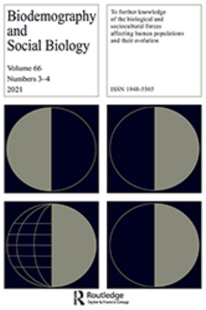

Biodemography and Social Biology

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/hsbi20

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To cite this article: Diamant Ulla-Britt, Winbo Annika, Karlsson Marcus, Edvinsson Sören & Rydberg Annika (2020) LQTS founder population in Northern Sweden – the natural history of a potentially fatal inherited cardiac disorder, Biodemography and Social Biology, 66:3-4, 191-207, DOI: 10.1080/19485565.2021.1999788

To link to this article: https://doi.org/10.1080/19485565.2021.1999788

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Published online: 11 Nov 2021.

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BIODEMOGRAPHY AND SOCIAL BIOLOGY
2021, VOL. 66, NOS. 3–4, 191–207
https://doi.org/10.1080/19485565.2021.1999788

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LQTS founder population in Northern Sweden – the natural history of a potentially fatal inherited cardiac disorder

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ABSTRACT

Long QT Syndrome (LQTS) is an autosomal dominant inherited cardiac disorder associated with life-threatening arrhythmias. In northern Sweden, a LQTS founder mutation (p.Y111C, KCNQ1 gene) was verified by genetic haplotype analysis and genealogical studies, and a common ancestor couple was identified. Clinical studies of this population revealed an apparent mild phenotype. However, due to early commencement of prophylactic treatment, the natural history of this disorder cannot be properly assessed based only on clinical data. By using the family tree mortality ratio method (FTMR), we assessed the natural history of the untreated LQTS founder population. The principle of FTMR is to compare the age-specific mortality rates in a historic population harboring an inherited disorder with the corresponding mortality rates in an unaffected control population.

Initially, we used the general Swedish population during the same period for comparison and observed an apparent increased longevity in the p.Y111C study population. However, when using a control population born in the same area, we observed no differences regarding overall mortality. Moreover, patterns suggesting age- and sex-stratified excess mortality, in accordance with previous LQTS studies, were evident.

This study shows the importance of being aware of historical demographic patterns to avoid misinterpreting when comparing historical data.

Introduction

"She was found dead with her face in a puddle, likely from fainting, to which she was predisposed" – this extract from a mid-19th century Västerbotten county parish register describes the circumstances surrounding the death of a local woman and illustrates what may be a case of a regionally occurring hereditary fainting disorder that we now have more knowledge of.

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Historical sources can assist us in identifying possible familial cases, as well as in analyzing the natural history of hereditary disorders, in times before diagnostic tools, and prophylactic treatments were available. In this study, we take a long-term perspective on the disorder historically described as "hereditary fainting" in a region where its prevalence is relatively high and investigate its possible impact on survival in families harboring the disorder.

Our questions are: Does heredity for the disorder increase overall mortality in the affected families? Are there different mortality patterns between the sexes and/or between different age groups in the affected families?

We studied this by using the family tree mortality ratio method (FTMR), with standardized mortality ratio (SMR) as the main outcome measure. Using this method, the mortality data derived from the affected families' multigenerational pedigrees is standardized to mortality data from the general population. We also assess the suitability of national and regional population data, respectively, for comparative purposes.

The first report of "hereditary fainting" was made by Professor Jervell with his associate Dr. Lange-Nielsen in 1957 in siblings with concomitant congenital hearing loss (Jervell and Lange-Nielsen 1957). "Hereditary fainting" without hearing loss was eventually named Romano-Ward Syndrome, after the doctors that first described the syndrome in the early '60s (Romano and Gemme et al. 1963; Ward 1964). The typical phenotype constituting familial loss-of consciousness, combined with electrocardiographic abnormalities in the form of a long QT interval on the resting surface electrocardiogram, contributed to the denomination "Long QT Syndrome" (LQTS) (Schwartz and Periti et al. 1975). The QT interval is measured on the resting surface electrocardiogram and represents the total time taken to de- and repolarize the ventricles. LQTS was found to be an inherited cardiac electrophysiological disorder with an autosomal dominant inheritance pattern, leading to a propensity for life-threatening arrhythmias on the basis of delayed cardiac repolarization. Beta-blocker pharmacotherapy was proven to be prophylactic, resulting in reduced arrhythmia symptoms and prevention of sudden cardiac death (Moss and Zareba et al. 2000). LQTS was further described as a heterogeneous disease with several variants of phenotype and genotype, where LQTS type 1 (LQT1) is the most common variant. LQT1 is characterized by events that are triggered primarily by exercise or stress (Schwartz and Priori et al. 2001). Age- and sex-related studies on LQTS patients have shown that cardiac events are higher in boys before puberty and females thereafter (Locati and Zareba et al. 1998).

LQT1 is caused by loss-of-function pathogenic sequence variants in the *KCNQ1* gene, situated on the short arm of chromosome 11. Several hundred different LQT1 causing variants have been identified in the *KCNQ1* gene, explaining part of the heterogeneous phenotype. Adding to the heterogeneity, most commonly, LQTS variants are unique to the index family in which they were identified.

