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Parental age and risk of genetic syndromes predisposing to nervous system tumors: nested case–control study

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Purpose: Phacomatoses are genetic syndromes that are associated with increased risk of developing nervous system tumors. Phacomatoses are usually inherited, but many develop de novo, with unknown etiology. In this population-based study, we investigated the effect of parental age on the risk of phacomatoses in offspring.

Patients and methods: The study was a population-based nested case–control study. All individuals born and residing in Sweden between January 1960 and December 2010 were eligible for inclusion. Using the Patient Register, 4625 phacomatosis cases were identified and further classified as familial or nonfamilial. Ten matched controls per case were randomly selected from the eligible population. Data were analyzed using conditional logistic regression. Analyses were conducted for neurofibromatosis alone (n=2089) and other phacomatoses combined (n=2536).

Results: Compared with offspring of fathers aged 25–29 years, increased risk estimates of nonfamilial neurofibromatosis were found for offspring of fathers aged 35–39 years (odds ratio [OR]=1.43 [95% CI 1.16–1.74]) and ≥40 years (OR=1.74 [95% CI 1.38–2.19]). For other nonfamilial phacomatoses, the risk estimate for offspring of fathers aged ≥40 years was OR=1.23 (95% CI 1.01–1.50). Paternal age was not associated with familial phacomatoses, and no consistent association was observed with maternal age.

Conclusion: The findings show a consistent increase in risk of de novo occurrence of phacomatoses predisposing to nervous system tumors in offspring with increasing paternal age, most pronounced for neurofibromatosis, while maternal age did not seem to influence the risk. These findings suggest an increasing rate of new mutations in the *NF1* and *NF2* genes in spermatozoa of older fathers.

Keywords: phacomatoses, nervous system tumor predisposition syndromes, parental age, registry, neurofibromatosis

Introduction

Genetic syndromes are established risk factors for various diseases, including cancer.¹ Phacomatoses are genetic syndromes with increased cancer susceptibility and are characterized by multiple hamartomas of the central and peripheral nervous system, eye, skin, and viscera.² There are several known phacomatoses that predispose individuals to development of nervous system tumors (Table 1), of which neurofibromatosis type 1 and type 2 (NF1 and NF2) and tuberous sclerosis complex (TSC) are the most common.^{3,4}

The birth prevalence of NF1, NF2, and TSC is, approximately, 1 in 3000,⁵ 1 in 35000,^{3,5} and 1 in 10000,^{3,6} respectively. They are autosomal dominant disorders; however, they develop de novo in a large proportion of patients with no previous family history of the disease. It is estimated that ~50% of NF1 and NF2 are de novo

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Table 1 Genetic syndromes predisposing to nervous system tumors

