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Prevalence of neurofibromatosis type 1 in the Finnish population

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Purpose: The incidence of neurofibromatosis 1 (NF1) is ~1/2,000 live births, but the current estimates of prevalence vary greatly. This retrospective total-population study was aimed at determining the prevalence of NF1 in Finland.

Methods: All secondary and tertiary referral centers of Finland were searched for NF1 patients. Patient records were manually reviewed and patients fulfilling the National Institutes of Health diagnostic criteria for NF1 were included. Prevalence on 31 December 2005 was determined. Data on incidence and survival were combined to refine the prevalence estimation.

Results: A total of 1,279 patients with NF1 were alive on 31 December 2005, yielding a prevalence of 1/4,088 (95% confidence interval (CI) 1/4,320–1/3,869). The survival of patients with NF1 was inferior compared with the general population (hazard ratio 3.10, 95% CI 2.73–3.53, $P < 0.001$). When the survival rates of NF1 patients and the Finnish population were combined with an estimate of NF1 incidence, a prevalence of 1/2,052 (95% CI 1/2,176–1/1,941) was estimated for NF1 in a population aged 0–74 years.

Conclusion: NF1 is a much more common disorder than previously thought. A large proportion of NF1 patients may not be correctly identified by health-care systems or they do not seek secondary health care for their NF1.

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Key Words: cancer predisposition; epidemiology; neurofibromatosis type 1; prevalence; survival

INTRODUCTION

Neurofibromatosis type 1 (NF1; OMIM 162200) is an autosomal-dominant syndrome caused by mutations in the *NF1* tumor suppressor gene on chromosome 17.[1] NF1 is most often diagnosed based on symptoms visible on the skin: cutaneous neurofibromas, café au lait macules, and skinfold freckling.[2–5] The diagnostic signs typically emerge during childhood and puberty.[6] NF1 is a multiorgan syndrome also associated with, e.g., learning deficits, skeletal abnormalities, pregnancy and delivery complications, and a wide range of malignancies.[4,7–9]

We recently published a birth incidence of ~1/2,000 for NF1 in Finland[10] and we now report the prevalence of NF1. Previous estimates of NF1 prevalence have typically been in the range of 1/6,000–1/3,000.[10] Prevalence estimates stratified by age are helpful in assessing the total number of patients in a certain population, e.g., for the allocation of health-care resources[11] and for cohort studies investigating associations between NF1 and other diseases. Age-specific prevalence is especially important in NF1 where mortality is high already at a young age and the prevalence declines by increasing age.[10,12–14]

MATERIALS AND METHODS

This register-based retrospective total population study was approved by the Ethical Committee of the Hospital District of Southwest Finland. Study permits were obtained from the National Institute for Health and Welfare and all participating hospitals.

The data collection of the Finnish NF1 cohort has been previously described.[10] Currently, the cohort consists of 1,476 patients (706 men and 770 women). The medical records related to inpatient and outpatient hospital visits in the 5 tertiary and 15 secondary referral centers of Finland were searched for diagnoses of neurofibromatosis during the ascertainment period 1987–2011. The search covered the whole country except a secondary referral center located in the autonomous Åland Islands of ~28,000 residents. All patients who fulfilled the National Institutes of Health diagnostic criteria for NF1[15] were included in the cohort. Therefore, the cohort is nationwide, population-based, and fully ascertained. Dates of birth, death, and emigration were retrieved from the Population Register Centre of Finland using personal identity code as a key, yielding complete follow-up. Personal identity code is a unique identifier that is given to every resident in Finland; it includes the date of birth and remains unchanged over the individual's lifetime. Statistics Finland provided the age-, sex-, and calendar year–specific mortality rates and population sizes of Finland.

Prevalence was calculated in 5-year age groups as the ratio of live NF1 patients and the population of mainland Finland.