In the early '70s Pediatric Cardiologist Hans Wendel at the University Hospital in Umeå, in northern Sweden, realized that he had diagnosed LQTS in several local families, suggesting that the disorder might be "uncommonly common" in the region. He also found that the phenotype seemed unusually mild; the patients suffered from recurrent fainting, but aborted cardiac arrest or sudden death was rare. In the '90s, with the arrival of the era of genetic diagnostics, it was shown that the majority of the regional LQTS patients carried the same pathogenic LQT1 sequence variant, p.Y111C (c.332A >G) in the *KCNQ1* gene. The following questions were raised: why was this specific sequence variant so commonly occurring, and was this indeed a comparatively benign LQT1 variant? These important questions inspired and initiated the LQTS research in Northern Sweden (Schwartz 2011; Winbo and Diamant et al. 2011, 2009).

Background

The northern region of Sweden, comprising over half of Sweden's total area, includes several geographically isolated river valleys spanning the region from northwest to southeast. These river valleys were sparsely populated with few initial settlers, who favored marrying persons in the same river valley, and consequently had a slow initial population growth (~50% 1571–1750;), followed by a marked population growth (~250% 1750–1950) (Einarsdottir and Egerbladh et al. 2007). These factors promote development of so-called founder effects, where genetic variation is lost as new populations are established by small population subsets. The resultant founder populations hence constitute descendants of common founders, sharing genetic information by descent. In the northern region prevalent founder effects are evident through genetic sub-isolates identified in the separate river valley regions (Einarsdottir et al. 2007), and a high frequency of several inherited disorders is present, e.g. hemochromatosis (Olsson and Ritter et al. 2008).

From early on, it was speculated that the common occurrence of the LQT1 p.Y111C sequence variant in the northern region might be secondary to founder effects. This was supported by the demonstration of geographical clustering of the ancestors of all 37 p.Y111C families, including the migration and spread of a subset of the ancestors and their descendants, along the Ångerman river valley between the 17th and 20th centuries (Figure 1**a+b**), (Winbo et al. 2011)). Genealogical studies of the p.Y111C families revealed a common ancestor couple born in 1605/1614, connecting 26/37 p.Y111C index families through transmission lines spanning over 13 generations (Figure 2) a+b, (Winbo et al. 2011)). The founder status of the entire p.Y111C population was further verified by genetic microsatellite marker analysis, revealing a shared haplotype block in all investigated families, irrespective of genealogical ties (Winbo et al. 2011).

As Dr. Wendel had suspected, clinical studies characterizing the large p.Y111C founder population revealed an apparent mild phenotype with a comparatively low incidence of aborted cardiac arrests and sudden cardiac death (Winbo et al. 2009). However, due to extensive diagnostic cascade-screening that has facilitated early detection of cases and early commencement of prophylactic treatment in the p.Y111C founder families, combined with the effectiveness of beta-blockers in preventing life-threatening cardiac events, the severity and natural history of this hereditary disorder cannot be properly assessed based on clinical data in isolation. Here we assess all-cause mortality in the p.Y111C founder population, during a time period when the disease typically was not identified or known and carriers of the pathogenic sequence variant hence untreated.

Materials and Methods

Data

In 2005 the regional LQTS Family Clinic was initiated as a part of the Center for Cardiovascular Genetics at Umeå University Hospital in Sweden. Clinical and genetic data was consecutively collected from consenting participant families, identified via local, regional or national referrals to the LQTS Family Clinic. Genealogical information was collected and compiled, facilitated by the unique Swedish parish records and catechetical examination registers dating from the 17th century onwards. These records constituted the basis for Swedish population registers until 1991, covering the complete population and recording all vital demographic events (Westberg and Engberg et al 2016). Historical national population demographic data was obtained from the Statistics Sweden (www.scb.se). Parish population statistics for the period 1749–1859 was obtained from the Tabellverket database at the Demographic Data Base, Umeå University (www.cedar.umu.se/english/ddb/databases/tabverk/). This registry, based on parish registers, includes annually recorded data on births, deaths, marriages, and migration of inhabitants in Swedish parishes, as well as figures on population structure (age, sex, marital status and occupation), per five-year period. Tabellverket was the basis for Swedish national population statistics, which made Sweden a forerunner in this respect, and these statistics are considered to be comprehensive and accurate (Sköld 2004). For the period from 1860 onwards, demographic data was collected from excerpts of parish registers available at Statistics Sweden (www.scb.se). Data from censuses accessible from the Swedish National Archives and their information homepage (www.svar.ra.se) was used for calculating population structure for the period after 1860. Digital genealogical archives and private genealogic databases have also been utilized.

Methods

The family tree mortality ratio method (FTMR) was first described by Rosendaal in 1991, studying mortality in hereditary antithrombin III deficiency (Brandjes and Heijboer et al. 1991). In 2001, the method was used to describe mortality in familial hypercholesterolemia – an inherited disorder leading to cardiac disease and premature death (Sijbrands and Westendorp et al. 2001). The FTMR has further been applied in several inherited cardiac disorders such as in familial hypertrophic cardiomyopathy and inherited arrhythmia disorders (Nannenberg and Sijbrands et al. 2012).

