tion for the preponderance of ΔF508 heterozygotes detected by the IRT/DNA newborn screening protocol. The IVS8–5T allele does not appear to influence neonatal pancreatic function but further investigation of its role in CF related disorders is required.

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Letters

Epidemiology of neurofibromatosis type 1 (NF1) in northern Finland

EDITOR—Neurofibromatosis type 1 (NF1), also known as von Recklinghausen’s disease, is an autosomal dominant neurocutaneous disease characterised by café au lait spots and neurofibromas. The gene responsible for the disorder is located in the chromosome region 17q11.2. The prevalence of NF1 has been estimated to be about 1/3500 in the population based study of NF1 was performed in Sweden by Samuelsson in 1981, who found 74 adult NF1 patients in the Gothenburg region, implying a prevalence of 1/4600. In 1983, Huson et al discovered 125 NF1 patients in 69 families in south east Wales, 83 of whom were index cases and 52 affected relatives, with a prevalence of 1/4150. The highest estimated prevalence for NF1, 1/2190, has been reported in Dunedin, New Zealand, by Fuller et al, who also showed that the prevalence peaked in the age group 20-29 years. A fourth report from north east Italy by Clementi et al quoted a prevalence of 1/6711 and a very high mutation rate of 6.5 × 10⁻⁸ gametes per generation.

The purpose of the present work was to determine the prevalence and genetic characteristics of NF1 in northern Finland, including a survey of first degree relatives of patients and linkage data, to assist in the diagnosis of affected subjects. Clinical data on the patients will be reported separately.

The study was carried out between October 1989 and December 1996 in the region of Oulu University Hospital (OUH) in northern Finland with a total population of 733 037 (31 December 1996). The basic material consisted of families attending the Department of Clinical Genetics at the OUH for genetic counselling from 1982 onwards. Additional patients with a diagnosis of neurofibromatosis (International Classification of Diseases (ICD), 9th revision), diagnosis codes 2377A or 2251A, or neurofibromatosis (von Recklinghausen) (ICD, 8th revision) diagnosis code 74340, were traced from the records of the University Hospital and the four central hospitals in the area, two in Lapland, one in Kainuu, and one in central Ostrobothnia. In addition, patients were traced by contacting paediatricians, neuropaediatricians, dermatologists, neurologists, ophthamologists, oncologists, pathologists, audiologists, otologists, surgeons, neurosurgeons, paediatric surgeons, and internists in the area. The OUH records concerning patients treated for neurofibroma, optic glioma, multiple menigiomas, or vestibular schwannomas were reviewed, and all patients with plexiform neurofibroma or congenital pseudoarthrosis were traced in order to examine them for NF. The histological specimens of surgical and necropsy specimens examined at the Department of Pathology, Oulu University Hospital, were reviewed and clinical and necropsy results scrutinised. Also, the two private pathological laboratories in the area were contacted and searched their records for any surgical
NF findings. Collectively, these sources provided information on 181 families with either confirmed or suspected NF in one or more members. These patients were then contacted through their own physicians to ascertain their willingness to participate in the study. Seven families with one NF1 patient refused to be included in the study, but if willing to participate in the study. Seven families with NF1 were nevertheless included in the series. The others were assessed clinically at the Department of Clinical Genetics and most of them were also examined by a dermatologist. Clinical examination performed by the patient’s doctor.

The NIH criteria for NF1 (National Institute of Health, Consensus Development Conference held in Bethesda, Maryland, July 1987) were used for inclusion.

Whenever possible, a family study was undertaken and the first-degree relatives living in the area were examined clinically even when it was not possible to confirm the diagnosis of NF1. When the hospital records indicated a positive family history but the index patient had died, relatives in the area were contacted with the help of the patient’s doctor.

