* mutations commonly found in certain regions, in these cases the local populations have been resident for at least 500-1000 years allowing founder mutations to become well established [3,15-19]. Although New Zealand was first colonised in the early nineteenth century, migration from other parts of the world, but primarily Europe, continued throughout the twentieth century. Such a timescale may be insufficient for establishment of a founder effect to the extent seen in European populations, but would still be consistent with unrelated probands sharing a common ancestor 5-7 generations antecedent.

Another scenario to explain multiple unrelated families with a mutation allele that has IBD is that numerous immigrants came to New Zealand from a population where the mutation had a high frequency due to a founder effect. This is almost certainly the case for the Afrikaner mutations, such as D206E/FH Afrikaner-1 which is present in 65–70% of FH patients in the Afrikaner population in South Africa [4].

Mutational processes have the potential to confound the use of haplotype analysis to assess IBD. In this study it is assumed that for any two individuals with the same *LDLR* mutation, but without a haplotype in common, they do not have a common ancestor and the mutations arose through separate mutational events. However, recombination events can interrupt part of a haplotype, and if these have occurred on both sides of *LDLR* only the markers closest to the gene may have alleles in common, as seen for *LDLR*:c.301G>A/E80K in this study. The recombination rate is estimated to be about 1–2% per meiosis (i.e. per generation) per Mb, so we should only expect a crossover event between *LDLR* and a marker 1 Mb away to occur once per 100 generations [12,20]. The actual recombination frequency maybe greater than that this in some chromosomal regions, but it is nevertheless a rare event. Replication slippage mutations which alter the length of the repeat tract of the STR may also confound the use of haplotype data, but it should also be assumed that this is a rare occurrence [21,22].

Although it is difficult to quantify how much recombination and slippage mutations affect the haplotype analysis, we can observe that a number of mutations with clear IBD across multiple index patients can be easily identified by a common five marker haplotype, which provides evidence that these processes are not disrupting the STR data to an extent that common IBD haplotypes are not discernible. This supports the assertion that for mutations where several patients do not have a common haplotype, they actually do not have a common ancestor, rather than that an allele that has IBD has been disrupted by recombination or mutation. We have observed evidence of likely historical recombination events at the edges of the haplotype block which are consistent with these mechanisms.

This work confirms our working hypothesis that IBD can explain most instances of *LDLR* mutations which have been identified in multiple unrelated FH index patients in New Zealand. The alternative scenario that these are hotspot mutations that had all arisen independently was generally discounted. IBD was excluded for 7 of the 26 mutations (27%) included in the study, although these mutations were each only seen in 2-3 index patients.

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