The principle of the FTMR is to compare mortality in a population harboring an inherited disorder with the mortality in the general population (Nannenberg et al. 2012). The assessment starts with at least two affected individuals from different index families, not apparently related but sharing the same pathogenic sequence variant. Then genealogical investigations are performed, tracing all maternal and paternal ancestral lines to identify a common pair of distant ancestors. In autosomal inherited diseases, all persons transmitting the pathogenic sequence variant to the next generation can be regarded as obligate carriers (100% probability) and all siblings and children of obligate carriers have a 50% probability to be carriers of the familial sequence variant. This makes it possible to assess the mortality in populations carrying a specific pathogenic sequence variant causing an autosomal

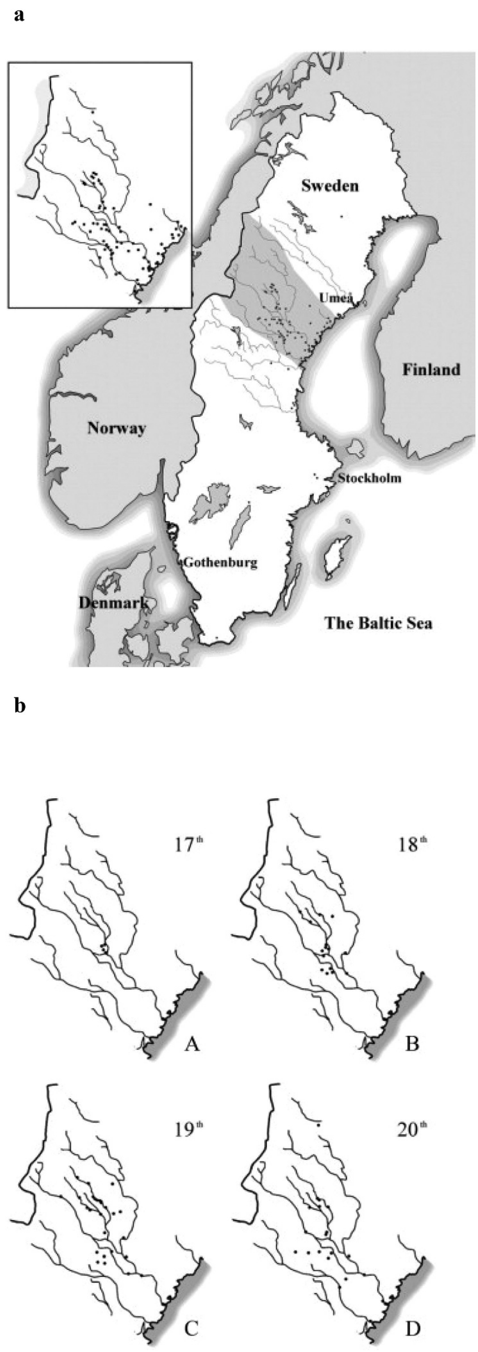

Figure 1. **a**. Map of Sweden/Scandinavia illustrating the geographic clustering of ancestors of all 37 long QT syndrome Y111C/KCNQ1 index families during the 19th century. The rivers and tributaries flowing from northwest to southeast across northern Sweden are depicted as lines. The river valley region of interest, shown in magnification in the upper left corner, is shaded in gray. Birthplaces of p.Y111C ancestors are indicated by dots. (Winbo, A. (2011). Reproduced with permission from Elsevier). **bBb** Regional maps (A-D) of the Ångerman River valley area in mid-northern Sweden during four centuries (17th–20th centuries). The birth places of the founder couple and their descendants, indicated by *dots*, demonstrate the migration and spread of the long QT syndrome Y111C/*KCNQ1* population over time. The Ångerman River is depicted by *forking lines*. The region is delimited by the Norwegian border on the left and the Gulf of Bothnia/Baltic Sea on the right. (Winbo et al. (2011). Reproduced with permission from Elsevier).

dominant inherited disease, identifying "historical" carriers by Mendelian randomization (Hille and Westendorp et al. 1997). To avoid survival bias from the transmission lines, only data from the 50% probability mutation carriers were included in the analysis, constituting the historical study population. Infants aged less than one year were excluded from the study population. This was done because infant deaths were not consistently recorded in the parish records, making identification of infant deaths and in particular allocation of infant deaths to the right family difficult, thereby risking infant mortality in the genealogical data to be underestimated. All data on birth, death and sex in the study population were included in the analysis. Age- and sex-stratified mortality rates were calculated, defined as the number of deaths in a particular population, scaled to the size of that population, per unit of time. Mortality rates in the study population were then compared with the mortality rates derived from the general population. The age- and sex-stratified data were presented using the standardized mortality ratio (SMR), where SMR is a relative risk calculated from the ratio of incidence rates in the study population and the general population (Hille et al. 1997). If the SMR is >1 there is excess mortality in the study population (Hille et al. 1997). The Poisson variable (one-sided) was used to calculate the CI (95%) of the SMR (Nannenberg and Michels et al. 2011; Nannenberg et al. 2012). The level of statistical significance was defined as a p-value < 0.05.

In our first data analysis (FTMR I) we calculated the SMR for the p.Y111C founder population gathered in a large multigenerational pedigree, where 27 index families shared a common geographic origin and a common ancestor couple. The mortality data of the founder population was then compared with the mortality in the general Swedish population. National figures are usually the readiest available and are those most frequently used for FTMR analyses, based on the assumption that they reflect historical mortality patterns with sufficient accuracy.