Syndrome (OMIM)	ICD-9/ICD-10	Gene	Locus	Inheritance	Nervous system tumors
Neurofibromatosis type 1 (162200)	237H/Q85.0	<i>NF1</i>	17q11.2	AD	Spinal neurofibromas, optic gliomas, astrocytomas, meningioma, malignant peripheral nerve sheath tumors
Neurofibromatosis type 2 (101000)	237H/Q85.0	<i>NF2</i>	22q12.2	AD	Schwannoma, meningioma, ependymoma, astrocytoma
Schwannomatosis (162091)	237H/Q85.0	<i>NF2/SMARCB1?</i>	22q12.2/22q11.23?	AD	Schwannoma
Tuberous sclerosis complex (191100)	759F/Q85.1	<i>TSC1/TSC2</i>	9q34.13/16p13.3	AD	Ependymoma, giant cell astrocytoma, retinal astrocytoma
Li-Fraumeni (151623)	759/Q85	<i>TP53/CHEK2</i>	17p13.1	AD	Astrocytoma, medulloblastoma
Gorlin (basal cell nevus syndrome) (109400)	759/Q85	<i>PTCH1/PTCH2/SUFU</i>	9q22.32/1p34.1/10q24.32	AD	Medulloblastoma
Turcot (276300)	759/Q85	<i>APC/hMLH1/hPMS2/hMSH2/hMSH6</i>	5q22.2/3p22.2/7p22.1/2p21-p16/2p16.3	AR	Medulloblastoma, astrocytoma, glioblastoma multiforme
Cowden (158350)	759/Q85	<i>PTEN</i>	10q23.31	AD	Astrocytoma, meningioma
Rubinstein–Taybi (180849)	759/Q85	<i>CREBBP</i>	16p13.3	AD	Oligodendroglioma, medulloblastoma, neuroblastoma, meningioma
Multiple hamartomas (601728)	759/Q85	<i>PMS2/PTEN</i>	7p22.2/10q23.31	AD	Oligodendroglioma, astrocytoma, meningioma, glioblastomas
Ataxia telangiectasia (208900)	334W/G11.3	<i>ATM</i>	11q22.3	AR	Medulloblastoma, gliomas
von Hippel–Lindau (193300)	759G/Q85.8C	<i>VHL/CCND1</i>	3p25.3/11q13.3	AD	Hemangioblastoma
Carney complex (160980)	759/Q85	<i>PRKAR1A</i>	17q24.2	AD	Melanotic schwannoma
Melanoma–astrocytoma (155755)	759/Q85	<i>CDKN2A</i>	9p21.3	AD	Astrocytoma, medulloblastoma, glioblastoma multiforme, ependymoma, glioma, meningioma, acoustic neurilemmoma
Hereditary retinoblastoma (180200)	759/Q85	<i>RBI</i>	13q14.2	AD	Retinoblastoma

Abbreviations: OMIM, Online Mendelian Inheritance in Man; ICD, International Statistical Classification of Diseases and Related Health Problems, Ninth and Tenth Revisions; AD, autosomal dominant; AR, autosomal recessive.

occurrences, while for TSC, the majority of cases are de novo (~65%–85%).^{3,4} Furthermore, it is known that some of the de novo mutations occur in cells after fertilization, resulting in mosaicism, eg, ~30% of de novo NF2 cases are due to mosaic mutations,³ while mosaic NF1 occurs less commonly, with birth prevalence of 1 in 36000.⁴

There is some inconclusive evidence on the association between perinatal factors, including advanced parental age, and phacomatoses in offspring, which is most likely due to the increased risk of new germ line mutations.^{7–9} The available studies are very few, are small, and focus on the association between parental age and risk of NF1 in offspring.^{7,8,10,11} In addition, it has been shown that perinatal factors, such as advanced parental age, are associated with various types of pediatric cancer, including nervous system tumors.^{12–14} Therefore, the observation of an increased risk of nervous system tumors related to advanced parental age, as well as related to genetic syndromes, led to the hypothesis that non-familial genetic syndromes may be associated with advanced parental age. Hence, in this study, we investigated the effect of

parental age on the risk of being born with a genetic syndrome associated with the occurrence of nervous system tumors.

Patients and methods

Study subjects and procedures

Study population

The study is designed as a case–control study nested within the Swedish population. The eligible population includes individuals who were born and resident in Sweden at any time during the period between 1 January 1960 and 31 December 2010 with information available about parental age for both biological parents.¹⁵ Informed consent was not required for this study since it was register based. The study was approved by the Regional Ethical Review Board in Stockholm, and the National Board of Health and Welfare assessed patient confidentiality before making deidentified and anonymous data available for analyses.