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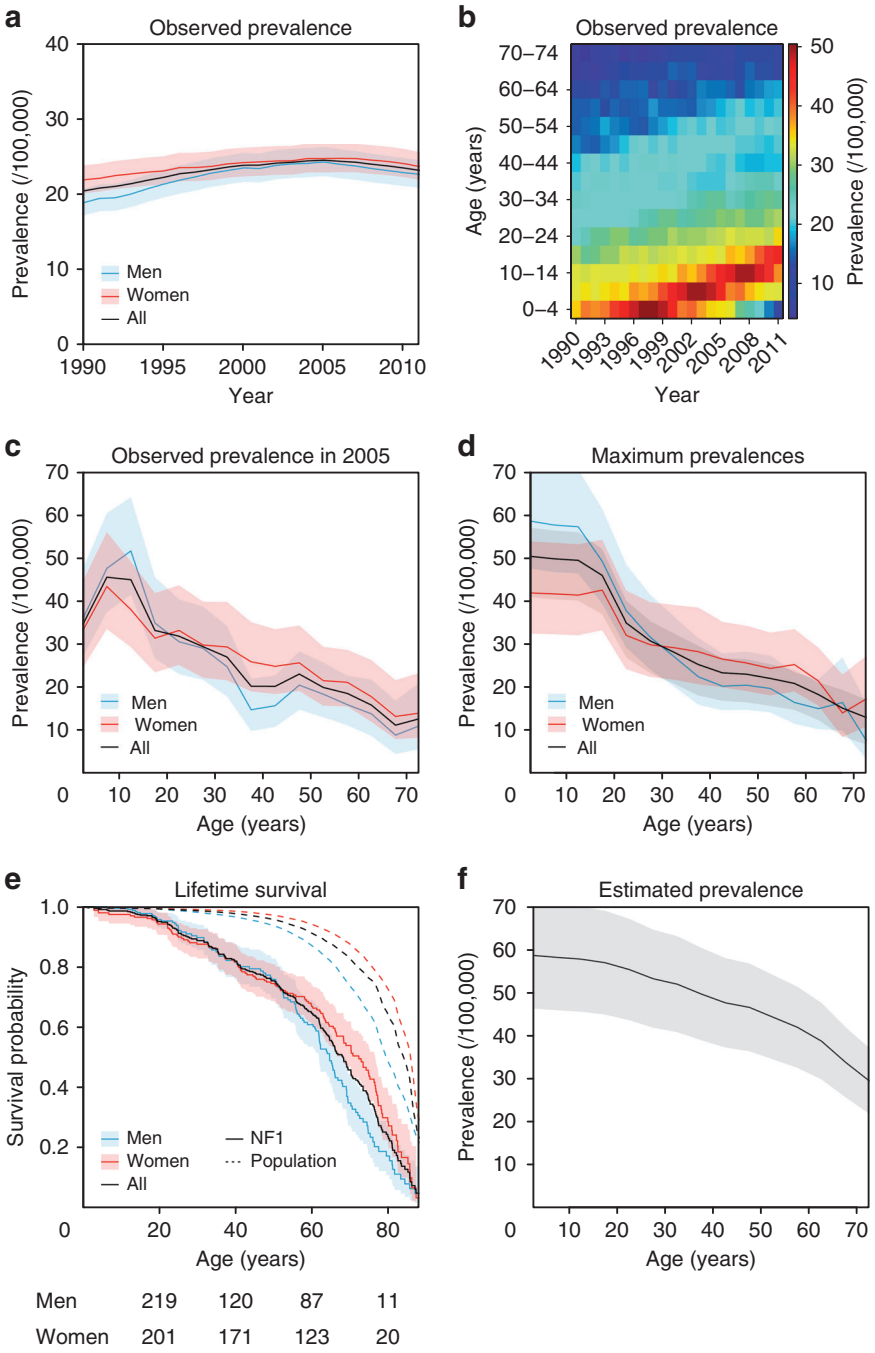