However, previous studies on Swedish population history have demonstrated large regional differences in mortality (Edvinsson and Gardarsdottir et al. 2008; Brändström and Edvinsson et al. 2000, 2002). Thus, national figures may not be accurate enough to use for comparison. In our second data analysis (FTMR II) we therefore identified the central areas of birth and residence for the p.Y111C families over time, and the mortality in the general population in these same areas was subsequently used for comparison to calculate the SMR for the p.Y111C founder population.

FTMR I

FTMR Ia: We collected genealogical data on birth, age at death and sex from 27 families and 535 individuals (266 males and 269 females) from the p.Y111C founder population during the time period 1751 to 2006 (Figure 2**a**)). All individuals on beta-blocker pharmacotherapy (after the year of 1973) were excluded from the analysis.

FTMR Ib: To correct for possible effects related to having chosen the wrong transmission lines in the analysis, entire transmission lines that involved intermarriage were excluded. The resulting cohort involved 313 individuals (150 males and 163 females) from the p.Y111C founder population during the time period 1751 to 2006 (Figure 2**b**)). As before, we also excluded all individuals on beta-blocker pharmacotherapy after 1973.

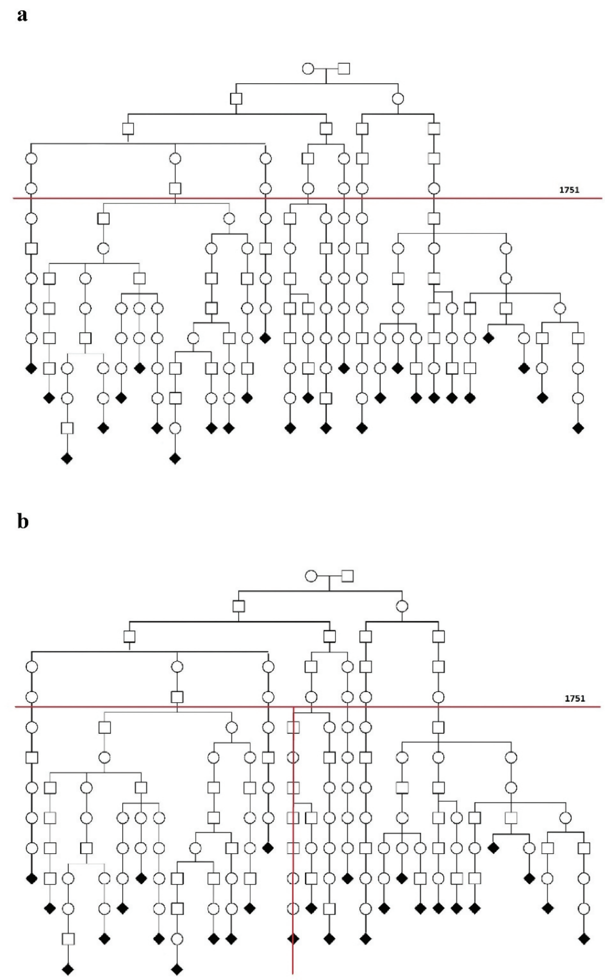

Figure 2. **a** The pedigree illustrates the transmission lines identified by genealogical investigation in 535 individuals in 27 p.Y111C families from the year of 1751 (horizontal line) until 2006. **b** The pedigree includes 313 individuals in p.Y111C families in the mortality analysis from the year of 1751 until 2006. To correct for possible effects related to having chosen the wrong transmission lines in the analysis, entire transmission lines that involved intermarriage were excluded (see example vertical line).

Mortality data in the p.Y111C founder population from Ia and Ib was compared to the expected mortality found in the general population of Sweden during the same period using FTMR statistics.

FTMR II

When we followed the 27 families from 1751 to 1930 they were all born in 11 parishes from 3 counties (Jämtland, Västernorrland and Västerbotten) (Table 1 and Figure 3).

Table 1. Birth parishes and counties for the p.Y111C population (1751 to 1930).

Parish		County
Alanäs	A	The County of Jämtland
Borgvattnet	B	The County of Jämtland
Hammerdal	C	The County of Jämtland
Dorotea församling	D	The County of Västerbotten
Dorotea församling (part of county)		The County of Västernorrland
Åsele	E	The County of Västerbotten
Bodum	F	The County of Västernorrland
Fjällsjö	G	The County of Västernorrland
Junsele	H	The County of Västernorrland
Ramsele	I	The County of Västernorrland
Tåsjö	J	The County of Västernorrland
		The County of Jämtland from 1974
Ström (part of county)	K	The County of Västernorrland
Ström		The County of Jämtland