Case identification

Cases were identified through linkage of the population to the Patient Register, using the unique personal identifier

assigned to each Swedish resident. The Patient Register was initiated in 1964 and contains information on diagnostic codes and surgical procedures for all in-hospital care, available nationwide since 1987, as well as outpatient specialist care with nationwide coverage since 2001.¹⁶ Eligible cases of neurofibromatosis (NF1, NF2, and schwannomatosis), TSC, von Hippel–Lindau disease (VHL), ataxia telangiectasia, and other unspecified phacomatoses were identified through the Patient Register using the International Statistical Classification of Diseases and Related Health Problems, Ninth and Tenth Revisions (ICD-9 and ICD-10), as specified in Table 1. Using data from the Patient Register gave us a unique opportunity to investigate these rare outcomes in a large population with sufficient statistical power. Included cases were individuals born in Sweden from 1960 who were still alive in 1987, when the ICD-9 version was introduced. As is evident from Table 1, the ICD codes do not always distinguish between specific subtypes of phacomatoses; hence, it was not possible to specify the specific phacomatosis type for 44% of the cases. For neurofibromatosis, the classification in the Patient Register did not distinguish between NF1, NF2, and schwannomatosis, but the vast majority of neurofibromatosis is NF1 (~90%–95%).¹⁷

Determination of heritability

Cases were further classified as familial or nonfamilial. First- and second-degree relatives of eligible individuals were identified through the Multigeneration Register, which includes the relationships between parents and their children for all individuals born since 1932 and resident in Sweden since 1960.¹⁸ Information on occurrence of genetic syndromes in first- and second-degree relatives was collected through linkage of the identified relatives with the Patient Register. To ensure that familial cases were not classified as nonfamilial, we defined cases as familial if any genetic syndrome was identified in a relative. This conservative approach was used as some of the diagnostic information in the Patient Register was coded according to earlier, less precise, ICD versions. Thus, for the period 1964–1967, ICD-7 code 759, and for 1968–1986, ICD-8 codes 759, 759.86, 759.87, 743.40 were used to define familial occurrence of phacomatosis, whereas from 1987 onward, the ICD-9 and ICD-10 codes listed in Table 1 were used.

To assess potential changes in completeness of case identification and classification into familial vs nonfamilial cases during the study period, we investigated the distribution of age at diagnosis according to birth cohort and heritability, frequency of identified familial and nonfamilial cases per calendar year, and the distribution of age at death among cases according to birth cohort. No apparent trends were observed.

Control selection

Ten controls per case were randomly selected from the eligible population, matched to the case on sex, birth year, and residence in Sweden at date of case detection.¹⁵ An additional eligibility criterion was that controls should not have a first- or second-degree relative diagnosed with a genetic syndrome.

Parental age and covariates

Information about parents' birth years and countries of birth was extracted from the Multigeneration Register. Parental education and parental country of birth were considered potential confounders. Information about parental education was collected from registers available at Statistics Sweden. We used educational information from the census conducted in 1970 and yearly information from the Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA) from 1990.

Statistical analyses

Conditional logistic regression was used to estimate the crude association between parental age and the risk of nonfamilial and familial phacomatoses in offspring. The results were later adjusted for parental education, parental country of birth, and mutually adjusted for maternal and paternal ages. Analyses were conducted for neurofibromatosis alone and all other phacomatoses combined. Sensitivity analyses were performed where the population was restricted to persons born 1987 or later. In 1987, the Patient Register became available nationwide and ICD-9 was introduced, which is likely to contribute to a complete case identification and thereby less misclassification of heritability. Parental education was defined as the highest achieved maternal/paternal educational level and was categorized into the following: low, elementary school; intermediate, high school or apprenticeship; and high, university or postgraduate. Maternal/paternal country of birth was categorized into Nordic and non-Nordic countries, where parental country of birth was considered Nordic if both parents were born in a Nordic country. The analyses were conducted using Stata statistical software version 13 (StataCorp, College Station, TX, USA) and SAS statistical software version 9.3 (SAS Institute, Inc, Cary, NC, USA).

Results

In total, we identified 4625 phacomatoses cases and 46250 matched controls. Distribution of phacomatoses subtypes was as follows: 2089 neurofibromatosis, of which 61% were nonfamilial; and 2536 other subtypes combined, of which 87% were nonfamilial. More than 45% of the cases were

diagnosed with neurofibromatosis. Less than 0.5% of the cases and controls had missing data on parental education and these were excluded from the analyses. The distributions of parental country of birth and parental education were similar among cases and controls. The demographic characteristics of cases and controls are summarized in Table 2.