The prevalence figures were calculated from the number of affected persons in the population at a particular time in relation to the total population. The point prevalence on 31 December 1996 was calculated based on the total number of affected persons in the population of 733,037 in the area (Central Statistical Office of Finland, 1997) and the period prevalence from the corresponding figures for a time period 1960 to 1995. For the incidence figures, the number of subjects born with NF was related to the number of live births in the area during 1960 to 1995. Thus, the youngest patients were 1 year old and the oldest 36 years old on the point prevalence day.

NF1 patients were considered to represent probable new mutations if the clinically examined parents did not show any signs of NF1 when studied by us or by another specialist experienced in NF1. The mutation rate was obtained by calculating the ratio of new mutation cases in a given period to the total number of live births.

Fitness was estimated by the method of Tanaka, in which relative fitness was calculated as a fraction comparing the frequency of NF1 among parents of index cases with the frequency of NF1 among offspring of index cases. The parental age of those cases assumed to represent new mutations was compared with the parental age of the fathers in the general population of Finland and the parental age of the mothers in the study area. The significance of the differences was evaluated by Student’s t test. The birth order effect in families representing new mutations was assessed by the method of Haldane and Smith, in which the sum of the birth orders of all the affected siblings in each family is compared with the theoretical value, calculated on the assumption that there is no birth order effect.

Values are expressed as means (SD). The independent samples t test was used to compare differences in mean ages at diagnosis between sexes, age groups, sporadic and familial cases, and sporadic cases in different decades. Two sided p values were calculated at a significance level of 0.05.

Segregation analysis was performed by comparing the number of affected offspring of an affected parent having a healthy spouse with the expected number using the $\chi^2$ test.

A total of 197 NF1 patients in 119 families were identified. For confidentiality reasons, pedigrees are not shown but are available on request. A total of 77 cases were sporadic and 117 familial. In addition, three patients had a mother with segmental NF (NF5). The diagnosis of NF1 was made by a dermatologist (29%), clinical geneticist (26%), paediatrician or neuro paediatrician (22%), paediatric surgeon or surgeon (13%), general practitioner (4%), and a neurologist (4%). Clinical examination performed by the first author of 239 relatives of 112/119 index cases with at least a 25% a priori risk showed 41 NF1 cases in addition to 37 earlier verified relative cases and excluded the disease in 198 people.

The age distribution of the patients ranged from 3 months to 73 years (mean 29 years). The mean age at the time of diagnosis was 20 years (SD 16), with a range of 3 months to 60 years. This figure was significantly lower in males than in females and in the younger generations. It was also four years lower in children of affected parents compared to sporadic cases. Sporadic cases were diagnosed an average of 10 years earlier in the 1980s (mean age 6 years (SD 4)) than in the 1960s (mean age 16 years (SD 9) (table 1).

By the prevalence day (31 December 1996), 29 of the 197 known NF1 patients had died and three had moved

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**Table 1** Neurofibromatosis type 1: age at diagnosis in different patient groups in 197 cases in northern Finland