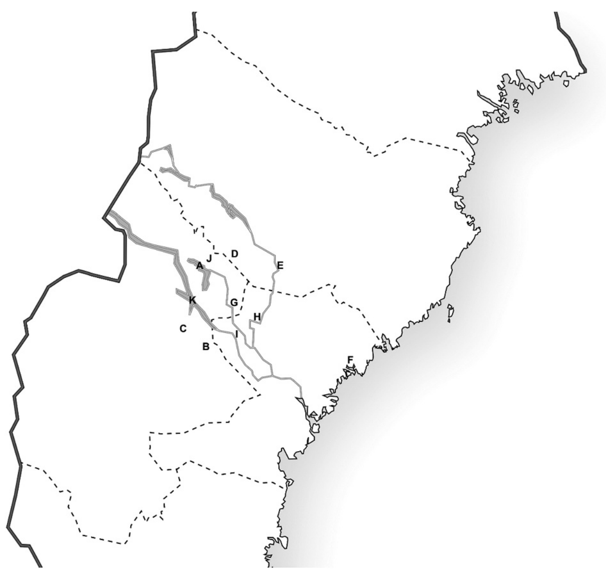

Figure 3. Map of mid-northern Sweden indicating the dotted outline of the counties where the p.Y111C founder population ancestors were born and resided during the time-period 1751–1930 (top Västerbotten County, bottom left Jämtland County, and bottom right Västernorrland County). The location of the parishes (named in Table 1) are denominated using capital letters (A-K). The Ångerman River is depicted by forking gray lines. The region is further delimited by the Norwegian border on the left and the Gulf of Bothnia/Baltic Sea on the right (shaded).

FTMR IIa and IIb: Mortality data in the p.Y111C founder population from FTMR Ia and Ib, respectively, was compared to the expected mortality found in the general population living in the same area as the study population, during the same period, using FTMR statistics (11 parishes from 3 counties; Jämtland, Västernorrland and Västerbotten, Table 1).

Table 2. Age-stratified standardized mortality ratio analysis in 27 p.Y111C families* derived by comparison with mortality rates in the general population in Sweden 1751–2006.

Age category (years of age)	Observed death	Expected death	SMR	95% CI
1–4	18	50.76	0.35	0.2–0.5
5–9	5	9.65	0.52	0.2–1.1
10–14	5	5.39	0.93	0.3–1.9
15–19	2	6.30	0.32	0–0.9
20–24	8	9.99	0.80	0.3–1.5
24–29	4	9.88	0.40	0.1–0.9
30–34	6	10.17	0.59	0.2–1.2
35–39	4	10.84	0.37	0.1–0.8
40–44	10	11.78	0.85	0.4–1.5
45–49	9	13.24	0.68	0.3–1.2
50–54	11	15.97	0.69	0.3–1.2
55–59	14	19.52	0.72	0.4–1.2
60–64	11	24.78	0.44	0.2–0.8
65–69	27	32.17	0.84	0.5–1.2
70–74	34	38.37	0.91	0.6–1.2
75–79	39	40.11	0.97	0.7–1.3
80–109	61	73.52	0.83	0.6–1.1
1–109	268	382.44	0.70	0.6–0.8

SMR- standardized mortality ratio
*Includes 535 individuals (266 males and 269 females) from all transmission lines in the p.Y111C family tree

Table 3. Age-stratified standardized mortality ratio analysis in p.Y111C families* derived by comparison with mortality rates in the general population in Sweden 1751–2006.

Age category (years of age)	Observed death	Expected death	SMR	95% CI
1–4	10	34.10	0.29	0.1–0.5
5–9	2	6.53	0.31	0–0.9
10–14	4	3.61	1.11	0.3–2.5
15–19	2	4.04	0.49	0–1.4
20–24	5	6.40	0.78	0.2–1.6
24–29	1	6.51	0.15	0–0.6
30–34	4	6.84	0.58	0.1–1.3
35–39	1	7.36	0.14	0–0.5
40–44	6	8.11	0.74	0.3–1.5
45–49	7	9.11	0.77	0.3–1.5
50–54	7	11.04	0.63	0.2–1.2
55–59	9	13.28	0.68	0.3–1.2
60–64	8	16.74	0.48	0.2–0.9
65–69	16	21.28	0.75	0.4–1.2
70–74	25	26.47	0.94	0.6–1.4
75–79	31	27.73	1.12	0.8–1.6
1–79	138	209.15	0.66	0.6–0.8

SMR- standardized mortality ratio
* Includes 313 individuals (150 males and 163 females), excluding entire transmission lines in the p.Y111C family tree involving intermarriage, to eliminate the risk of inbreeding and of having chosen the wrong transmission lines in the analysis.

Results

FTMR I

In this analysis, the SMR was derived from comparison of mortality rates between the p.Y111C study population and the general population in Sweden during the same period.

FTMR Ia

In the 27 p.Y111C families, a total of 268 deaths were observed between 1751 and 2006 among 535 people analyzed for 25318 person years. The age-stratified SMRs for the study population is presented in Table 2. The mean SMR for the p.Y111C study population was 0.70; however, the difference in mortality rates between the populations was not significant (p = .940).

FTMR Ib

In the p.Y111C founder population corrected for effects of intermarriage, a total of 138 deaths were observed between 1751 and 2006 among 313 people analyzed for 15510 person years. The age-stratified SMRs for the study population is presented in Table 3. The mean SMR for the p.Y111C study population was 0.66 (p = .861).

FTMR II

In this analysis, the SMR was derived from comparison of mortality rates between the p.Y111C study population and the control population born in the same area (eleven parishes) during the same period. We also analyzed females and males separately.

FTMR IIa

A total of 268 deaths occurred in 535 individuals (25318 person years) between 1751 and 2006. The age-stratified SMRs for the study population are presented in Table 4. The mean SMR was 0.96 for the whole founder population, revealing no significant difference in mortality for the p.Y111C founder population as compared to the control population in the same area (p = .940).

Table 4. Age-stratified standardized mortality ratio analysis in 27 p.Y111C families* derived by comparison with mortality ratio in a control population born in the same area 1751–1930.

