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# Genetic basis of transferase-deficient galactosaemia in Ireland and the population history of the Irish Travellers

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Transferase-deficient galactosaemia, resulting from deficient activity of galactose-1-phosphate uridylyltransferase (GALT), is relatively common among the Travellers, an endogamous group of commercial/industrial nomads within the Irish population. This study has estimated the incidence of classical transferase-deficient galactosaemia in Ireland and determined the underlying GALT mutation spectrum in the Irish population and in the Traveller group. Based upon a survey of newborn screening records, the incidence of classical transferase-deficient galactosaemia was estimated to be 1 in 480 and 1 in 30 000 among the Traveller and non-Traveller communities respectively. Fifty-six classical galactosaemic patients were screened for mutation in the GALT locus by standard molecular methods. Q188R was the sole mutant allele among the Travellers and the majority mutant allele among the non-Travellers (89.1%). Of the five non-Q188R mutant alleles in the non-Traveller group, one was R333G and one F194L with three remaining uncharacterised. Anonymous population screening has shown the Q188R carrier frequency to be 0.092 or 1 in 11 among the Travellers as compared with 0.009 or 1 in 107 among the non-Travellers. The Q188R mutation was shown to be in linkage disequilibrium with a *Sac* I RFLP flanking exon 6 of the *GALT* gene. This represents the first molecular genetic description of classical transferase-deficient galactosaemia in Ireland and raises intriguing questions concerning the genetic history of the Irish Travellers.

**Keywords:** Galactosaemia; galactose-1-phosphate uridylyltransferase; Irish Travellers; mutation spectrum; allele frequency; population genetics

## Introduction

Transferase-deficient galactosaemia (MIM 230400) is an autosomal recessive condition resulting from defi-

cient activity of galactose-1-phosphate uridylyltransferase (GALT), one of the enzymes of the Leloir pathway. Disruption of this pathway, by which galactose is metabolised, leads to the accumulation of various metabolites including galactose, galactose-1-phosphate, galactitol and galactonate.<sup>1</sup> The clinical sequelae include coagulopathy, vomiting, failure to thrive and jaundice; in untreated infants *E. coli* sepsis (frequently fatal), cirrhosis of the liver, cataract formation and cognitive impairment are also observed. Treatment is

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by means of a galactose-free diet which largely reverses or prevents symptoms in the neonate. However, long term complications are frequently observed which include ovarian dysfunction, developmental delay and a range of neurologic abnormalities.<sup>1,2</sup>

In the majority of cases of transferase-deficient galactosaemia the severe clinical picture is associated with extremely low GALT enzyme activity ( $<0.5 \mu\text{mol}$  of substrate converted/per gram of haemoglobin); this is referred to as 'classical' galactosaemia. In addition, individuals are sometimes observed with mild to negligible symptomatology and intermediate levels of enzyme activity associated with 'non-classical' forms of the enzyme such as the Duarte variant.<sup>3,4</sup>

The molecular analysis of transferase-deficient galactosaemia has been made possible by the characterisation of the GALT genomic and transcript sequences.<sup>5-8</sup> The *GALT* gene maps to human chromosome 9p13, is approximately 4kb in length and encodes a protein of 43 kDa.<sup>7,9,10</sup> Considerable work has been done to define the spectrum of GALT mutations giving rise to transferase-deficient galactosaemia. A collaborative database of GALT mutations has recently been established (*GALTdb*:<http://www.ich.bris.ac.uk/galtdb>), documenting GALT mutations using GenBank accession number M96264 as the reference sequence.<sup>7</sup> Q188R is the most common mutation, occurring at a relative frequency of 60% in a pan-ethnic galactosaemic patient population, and is due to an A to G transition resulting in a glutamine (Q) to arginine (R) amino-acid substitution at codon 188.<sup>7,11,12</sup>