<table>
<thead>
<tr>
<th>Patient groups</th>
<th>Age at diagnosis (SD)</th>
<th>Range (y)</th>
<th>p value</th>
<th>Compared group</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cases</td>
<td>197</td>
<td>20 (16)</td>
<td>3 mth–60 y</td>
<td>p&lt;0.001 Born before 1960 (n=81)</td>
</tr>
<tr>
<td>Born 1960 to 1995</td>
<td>116</td>
<td>10 (9)</td>
<td>3 mth–36 y</td>
<td>p&lt;0.001 Females (n=102)</td>
</tr>
<tr>
<td>Males</td>
<td>95</td>
<td>15 (14)</td>
<td>3 mth–54 y</td>
<td>p=0.113 Sporadic cases (n=77)</td>
</tr>
<tr>
<td>Females</td>
<td>102</td>
<td>25 (17)</td>
<td>6 mth–60 y</td>
<td>p&lt;0.001 Sporadic cases born before 1960 (n=30)</td>
</tr>
<tr>
<td>Children of an affected parent</td>
<td>81</td>
<td>15 (15)</td>
<td>3 mth–57 y</td>
<td>p&lt;0.001 Sporadic cases born before 1970 (n=41)</td>
</tr>
<tr>
<td>Sporadic cases</td>
<td>77</td>
<td>19 (16)</td>
<td>6 mth–60 y</td>
<td>p&lt;0.001 Sporadic cases born in 1960s (n=4)</td>
</tr>
<tr>
<td>Sporadic cases born in the 1960s</td>
<td>11</td>
<td>16 (9)</td>
<td>3–33 y</td>
<td>p=0.002 Sporadic cases born in 1960s and 1970s (n=21)</td>
</tr>
<tr>
<td>Sporadic cases born in the 1970s</td>
<td>10</td>
<td>9 (6)</td>
<td>3–22 y</td>
<td></td>
</tr>
<tr>
<td>Sporadic cases born in the 1980s</td>
<td>19</td>
<td>6 (4)</td>
<td>4 mth–13 y</td>
<td></td>
</tr>
</tbody>
</table>

www.jmedgenet.com
out of the area. Based on the remaining 165 patients, the prevalence of NF1 in northern Finland was 1/4436 (23/100 000). The period prevalence calculations gave a peak prevalence of 1/2983 (34/100 000) for the age group 10-19 years (fig 1).

There were 116 new NF1 cases and 423 075 live births in the area during the period 1960-1995, giving an incidence of 1/3647 (27/100 000). By decades, the corresponding incidences were 1/4545 for the 1960s and 1970s and 1/2941 for the 1980s. The incidence for the six year period 1990-1995 was 1/2703. It can be estimated that three new NF1 children will be born in the area annually.

Of the 197 patients, 119 were familial cases. There were four four generation, 10 three generation, and 25 two generation families with NF1. Three patients had a mother with segmental NF (NF5). With 95 male patients and 102 females, the sex ratio was 0.93. The geographical distribution of the patients roughly corresponds to that of the general population in the area. Ninety six of the 197 cases of NF1 identified (49%) represented possible new mutations of the disease gene. Of these, in 39 cases both parents were personally examined by the authors of the present study, in 13 cases only one of the parents was seen, and in 44 cases the family history was obtained from the patient and from hospital records.

The mean maternal age at the birth of a child with NF1 resulting from a probable new mutation was 30 years (SD 6) (range 21–43 years), the corresponding mean overall maternal age in the area during the same time period being 27.5 years (P=0.006). The mean paternal ages were 33 years (SD 6) (range 19–50 years) for NF1 children and 30.0 years for fathers in Finland in general (P=0.008), respectively. The mean birth order was 2.9 (SD 1.7) calculated from the 33 cases classified as new mutations and the size of the sibship being at least two. The difference between the observed and theoretical sum of the birth orders of affected subjects divided by the standard error of the theoretical mean value was 3.3, showing that the later born sibs are more likely to be affected (P=0.002).

Of 20 families studied for genetic linkage, one was shown to have a deletion of the NF1 gene encompassing the loci from EVI-20 to INT-38. In addition, seven other familial and 39 sporadic cases in informative families were screened for deletions with intragenic linked markers. One deletion for the INT-27 locus was found in a sporadic case. Thus, deletions were found in 2/66 families (3%). The sporadic deletion occurred in the maternally derived chromosome 17.

Among those familial cases in which the parental origin of the new mutation in the first affected subject could be evaluated with linked markers, six of the seven cases studied had the mutation in the paternally derived chromosome 17.

Of the 197 cases, 48 females and 18 males had children. Out of a total of 178 offspring of 66 of the parents with NF1, 78 (44%) were affected, whereas 89 (50%) would have been expected on the assumption of autosomal dominant inheritance. The ratio, 0.44 (78/178), did not differ significantly from the expected (χ²=2.7). The 48 NF1 mothers had a total of 147 pregnancies, of which 11 ended in a miscarriage, 60 in the birth of a NF1 child, and 76 unaffected children. The corresponding figures for the 18 NF1 fathers were 42 pregnancies, yielding 18 NF children and 24 unaffected ones, but no reported miscarriages.