Figure 1 The prevalence of neurofibromatosis type 1 (NF1) in Finland by calendar year and age. (**a**) The observed prevalence of NF1 by calendar year. (**b**) The observed prevalence of NF1 stratified by calendar year and age group. Red color represents the highest prevalence while dark blue shows the lowest prevalence (vertical bar on the right). (**c**) The observed prevalence of NF1 by age on 31 December 2005. (**d**) Maxima of NF1 prevalences observed 1990–2011 by age. (**e**) Overall survival of NF1 patients (solid line) and the Finnish general population (dashed line). The numbers of NF1 patients at risk of death are shown below the figure. The population survival is weighted by the sex- and calendar year–specific distribution of person years observed in the NF1 cohort. The total follow-up time in the NF1 cohort was 21,742 person-years, median 15.0 years per person, range 0.01–28.0 years. (**f**) The prevalence of NF1 by age as estimated by multiplying the incidence of NF1 by the ratio of NF1- and population-specific survival probabilities. The shaded areas show 95% confidence intervals for men and women (**a** and **c**–**e**) or for the whole population (**f**).

The 95% confidence interval (CI) of the proportion was estimated using the Wilson score interval with continuity correction. Most NF1 patients fulfill the diagnostic criteria by the age of 6 years.[6,12] We analyzed prevalence on 31 December 2005 since the children born in 2005 should present the diagnostic signs by the end of the ascertainment period. In addition to the raw observed prevalence, the prevalence of NF1 was estimated by assuming a constant

Table 1 The observed and estimated prevalence of neurofibromatosis type 1 (NF1) by age

Age group	Men, observed[a]			Women, observed[a]			All, observed[a]			All, estimated[b]	
	n	Estimate	95% CI	*n*	Estimate	95% CI	*n*	Estimate	95% CI	Estimate	95% CI
0–4	52	1/2,786	1/3,694–1/2,107	46	1/3,015	1/4,071–1/2,240	98	1/2,894	1/3,546–1/2,364	1/1,706	1/2,158–1/1,410
5–9	71	1/2,100	1/2,669–1/1,655	62	1/2,303	1/2,979–1/1,784	133	1/2,195	1/2,611–1/1,846	1/1,719	1/2,176–1/1,421
10–14	86	1/1,936	1/2,406–1/1,559	61	1/2,629	1/3,408–1/2,032	147	1/2,223	1/2,622–1/1,886	1/1,731	1/2,192–1/1,431
15–19	57	1/2,864	1/3,747–1/2,194	49	1/3,184	1/4,259–1/2,388	106	1/3,012	1/3,661–1/2,480	1/1,757	1/2,225–1/1,451
20–24	52	1/3,270	1/4,334–1/2,473	54	1/3,011	1/3,970–1/2,290	106	1/3,138	1/3,815–1/2,584	1/1,807	1/2,290–1/1,492
25–29	49	1/3,442	1/4,603–1/2,581	48	1/3,355	1/4,501–1/2,508	97	1/3,399	1/4,169–1/2,773	1/1,879	1/2,385–1/1,550
30–34	39	1/4,039	1/5,604–1/2,923	44	1/3,404	1/4,630–1/2,512	83	1/3,703	1/4,620–1/2,971	1/1,924	1/2,445–1/1,586
35–39	26	1/6,771	1/10,153–1/4,550	44	1/3,859	1/5,248–1/2,847	70	1/4,941	1/6,292–1/3,886	1/2,012	1/2,562–1/1,657
40–44	30	1/6,361	1/9,262–1/4,396	46	1/4,022	1/5,432–1/2,988	76	1/4,946	1/6,235–1/3,929	1/2,098	1/2,676–1/1,725
45–49	39	1/4,879	1/6,770–1/3,531	48	1/3,894	1/5,225–1/2,912	87	1/4,336	1/5,382–1/3,498	1/2,145	1/2,741–1/1,762
50–54	36	1/5,440	1/7,654–1/3,884	42	1/4,645	1/6,365–1/3,403	78	1/5,012	1/6,299–1/3,994	1/2,257	1/2,891–1/1,851
55–59	33	1/6,267	1/8,958–1/4,407	44	1/4,728	1/6,430–1/3,488	77	1/5,387	1/6,781–1/4,286	1/2,380	1/3,061–1/1,947
60–64	20	1/7,232	1/11,520–1/4,592	27	1/5,618	1/8,357–1/3,804	47	1/6,305	1/8,486–1/4,699	1/2,577	1/3,335–1/2,099
65–69	10	1/11,258	1/22,154–1/5,908	17	1/7,565	1/12,571–1/4,620	27	1/8,933	1/13,289–1/6,049	1/2,947	1/3,867–1/2,380
70–74	10	1/9,049	1/17,807–1/4,749	16	1/7,140	1/12,065–1/4,293	26	1/7,874	1/11,808–1/5,292	1/3,380	1/4,545–1/2,690