The incidence of transferase-deficient galactosaemia varies considerably between countries but has been estimated at 1 in 62 000 in a large human pan-ethnic study population.<sup>13</sup> Ireland is of particular interest in this context due to the existence within the population of an endogamous group, known as 'Travellers'. The Travellers are a community who maintain a distinct identity within Irish society, tend to travel in family groups and are commercial/industrial rather than pastoral nomads.<sup>14</sup> Based upon 1996 data, the Traveller sub-population numbers 4318 households (mean household size = 4.9 individuals) corresponding to a sub-population size of approximately 21 000 in the total Republic of Ireland population of approximately 3.6 million.<sup>15</sup> In 1996 Traveller families had an average of 3.5 children as compared with 1.8 for the general population.<sup>15</sup> The incidence of transferase-deficient galactosaemia has recently been estimated at 1 in 700 in the Traveller group and 1 in 23 000 in the non-Traveller

population in Ireland.<sup>16</sup> The Travellers' Health Status Study of 1986–87<sup>17,18</sup> estimated that the population numbered 15 888 with a median age of 14 years as compared with 27 years in the non-Traveller population. There were 554 live births in 1986 corresponding to a crude birth rate of 34.9 per 1000 (16.6 per 1000 non-Travellers) with a perinatal mortality rate of 28.3 per 1000 (9.9 per 1000 non-Travellers). Several metabolic defects, including glutaric acidemia type I (MIM 231670) and transferase-deficient galactosaemia are common among them. The origins of the Travellers as a distinct group within the Irish population are the subject of some debate but two main views are extant. The 'migration hypothesis' suggests that the Travellers are derived from a group of nomadic craftspeople who migrated into Ireland from Europe at some point in the past, and who have subsequently maintained genetic isolation and have retained many distinct cultural characteristics. The 'endogenous hypothesis' suggests that the Travellers are descended from a genetic isolate derived from the original population of the island which, over time, has evolved an ethnic identity distinct from that of the general population.<sup>14</sup>

The present study has attempted to obtain more accurate figures for the incidence of classical transferase-deficient galactosaemia and to define the GALT mutation spectrum among patients in both of the Irish population groups.<sup>19</sup> Knowledge of the genetics of this disease in Ireland will provide a basis for the provision of improved diagnostic and genetic counselling services to the Traveller community and may begin to shed some light on their genetic history.

## Subjects and Methods

### Subjects

Seventy-three children with classical transferase-deficient galactosaemia were detected by newborn screening in the 25 year period from 1972 to 1996. Of these, 56 (including 39 unrelated individuals) were recruited to the present study through the National Newborn Screening Programme, The Children's Hospital, Temple Street, Dublin and blood samples were subjected to genotypic analysis. Ethical approval for the study was obtained from the Ethics Committee of The Children's Hospital. Biochemical diagnosis of the transferase-deficient phenotype was made using a bacterial inhibition assay<sup>20</sup> in conjunction with the Beutler assay.<sup>21</sup> Levels of GALT enzyme activity were measured by standard methods in the Department of Clinical Chemistry, Southmead Hospital, Bristol, UK. All patients admitted to the study had a clinical diagnosis of 'classical' galactosaemia; that is galactose-1-phosphate uridylyltransferase activity of  $<0.5 \mu\text{mol}$  of substrate converted/hour per gram of haemoglobin, thus excluding all cases exhibiting the Duarte phenotype. For carrier screening, samples were drawn anonymously from 1000

unaffected individuals via the National Newborn Screening Programme; this group, consisting of 750 non-Travellers and 250 Travellers, were all drawn from a single calendar year (1996) to minimise bias due to inclusion of siblings. Irish control DNA samples ( $n = 60$ ) were obtained from students in the Medical School of the Royal College of Surgeons in Ireland. Data on number of classical galactosaemic cases diagnosed per year was obtained from the records of the National Newborn Screening Programme.

### Methods

Bloods were collected on to Guthrie cards and, for PCR analysis, a segment of the blood spot (approximately 1mm in diameter) was excised from each of the cards to serve as the DNA template.

The Q188R mutation (exon 6) and a *Sac* I biallelic polymorphism (intron E) were detected by PCR-RFLP methods.<sup>12,19,22</sup> Selected Q188R homozygotes were confirmed by cycle sequencing (fmol™ cycle sequencing kit, Promega Corp. WI, USA) with radioisotopic detection. In genotyping the *Sac* I biallelic polymorphism, alleles were scored as *Sac* I(+) if the restriction site was present and *Sac* I(-) if the site was absent. Untyped mutant alleles were screened for sequence alteration in exons 5, 7 & 10 of the *GALT* gene by means of single strand conformation polymorphism (SSCP) analysis by the method of Orita *et al*<sup>23</sup> using PCR product sizes of approximately 200bp to maximise detection efficiency.<sup>24</sup> The primer pairs used for SSCP analysis were: exon 5, 5'-TTGGGGTTCGCCCTGCCCGTA-3' and 5'-CAAAGCTTCATCACCCCTCC-3'; exon 7, 5'-TGGGACAGAGGAAATATGCCA-3' and 5'-CCTTTA-CACACCTCTCATG-3'; exon 10, 5'-AGGTGC-TAACCTGGATAACTG-3' and 5'-CACATACTGCATGT-GAGAGTC-3'. These exons were targeted because they harbour the highest number of reported mutations (*GALTdb*).