Age category (years of age)	Observed death	Expected death	SMR	95% CI
1–4	18	16.00	1.12	0.7–1.7
5–9	5	6.15	0.81	0.2–1.7
10–14	5	4.56	1.10	0.3–2.3
15–19	2	5.73	0.35	0–1
20–24	8	9.33	0.86	0.4–1.6
24–29	4	8.17	0.49	0.1–1.1
30–34	6	7.68	0.78	0.3–1.5
35–39	4	7.91	0.51	0.1–1.1
40–44	10	9.94	1.01	0.5–1.7
45–49	9	9.43	0.95	0.4–1.7
50–54	11	12.13	0.91	0.4–1.5
55–59	14	14.10	0.99	0.5–1.6
60–64	11	18.51	0.59	0.3–1
65–69	27	24.54	1.10	0.7–1.6
70–74	34	30.18	1.16	0.8–1.5
75–79	39	32.60	1.20	0.8–1.6
80–109	61	64.30	0.95	0.7–1.2
1–109	268	282.16	0.96	0.8–1.1

SMR- standardized mortality ratio
* Includes 535 individuals (266 males and 269 females) from all transmission lines in the p.Y111C family tree

Table 5. Age- and sex-stratified standardized mortality ratio analysis in 27 p.Y111C families* derived by comparison with mortality ratio in a control population born in the same area 1751–1930.

	Female and male		Female		Male	
Age category (years of age)	SMR	95% CI	SMR	95% CI	SMR	95% CI
1–4	1.12	0.7–1.7	1.43	0.7–2.5	0.89	0.4–1.6
5–9	0.81	0.2–1.7	0.35	0–1.4	1.20	0.3–2.7
10–14	1.10	0.3–2.3	0.89	0.1–2.6	1.30	0.2–3.2
15–19	0.35	0–1	0.00	0.4–0.4	0.64	0.1–1.9
20–24	0.86	0.4–1.6	1.00	0.3–2.3	0.75	0.2–1.7
24–29	0.49	0.1–1.1	0.76	0.1–1.9	0.24	0–0.9
30–34	0.78	0.3–1.5	0.74	0.1–1.8	0.83	0.1–2.1
35–39	0.51	0.1–1.1	0.25	0–1	0.76	0.1–1.9
40–44	1.01	0.5–1.7	1.37	0.5–2.7	0.72	0.2–1.6
45–49	0.95	0.4–1.7	0.95	0.2–2.1	0.96	0.3–2
50–54	0.91	0.4–1.5	1.03	0.3–2.2	0.83	0.3–1.6
55–59	0.99	0.5–1.6	0.82	0.2–1.7	1.13	0.5–2
60–64	0.59	0.3–1	1.08	0.5–2	0.27	0–0.7
65–69	1.10	0.7–1.6	1.49	0.8–2.4	0.83	0.4–1.4
70–74	1.16	0.8–1.5	1.24	0.7–2	1.11	0.7–1.7
75–79	1.20	0.8–1.6	1.17	0.7–1.8	1.22	0.7–1.8
80–109	0.95	0.7–1.2	0.91	0.6–1.3	1.00	0.7–1.4
1–109	0.96	0.8–1.1	1.00	0.8–1.2	0.91	0.8–1.1

SMR- standardized mortality ratio
* Includes 535 individuals (266 males and 269 females) from all transmission lines in the p.Y111C family tree

Table 6. Age-stratified standardized mortality ratio analysis in p.Y111C families, derived by comparison with mortality ratio in a control population born in the same area 1751–1930.

Age category(years of age)	Observed death	Expected death	SMR	95% CI
1–4	10	10.25	0.98	0.5–1.7
5–9	2	3.91	0.51	0–1.5
10–14	4	2.94	1.36	0.3–3.1
15–19	2	3.36	0.60	0.1–1.7
20–24	5	5.54	0.90	0.3–1.9
24–29	1	4.99	0.20	0–0.8
30–34	4	4.87	0.82	0.2–1.8
35–39	1	5.12	0.20	0–0.8
40–44	6	7.03	0.85	0.3–1.7
45–49	7	6.23	1.12	0.4–2.1
50–54	7	8.05	0.87	0.3–1.7
55–59	9	9.08	0.99	0.4–1.8
60–64	8	11.98	0.67	0.3–1.2
65–69	16	15.46	1.04	0.6–1.6
70–74	25	20.15	1.24	0.8–1.8
75–79	31	22.18	1.40	0.9–1.9
80–109	40	43.46	0.92	0.7–1.2
1–109	178	184.61	0.83	0.8–1.1

SMR- standardized mortality ratio
* Includes 313 individuals (150 males and 163 females), excluding entire transmission lines in the p.Y111C family tree involving intermarriage, to eliminate the risk of inbreeding and of having chosen the wrong transmission lines in the analysis.

Sex-stratified SMRs for each age group are presented in Table 5 and indicated potential excess mortality in p.Y111C females aged 40–44 years, SMR of 1.37. However, this finding was not significant (p = .279).

Table 7. Age and sex-stratified standardized mortality ratio analysis in p.Y111C families, derived by comparison with mortality ratio in a control population born in the same area 1751–1930.