CI, confidence interval.
[a]Observed prevalence in the Finnish population on 31 December 2005. [b]Prevalence estimated using incidence and age-specific survival rates.

incidence, and the maximum of prevalences observed from 1990 to 2011 was computed for each age group. A similar approach has previously been used to reduce year-to-year variation in the incidence estimation of NF1.[11]

To further assess the true change in NF1 prevalence by age, survival of NF1 patients was estimated using the Kaplan–Meier method with delayed entry. Patients entered the analysis on the day of their first NF1-related hospital visit 1987–2011, and the follow-up ended at death, or censoring due to emigration or end of the study period on 31 December 2014. Survival of NF1 patients and the general population were compared using the Cox proportional hazards model. To account for time-dependent changes over the study years, survival data of the population was weighted by the sex-specific follow-up time observed in the NF1 cohort in different calendar years. Since girls with NF1 may be diagnosed later than boys (see Results), the highest prevalence of NF1 observed among boys aged 0–4 years was assumed to reflect the birth incidence of NF1. The change in prevalence could be estimated as

$$prevalence = incidence * \frac{survival(NF1)}{survival(population)}$$

The CIs of the product were computed using the asymptotic normal distribution method.[16] The resulting estimated prevalence was only analyzed over age 0–74 years because the data for older NF1 patients was sparse.

Prevalence by sex was analyzed using the Pearson's chi-square test with Yates' continuity correction. Age at the diagnosis of NF1 was compared using the two-sided Wilcoxon rank sum test with continuity correction. All analyses were carried out using the statistical software R (www.r-project.org) version 3.3.0 with packages survival (version 2.41-3) and RMediation (version 1.1.4).

RESULTS

The observed prevalence of NF1 changed slightly over the years 1990–2011, the peak prevalence being observed in 2005 (**Figure 1a**). When the observed prevalence was stratified by both calendar year and age group, the highest prevalence was observed among those born in the mid-1990s and comprehensively diagnosed (**Figure 1b**). Based on our cohort, the overall observed prevalence of NF1 in the Finnish population was 1/4,088 (95% CI 1/4,320–1/3,869) with a total of 1,279 live NF1 patients on 31 December 2005. The prevalence among men was 1/4,128 (95% CI 1/4,469–1/3,812) and among women 1/4,051 (95% CI 1/4,376–1/3,751). Observed prevalence by age is shown in **Table 1** and **Figure 1c**. When the maxima of prevalences observed 1990–2011 in different age groups were studied, the estimated prevalence at the youngest age groups was high, and a steep decrease was noted around 15 years of age (**Figure 1d**).

The follow-up of the NF1 cohort yielded 21,742 person-years with a median of 15.0 years per person. The overall survival of the patients with NF1 was poorer than in the general population (**Figure 1e**; hazard ratio 3.10, 95% CI 2.73–3.53, $P < 0.001$). When the survival functions were combined with the highest prevalence among boys aged 0–4

years, 1/1,705, a steady decline in estimated prevalence was observed (**Figure 1f**; **Table 1**). Applying these age-specific estimates to the Finnish population resulted in an overall estimated NF1 prevalence of 1/2,052 (95% CI 1/2,176–1/1,941) in population aged 0–74 years.