The relative fitness of the subjects with NF1 was analysed for 68 index cases where both parents were seen by us and for 46 adult index cases where all the children were seen. The relative fitness was 0.48, 0.24 for males and 0.72 for females.

The members of the 20 families with an affected parent and at least one affected child were analysed with linked microsatellite markers in order to search for possible non-penetrance. Out of 87 informative meioses, 54 were associated with the established at risk haplotype of the family. Fifty two of these subjects were affected and two were unaffected. Of the unaffected at risk haplotype carriers, one 15 year old girl had no clinical signs of NF1. In addition, there was a pair of 8 and 11 year old sisters who had inherited different haplotypes from their affected father and again neither of them showed signs of NF. All those 33 persons who had inherited the “non-risk” haplotype were healthy. No recombinants were observed for NF1, nor could any linkage disequilibrium be shown with the linked polymorphic markers used here.

This population based study of NF in northern Finland identified 197 NF1 patients in 119 families. The diagnoses were based both on clinical and imaging findings. In 20 familial cases also, DNA studies with linked DNA markers were carried out.

![Figure 1 Age related prevalences of NF1 in 10 year age groups.](www.jmedgenet.com)
We believe that these 197 patients ascertained represent the great majority of the NF1 patients in northern Finland. In addition to patient diagnosis lists of the hospitals of the region, cases were searched for by asking the paediatricians, neuropaediatricians, dermatologists, neurologists, ophthalmologists, oncologists, pathologists, audiologists, otologists, surgeons, neurosurgeons, paediatric surgeons, and internists in the study area about their NF1 patients. Mildly affected patients diagnosed and treated only in local health centres, however, may have been missed in our search. In addition, undiagnosed cases certainly exist in the study area. This is reflected by the fact that we diagnosed 41 new cases among the relatives of our index cases. Thus, the figures calculated in this study represent minimal incidence and prevalence of NF in northern Finland.

The observed overall prevalence ($1/4436$ or $23 \times 10^{-5}$) of NF1 in northern Finland and the incidence ($1/3647$ or $27 \times 10^{-5}$) are comparable to findings in other populations studied to date (table 2).4–7 There was no evidence of very large families or of geographical clustering of NF1, neither was there any sign of possible linkage disequilibrium in the DNA studies.

The overall prevalence and incidence figures obtained for NF1 have in most cases proved to be minimum estimates, and this is also apparent in the present study. The fact that the age at diagnosis of NF1 was lower in the younger age groups and the age dependent prevalence/incidence figures were significantly higher in younger age groups, despite the slow accumulation of diagnostic signs in very young children, may reflect a better awareness of the importance of diagnosing NF in suspected cases, improved knowledge of the diagnostic features, and a greater willingness to refer suspected cases for detailed examination. A careful study of the first degree relatives uncovered 41 undiagnosed cases, especially in the relatives of an affected child. The higher prevalence figures among the young may partly be explained by the increased mortality suggested to be associated with NF1.28–31 The results suggest that the incidence figures are most reliable for patients under 20 years of age, and for prevalence figures the age related period prevalences are better. The observed sex ratio, 0.93, did not differ significantly from what was expected, as has also been reported in the other studies.4–6