A codon 333 mutation (exon 10) was detected by SSCP and restriction analysis.<sup>7</sup> Codon 333 of the *GALT* locus incorporates a CpG dinucleotide motif and is thus a 'hot spot' for mutation<sup>25</sup> with three recorded allelic variants, R333W, R333G and R333Q.<sup>7,11</sup> Mutation at this position, which eliminates a *Hpa* II restriction site, was detected by PCR amplification of exon 10 followed by *Hpa* II digestion. The nucleotide substitution was characterised by automated fluorescent DNA sequencing (ALFexpress, Pharmacia, Sweden) as a C to G transversion, corresponding to the inferred amino-acid substitution R333G. Automated fluorescent DNA sequencing was also used to detect the F194L (exon 7) mutation.

## Results

Surveying newborn screening records for the Irish Republic covering a 25 year period (1972–1996, Table 1), the overall incidence of classical transferase-deficient galactosaemia was found to be 73 cases (31 Traveller, 42 non-Traveller) in 1 540 585 live births or approximately 1 in 21 000. The only accurate data on annual birth rate among the Traveller community derives from the Travellers' Health Status Study, which documented 554 Traveller live births in 1986. To

**Table 1** Ascertainment of classical galactosaemia cases by newborn screening

Year	Total births	Total cases	Traveller cases	Non-Traveller cases
1972	67643	3	1	2
1973	67992	0	0	0
1974	67784	2	0	2
1975	67508	1	0	1
1976	68167	3	2	1
1977	68436	2	1	1
1978	69844	2	1	1
1979	72352	2	1	1
1980	74388	2	2	0
1981	72355	3	0	3
1982	70933	5	0	5
1983	66815	3	1	2
1984	64237	4	1	3
1985	62150	3	1	2
1986	61425	1	0	1
1987	58864	5	2	3
1988	54300	6	3	3
1989	51659	0	0	0
1990	52954	1	0	1
1991	52890	5	2	3
1992	51584	3	2	1
1993	49456	8	6	2
1994	47929	2	1	1
1995	48530	5	4	1
1996	50390	2	0	2
Total	1540585	73	31	42

minimise the influence of changes in the population demographics of the Traveller community during this period, estimates of disease incidence among the population groups were made for a 7 year interval centred on 1986 and assuming a constant Traveller birth rate of 550 per annum. On this basis, disease incidence estimates of 1 in 480 and 1 in 30 000 were obtained for the Traveller and non-Traveller groups respectively.

The patient cohort recruited to the study was screened for mutations in the *GALT* gene as described (Table 2a and 2b). The predominant mutant allele was found to be Q188R, occurring at a relative allele

**Table 2(a)** Mutant genotype distribution among the transferase-deficient galactosaemic patient cohort presented as genotype frequencies

Mutant genotype	Total cases (n = 39)	Traveller cases (n = 16)	Non-Traveller cases (n = 23)
Q188R/Q188R	34 (87.18%)	16 (100%)	18 (78.26%)
Q188R/R333G	1 (2.56%)	0 (0%)	1 (4.35%)
Q188R/F194L	1 (2.56%)	0 (0%)	1 (4.35%)
Q188R/?	3 (7.69%)	0 (0%)	3 (13.04%)

Q188R/? refers to compound heterozygotes for Q188R and an uncharacterised classic galactosaemia allele

**Table 2(b)** Mutant genotype distribution among the transferase-deficient galactosaemic patient cohort presented as allele frequencies