When the observed prevalence of NF1 in the age group 0–4 years was highest, the prevalence was significantly lower among girls than among boys (1/2,385 vs. 1/1,705, $P = 0.04$). Age at diagnosis was not available for the whole cohort, but analysis of 85 male and 80 female NF1 patients from a previously published subset of our cohort[14] suggests that the difference is due to a delayed diagnosis of girls rather than a sex difference in incidence. The median age at diagnosis was 9.9 years (interquartile range 16.8) among men and 17.9 years (interquartile range 25.1) among women ($P = 0.001$) in this subcohort collected in the early 1990s.[14]

DISCUSSION

The results imply that the prevalence of NF1 is higher than previously thought. The survival of patients with NF1 was inferior compared with the general population, and subsequently the estimated prevalence declined from 1/1,706 among children aged 0–4 years to 1/3,380 in the age group 70–74 years.

The number of patients in the Finnish NF1 cohort and, consequently, the observed prevalence of NF1 increase along with years since the beginning of the ascertainment period. This is due to an increasing proportion of patients being diagnosed at an early age. The peak incidence of NF1 in the Finnish cohort was reported among those born 1994–1996.[10] The National Institutes of Health 1987 diagnostic criteria[15] had been established in clinical practice by the time these patients developed symptoms of NF1, and the symptoms had emerged by the end of the ascertainment period.[10] This is consistent with the highest prevalence being observed in 2005.

Figure 1c shows an increase in NF1 prevalence from birth to 10 years of age. However, the true prevalence of NF1 does not increase by age, and the lower numbers observed in the youngest age groups are due to children not yet diagnosed. The age-stratified maxima of prevalences observed over calendar time provide a better estimate of the prevalence among children (**Figure 1d**), yet the steep decrease in prevalence observed around 15 years of age is clearly artificial and likely due to lower diagnosis rate among older persons. The true prevalence at ages > 15 years is apparently higher than observed in the current cohort.

The combination of survival and prevalence data allows estimating the change in prevalence over lifetime, although no more than 28 years of follow-up are available for any individual. Although indirect, the resulting estimates are the best approximation of NF1 prevalence currently obtainable using the Finnish NF1 cohort. Accumulating follow-up time will refine the estimates in the future and allow direct calculation of prevalence. Because the prevalence estimates were obtained using survival data, they reflect the age distribution of the population and access to health care, and may not be fully generalizable to populations with different demographics or health care. Increased awareness and mutation analyses have enhanced the identification of NF1, and ongoing epidemiological studies are likely to re-estimate the prevalence in different parts of the world. Future studies should aim at elucidating also the effects of demographic factors other than age and sex on the prevalence of NF1, such as education, occupation, income, and marital status.

The gap between observed and estimated prevalence suggests that a large proportion of NF1 patients may not be correctly identified by health-care systems or they do not seek secondary health care for their NF1. This is the case especially for older patients with NF1 whose symptoms have emerged before the establishment of the modern diagnostic criteria and broader awareness of NF1. It seems that older persons are less likely to be diagnosed with NF1 than those whose symptoms are noticed already in childhood or youth. In addition, the data collection may have missed patients who have been diagnosed with NF1 but have not been referred to secondary or tertiary hospitals. Underascertainment may also be due to missing diagnostic information in medical records of patients treated for ailments not directly related to NF1.

The observed prevalence among boys aged 0–4 years was significantly higher than among girls in this age group, and the difference seems to be due to earlier NF1 diagnosis of the boys. The sex difference in the age of diagnosis needs to be replicated in other studies, and its reasons remain to be elucidated. Although no sex difference in fulfilling the diagnostic criteria of NF1 has been reported, boys may get earlier medical attention due to higher incidence of other symptoms, e.g., muscular hypotonia as an infant, delayed motoric development, or speech delay. In addition, symptoms of autism spectrum disorder have been found to be more common among boys than among girls with NF1.[17]

Despite the apparently missing patients, the current cohort represents the most comprehensive completely ascertained NF1 cohort to date. Consequently, the resulting prevalence estimates are among the highest reported with stratification by age group.

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DISCLOSURE

The authors declare no conflict of interest.

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