Our linkage studies showed that linked markers/haplotypes show the same result as careful clinical examination in familial cases of NF1, although contradictory results were obtained in two families where linkage data showed the NF1 risk haplotype in a healthy child of an affected parent. One explanation may be that the children were affected but were still at a presymptomatic stage. This would be exceptional, as all our affected cases (reported separately) had developed café au lait macules by the age of 5 years (96% of all patients), and similar observations have been made in earlier reports.19–21 Another explanation would be that even though the affected parents in both families fulfilled the NIH diagnostic criteria for NF1 (in the first family CPS and freckles, and in the second family neurofibromas and Lisch nodules), they both have another type of NF which is not linked to the NF1 gene. A third explanation would be mosaicism in a parent with NF1 in whom some of the germ cells do not carry the NF1 mutation. A fourth explanation would be non-penetrance of the NF1 mutation in the children in question, which has previously been reported in only three cases, a 50 year old woman who had an affected brother, son, and grandson,22 a 45 year old man with an affected mother and daughter,23 and a subject with an affected father and two affected daughters.24 Although non-paternity is not probable, one should exclude it with other markers. The finding of possible non-penetrance in the two families in this series will be finally answered only after the families’ NF1 mutation has been found.

New mutations accounted for a maximum of 49% of our patients as estimated, a figure that is in agreement with those published earlier.4–6

Genetic fitness of NF1 (0.48) had decreased to about half of the expected, the effect being more marked in males (0.24) than in females (0.72). Similar reductions have been reported by Crowe et al.,24 Huson et al.,4 and Samuelsson,4 who attribute them partly to biological factors and partly to non-biological factors, such us selection against affected subjects marrying.

The mutation rate for the NF1 gene, $4.37 \pm 0.72 \times 10^{-5}$, is comparable to the published rates (table 2), and confirms the very high mutation rate of this gene. The observation of a birth order effect in new mutation cases ($2.9 \pm 1.7$), showing that later born sibs are more likely to be affected, suggests that parental age has an effect on the mutation rate. The mean paternal age in the cases with a new mutation was significantly higher than in the general population, as also observed by Sergeyev,22 Riccardi et al.,24 Bunin et al.,25 and Takano et al.,26 while Borberg,2 Samuelsson,4 Huson et al.,4 Clementi et al.,4 Rodenlilisedet al.,26 and Jadayel et al.27 did not report any significant effect of paternal age. The observation of significantly increased maternal age is exceptional and has been reported previously by Riccardi et al.24 The present study population is, however, too small for a definitive answer to the parental age effect.
More than 246 mutations involved in NFI gene have been reported by the NFI Genetic Analysis Consortium up to November 1997, 45% of them deletions. Our intragenic linkage study pointed to 61 cases with a deletion, 3% of those investigated. The small sizes of the families and the low number of families containing several generations, the non-clustering of the cases, and the absence of disequilibrium in linkage studies rule out any founder effect for NFI in northern Finland. Observations in other population based NF studies are similar and confirm the findings of small family size and few generations. In the familial cases examined by linkage study here, six out of seven of the first affected subjects in the family had inherited the mutation from the father, a phenomenon which has been shown in 34 out of the 37 published cases (92%) including our data.

We would like to thank the patients and families and their clinicians who participated in this study.

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Genetic registers in clinical practice: a survey of UK clinical geneticists

EDITOR—Genetic registers have now been in use in the United Kingdom for nearly 30 years, although they are not widespread in Europe. They are an integral part of most UK medical genetics services and yet their functions vary from centre to centre. Many registers were originally developed for research purposes, often in connection with one specific inherited disease, while others, designed for service use, may cater for many genetic disorders. The WHO report of 1969 suggested that a list or register of pedigreed data should be maintained by each genetic centre, although the purpose of the list was not specified. In its 1972 report, the WHO recommended setting up of family orientated genetic registries as part of a system to provide counselling and diagnostic services, treatment, and long term follow up for patients with genetic disorders. In 1978, the definition of genetic register functions was clarified by Emery et al, who suggested five main roles, which are not mutually exclusive. These were the clinical or diagnostic role, to monitor outcome of service provision, to act as a research tool, and to assist in the prevention of genetic disease through complete ascertainment and family follow up. Since that time, the use of genetic registers for family