Mutant allele	Total alleles (n = 78)	Traveller alleles (n = 32)	Non-Traveller alleles (n = 46)
Q188R	73 (93.59%)	32 (100%)	41 (89.13%)
R333G	1 (1.28%)	0 (0%)	1 (2.17%)
F194L	1 (1.28%)	0 (0%)	1 (2.17%)
Other	3 (3.85%)	0 (0%)	3 (6.52%)

Other refers to an uncharacterised classical galactosaemia allele or alleles

frequency of 93.6% overall. Excluding siblings and dividing the patient cohort into Travellers and non-Travellers, Q188R was found to be the sole mutant allele among the Travellers and the majority mutant allele among the non-Travellers (89.1%). Of the five non-Q188R mutant alleles in the non-Traveller group, one was R333G and one F194L, three alleles remaining uncharacterised (Table 2b).

The allele and heterozygote (carrier) frequencies of Q188R in the Irish population were estimated by anonymous population screening. One thousand individuals, 250 Travellers and 750 non-Travellers, were screened by means of the PCR-RFLP assay for Q188R (Table 3). Among the non-Travellers seven Q188R alleles were detected, corresponding to an allele frequency of 0.005 and a carrier frequency of 0.009 or 1 in 107. Significantly higher values were obtained for the Traveller group: 23 Q188R alleles were detected, corresponding to an allele frequency of 0.046 and a carrier frequency of 0.092 or 1 in 11.

The Q188R mutation has previously been shown to be in disequilibrium with one of the alleles of the *Sac* I RFLP (*ivs5nt-24g→a*) flanking exon 6 of the *GALT* gene.<sup>22</sup> The patient group who were homozygous for the Q188R allele, together with a control group (*n* = 60 individuals), were screened for the presence or absence of the restriction site (Table 4). The *Sac* I restriction site was found to be present on all 68 Q188R alleles, both Traveller and non-Traveller. In contrast, among the

**Table 3** Determination of Q188R heterozygote (carrier) and allele frequencies in the Traveller and Non-Traveller populations by anonymous screening

	Q188R heterozygotes	Frequency	Q188R alleles	Frequency
Travellers (n = 250)	23	0.092 (1/11)	23/500	0.046
Non-Travellers (n = 750)	7	0.009 (1/107)	7/1500	0.005

All samples were drawn from infants born in the calendar year 1996 to minimise bias due to the inclusion of siblings

**Table 4** Frequency of the *Sac* I polymorphism on control chromosomes and on chromosomes harbouring the Q188R mutation

Chromosomes	<i>Sac</i> I (+)	<i>Sac</i> I (–)
Control (n = 120)	106 (88.3%)	14 (11.7%)
Q188R (n = 68) <sup>a</sup>	68 (100%)	0 (0%)
Q188R/Traveller (n = 32)	32 (100%)	0 (0%)
Q188R/Non-Traveller (n = 36)	36 (100%)	0 (0%)

<sup>a</sup>These figures refer only to unrelated individuals who were homozygous for Q188R

control group, the *Sac* I restriction site was present on 88.3% of chromosomes and absent from 11.7% of chromosomes. Given that the Duarte allele has a relative frequency of 5–10% in Europe, it is reasonable to suggest that a proportion of the *Sac* I(–) control chromosomes harbours the N314D mutation.<sup>3,4</sup> Our analysis has shown that the R333G and F194L, together with two of the three uncharacterised mutant alleles, were *Sac* I(+).

## Discussion

Most commonly, galactosaemia results from a deficiency in galactose-1-phosphate uridylyltransferase (*GALT*) activity,<sup>1</sup> referred to as transferase-deficient galactosaemia. The incidence of transferase-deficient galactosaemia worldwide is approximately 1 in 62 000 live births.<sup>13</sup> In the Republic of Ireland population we have found that the overall incidence of the disease is significantly higher, at approximately 1 in 21 000. When the incidence figures were broken down for the Traveller and non-Traveller population groups, the incidences were estimated to be 1 in 480 and 1 in 30 000 respectively. The incidence estimated for the non-Traveller community is comparable with the figures of 1 in 41 938 and 1 in 44 000 previously reported for the German and UK populations,<sup>13,26</sup> but the value of 1 in 480 estimated for the Traveller community is one of the highest incidences of transferase-deficient galactosaemia yet reported.<sup>13</sup>