	Female and male		Female		Male	
Age category (years of age)	SMR	95% CI	SMR	95% CI	SMR	95% CI
1–4	0.98	0.5–1.7	1.10	0.3–2.3	0.88	0.3–1.8
5–9	0.51	0–1.5	0.56	0–2.2	0.47	0–1.9
10–14	1.36	0.3–3.1	0.69	0–2.7	2.02	0.4–5
15–19	0.60	0.1–1.7	0.00	0.2–0.2	1.13	0.1–3.3
20–24	0.90	0.3–1.9	1.61	0.4–3.6	0.33	0–1.3
24–29	0.20	0–0.8	0.40	0–1.6	0.00	0.4–0.4
30–34	0.82	0.2–1.8	1.13	0.2–2.8	0.45	0–1.8
35–39	0.20	0–0.8	0.00	0.4–0.4	0.40	0–1.6
40–44	0.85	0.3–1.7	1.68	0.5–3.5	0.25	0–1
45–49	1.12	0.4–2.1	0.71	0.1–2.1	1.47	0.4–3.1
50–54	0.87	0.3–1.7	1.20	0.3–2.7	0.64	0.1–1.6
55–59	0.99	0.4–1.8	0.72	0.1–1.8	1.22	0.4–2.4
60–64	0.67	0.3–1.2	0.97	0.3–2	0.44	0.1–1.1
65–69	1.04	0.6–1.6	1.15	0.5–2.1	0.94	0.4–1.7
70–74	1.24	0.8–1.8	1.32	0.7–2.2	1.18	0.6–1.9
75–79	1.40	0.9–1.9	1.31	0.7–2.1	1.49	0.8–2.3
80–109	0.92	0.2–0.5	0.88	0.6–1.3	0.98	0.6–1.5
1–109	0.83	0.8–1.1	0.81	0.8–1.2	0.92	0.7–1.1

SMR- standardized mortality ratio

* Includes 313 individuals (150 males and 163 females), excluding entire transmission lines in the p.Y111C family tree involving intermarriage, to eliminate the risk of inbreeding and of having chosen the wrong transmission lines in the analysis.

FTMR IIb

In the p.Y111C founder population corrected for effects of intermarriage, a total of 138 deaths occurred in 313 individuals (15510 person years) between 1751 and 2006. The age-stratified SMRs for the study population is presented in Table 6. The SMR analysis revealed no significant excess mortality in the p.Y111C founder population, as compared to the control population born in the same area, mean SMR 0.83 ($p = .861$).

Sex-stratified SMRs for each age group are presented in Table 7 and indicated potential excess mortality among boys aged 10–14 years, SMR 2.02 ($p = .187$) and females aged 40–44 years, SMR 1.68 ($p = .181$).

Discussion

Using the family tree mortality ratio method, we aimed to assess the “natural history” of an untreated LQT1 founder population carrying the same pathogenic sequence variant in the *KCNQ1* gene. The expression “natural history” can of course be questioned, since diseases are always affected by historical contexts and developments. Initially, we used the mortality of the general Swedish population during the same period for comparison and found, surprisingly, an SMR <1, representing a comparatively increased longevity in the p.Y111C population with a 0.5 probability of having a pathogenic sequence variant, causing a potentially life-threatening disease. This study includes mortality data for individuals born between 1751 and 2006. At the beginning of the studied period, Sweden was experiencing the initial phases of a demographic transition. Life expectancy was 33.7 years for men and 36.4 years for women during the latter half of the 18th century. The mortality decline started by the turn of the 19th century, and steadily increased life expectancy throughout the studied period. Male life expectancy increased to 50.9 years and female to

53.6 years in 1891–1900. In 2010, males could be expected to live 79.5 years and females 83.5 years (www.scb.se). Mortality in the 18th and 19th centuries was characterized by a high mortality among infants and young children. Cause of death was typically different infectious diseases, mostly of epidemic character. The fact that infectious diseases dominated mortality as well as the disease pattern, led to large spatial differences within the country depending on how different regions and environments were exposed to infections (Edvinsson and Gardarsdottir et al. 2008; Brändström, Edvinsson, and John Rogers 2000, 2002). Urban settings were particularly exposed due to poor sanitary conditions, overcrowded living conditions and frequent personal contacts and communication. People in remote and sparsely populated areas, such as the parishes where the p.Y111C founder population ancestors lived, therefore had an advantage. Life expectancy was as high as 55 years already in the early 19th century in the county of Jämtland, a county that contains four of the parishes included in the area identified as the center for the founder population settlements (life expectancy calculated from county statistical tables 1816–1820, National Archives, Sweden).

When mortality from infectious diseases started to decline, the difference between regions and environments, urban and rural settings, diminished. This process took place during the 19th and early 20th century, particularly during the last decades of the 19th century. In the 1920s and 1930s, there were no longer any particular difference in mortality levels between urban and rural settings, and the regional differences were now much smaller than before. For the time thereafter until the present, remote places were in fact more disadvantaged. Mortality has moreover changed to become dominated by chronic diseases and most deaths occur in old age (Sundin and Willner 2007).

When using comparable data (i.e. a control population born in the same area), we found no significant differences regarding mortality in the p.Y111C founder population as compared to the general population. This supports our previous conclusion that the p.Y111C mutation in the *KCNQ1* gene, despite being predicted to cause dominant-negative effects via impaired trafficking (Dahimene and Alcolea et al. 2006), has a comparatively mild clinical expression in the setting of this specific founder population (Winbo et al. 2009). Having established that the p.Y111C families share a common haplotype, we hypothesized that there might be genetic material with ameliorating modifying properties co-segregating with p.Y111C in the founder pedigree (Winbo et al. 2011). Potentially protective effects of genetic modifiers on LQT1 patients have since been reported (Amin and Giudicessi et al. 2012; Lee and Sala et al. 2021). In 2012, potentially ameliorating effects of allele-specific gene suppression due to variants in the 3′untranslated region of the *KCNQ1* gene in LQT1 populations were reported (Amin et al. 2012). In a recent study including human-induced pluripotent stem cell-derived cardiomyocytes from two patients with p.Y111C, variants in the Myotubularin-related protein 4 (*MTMR4*) gene were associated with protective effects, proposed to be mediated via decreased Nedd4L activity (Lee et al. 2021). The same *MTMR4* variants were also present in 10/13 unrelated asymptomatic p.Y111C patients (Lee et al. 2021). Future studies will reveal whether variants in the 3′untranslated region of the *KCNQ1* gene and *MTMR4* gene are associated with protective effects in the p.Y111C founder population.

It has previously been demonstrated that specific LQT1 pathogenic sequence variants may be more malignant, inferring an increased risk for cardiac events, in support of genotype-specific risk stratification and management (Crotti and Spazzolini et al. 2007).

It has also been previously shown that, even among carriers of identical pathogenic sequence variants, sex and age influences risk for cardiovascular events in LQTS. In our study, we could find a tendency toward higher SMR in pre-pubertal boys, which is supported by many earlier studies. During childhood (0–12 years) boys with LQTS type 1 have a more than 2-fold increased risk for aborted cardiac death or sudden cardiac death as compared to girls (Costa and Lopes et al. 2012). Locati et al. showed that male gender is independently associated with an increased risk among probands and affected family members (Locati et al. 1998). The risk of syncope, aborted cardiac arrest or sudden cardiac death is highest among males before 15 years of age, and thereafter there is a reversed risk, where the females from the age of 14 years have a higher risk for syncope and aborted cardiac arrest or sudden cardiac death, as compared to males. Indeed, during childhood, LQT1 boys exhibit a 71% increase in the risk of a first cardiac event, as compared to girls of the same age (Zareba and Moss et al. 2003). This study also demonstrated gender risk reversal after the age of 16 years, in which the risk of cardiac events was more than 3-fold higher among both LQT1 and LQT2 girls as compared to boys of the same genotype. The risk of aborted cardiac arrest or death from the age of 41 to 75 years was assessed in 2759 subjects from the International LQTS Registry (Goldenberg and Moss et al. 2008). It was shown that it is possible to distinguish different risk factors also in older age groups after 40 years of age. LQTS women with prolonged QTc display a significant higher cumulative risk of aborted cardiac arrest or death than LQTS women with borderline or normal QTc. This is also in line with our findings of a tendency toward higher SMR in women over 40 years of age.

The finding that SMR results differ depending on what normal population is used for comparison demonstrates, and underscores, the importance of being conscious about historical demographic patterns and trends when conducting research. In historical time, spatial differences in mortality were large, thus making the right choice on which normal population to use for comparison crucial. A perfect reference group can be difficult to identify and collect, but we must aim for defining the population as close to the geographical area of the studied group as possible. However, we realize that these data are not always possible and available in every country. In the case of this study, we identified a geographically restricted area where the population could be followed through several generations. Using the comprehensive preserved Swedish population records, it was possible to reconstruct genealogical trees and to relate survival to general contemporary population patterns.

This study clearly shows the importance of being aware of the historical demographic conditions, patterns, and trends to give more insights in the natural history of a disease and to increase the accuracy of interpreting historical data.

Limitations

Individuals on beta-blocker therapy were excluded from the SMR analysis due to the well documented protective effect of beta-blockers in the prophylactic treatment of LQT1. In our clinical practice, all LQTS children, irrespective of phenotype, and all adult LQTS patients with a prolonged QT or a symptomatic phenotype are recommended beta-blockers. As a more severe phenotype is associated with higher probability of being on beta-blockers, especially among adults, the exclusion of individuals on beta-blocker therapy constitutes a possible inclusion bias toward individuals with a less severe phenotype for the SMR analyses. However, our previous study on the clinical phenotype of the p.Y111C founder population, including individuals on beta-blockers, revealed a low incidence of aborted cardiac arrest and sudden cardiac death (Winbo et al. 2009).

Infant mortality (death <1 year of age) was omitted from the SMR analysis due to the uncertainty of historical data registration of infant deaths. This precludes us from assessing potential excess infant mortality due to LQT1 in the p.Y111C founder population and conveys a risk of missing important early traits of the disease. However, based on current knowledge, heterozygous LQT1 is typically associated with a mild phenotype in infancy, which should limit the impact of omitting infant mortality from the SMR analysis.

Acknowledgement

Acknowledgements to Eline Nannenberg for great assistance in data analysis.

Acknowledgements to Erik Winbo for providing original artwork in Figures 1a+b and Figure 3.

Disclosure Statement

No potential conflict of interest was reported by the author(s).

Funding

This work was supported by the Swedish Heart-Lung Foundation [grant number 20120244].

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