Among the Traveller group, Q188R was found to be the sole *GALT* mutation (Table 2b), whilst among non-Travellers it accounted for 89.1% of mutant alleles. In the non-Traveller group a number of other mutant alleles were detected, including R333G (2.2%) and F194L (2.2%). The Q188R carrier frequency was determined in a group of 1000 unrelated individuals (250 Travellers and 750 non-Travellers) by anonymous population screening. Carrier frequencies for Q188R differed by approximately one order of magnitude

between Travellers and non-Travellers, being 1 in 11 (0.092) and 1 in 107 (0.009) respectively. When the Q188R allele frequency data obtained by population screening were used to predict the frequency of affected individuals (under the assumption of Hardy-Weinberg equilibrium), values in broad agreement with those calculated from the newborn screening records were obtained (1 in 470 Traveller and 1 in 37 300 non-Traveller). The similarity between observed and expected values would suggest that the disease incidence among the Travellers reflects the high Q188R allele frequency and that inbreeding may not be a significant factor contributing to the high incidence in that population.

The findings of this study raise a number of interesting questions about the population genetics of galactosaemia and the genetic history of the Travellers in Ireland.

- (i) Has Ireland been a centre of diffusion for the Q188R mutation in north-western Europe?

We have demonstrated that Q188R is the predominant allele in the Irish population, having an overall relative allele frequency of 93.6%. Q188R relative allele frequencies have been measured in neighbouring European populations: 77% in England, 65% in Germany, 60% in Austria.<sup>27,28</sup> It has been suggested by Holton *et al*<sup>28</sup> that the apparent cline of Q188R relative allele frequencies in a south-easterly direction is consistent with Ireland having been the centre of diffusion of this mutation. Our demonstration of the highest Q188R frequencies in Ireland is consistent with this hypothesis. If true, this would directly parallel the independent origin of the R408W haplotype 1.8 Phenylketonuria mutation in Ireland and its spread into mainland Europe.<sup>29–31</sup>

- (ii) Why is the Q188R allele frequency significantly higher among the Traveller community in Ireland?

The increased frequency relative to the non-Traveller group may be the result of a founder effect. It is possible that the founders of the modern Irish Traveller population may have harboured mutant alleles (including Q188R) which increased dramatically in frequency over time as the population underwent expansion. That founder effect coupled with rapid expansion can produce substantial increases in allele frequency has been elegantly demonstrated by genetic and genealogic studies of the modern Saguenay population in Quebec.<sup>32,33</sup> Given a high rate of population expansion and

consistently large family size across generations, a mutant allele can reach a frequency of 5% in the population in five to six generations even if just 2% of the founder group carried the mutant allele.<sup>32</sup> Family sizes among the Travellers are consistently large and there is evidence from recent surveys that the Traveller population has undergone considerable expansion; for example, in the 10 years between 1986 and 1996 the Traveller population may have increased in number by as much as 33% (15 888 vs about 21 000).

- (iii) What inferences about the genetic history of the Travellers can be drawn from our observations?

The origins of the Travellers are the subject of some debate with two main hypotheses predominating: the 'migration' and 'endogenous' hypotheses. The fact that Q188R is the sole mutant allele among the Travellers as compared to the non-Traveller group may be the result of a founder effect in the isolation of a small group of the Irish population from their peers as founders of the Traveller sub-population. This would favour the second, endogenous, hypothesis of Traveller origins. Our genotypic data derived from the analysis of the *Sac* I RFLP (Table 4) may support this. Previous studies have demonstrated that the Q188R mutation is in linkage disequilibrium with the *Sac* I RFLP in African-American, Asian, Caucasian and Latino galactosaemic patients. This has been interpreted to indicate that the Q188R mutation arose once in the history of the modern human population, being spread worldwide by demic diffusion.<sup>22</sup> We have demonstrated a similar disequilibrium in the Irish population where the *Sac* I restriction site was found to be present on all Q188R chromosomes. This may suggest that the Q188R mutation, on a *Sac* I(+) chromosomal 'background', was present in the indigenous population before the Travellers separated and was carried into the Traveller population by its founders. Our findings thus suggest that the modern Traveller sub-population in Ireland had an endogenous origin. Clearly, further consideration of these issues will only be possible on the basis of detailed demographic studies of the Traveller population and of molecular genetic studies of the Irish population, employing perhaps extended autosomal and sex chromosome haplotypes.

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