Table 3 illustrates the association between paternal and maternal ages at birth and prevalence of familial and non-familial neurofibromatosis in offspring. In crude analyses, for offspring of fathers aged 35–39 years, compared with offspring of fathers aged 25–29 years, the odds ratio (OR) was estimated at 1.44 (95% CI 1.21–1.71), increasing to OR = 1.72 (95% CI 1.42–2.08) in offspring of fathers aged ≥40 years. An elevated risk estimate was also observed for offspring of mothers aged 35–39 years (OR = 1.23 [95%

CI 1.02–1.49]). We found no indication of associations between advanced paternal or maternal age and risk of familial neurofibromatosis. In adjusted analyses, compared with offspring of fathers aged 25–29 years, elevated risk estimates were observed for nonfamilial neurofibromatosis among offspring of older fathers; in the category of paternal age 35–39 years, the OR was estimated at 1.43 (95% CI 1.16–1.74), increasing to OR = 1.74 (95% CI 1.38–2.19) in offspring of fathers aged ≥40 years. No associations were observed between advanced paternal age and risk of familial neurofibromatosis. Furthermore, there was no consistent association between advanced maternal age and neurofibromatosis in offspring.

Results for other nonfamilial phacomatoses were similar but less pronounced (Table 4). For offspring of fathers

Table 2 Descriptive characteristics of study participants born since 1960

Characteristics	NF	Nonfamilial NF	Familial NF	NF-matched controls	Other phacomatoses combined	Nonfamilial phacomatoses	Familial phacomatoses	Other phacomatoses-matched controls
Number of participants, n (%)	2089	1283 (61)	806 (39)	20890	2536	2195 (87)	341 (13)	25360
Paternal age in years, mean, SD	32.13, 0.14	32.61, 0.19	31.35, 0.21	31.40, 0.04	31.37, 0.13	31.41, 0.13	31.17, 0.35	31.14, 0.04
Maternal age in years, mean, SD	28.71, 0.12	29.02, 0.15	28.22, 0.18	28.52, 0.04	28.27, 0.11	28.28, 0.11	28.25, 0.28	28.19, 0.03
Sex, n (%)								
Male	1051 (50)	657 (51)	394 (49)	10510 (50)	1348 (53)	1169 (53)	179 (52)	13480 (53)
Female	1038 (50)	626 (49)	412 (51)	10380 (50)	1188 (47)	1026 (47)	162 (48)	11880 (47)
Parental education level, n (%)								
Low ^a	283 (14)	164 (13)	119 (15)	2175 (10)	262 (10)	230 (11)	32 (9)	2530 (10)
Intermediate ^b	1051 (50)	568 (44)	483 (60)	9603 (46)	1183 (47)	1014 (46)	169 (50)	11925 (47)
High ^c	749 (36)	546 (43)	203 (25)	9083 (44)	1089 (43)	950 (43)	139 (41)	10847 (43)
Missing	6 (0)	5 (0)	1 (0)	29 (0)	2 (0)	1 (0)	1 (0)	58 (0)
Parental country of birth, ^d n (%)								
Nordic countries	1809 (87)	1098 (86)	711 (88)	18329 (88)	2261 (89)	1962 (89)	299 (88)	22512 (89)
Non-Nordic countries	280 (13)	185 (14)	95 (12)	2561 (12)	275 (11)	233 (11)	42 (12)	2848 (11)
Missing	–	–	–	–	–	–	–	–
Birth year, n (%)								
1960–1969	355 (17)	240 (19)	115 (14)	3550 (17)	398 (16)	329 (15)	69 (20)	3980 (16)
1970–1979	370 (18)	225 (17)	145 (18)	3700 (18)	469 (18)	408 (19)	61 (18)	4690 (18)
1980–1989	458 (22)	279 (22)	179 (22)	4580 (22)	860 (34)	775 (35)	85 (25)	8600 (34)
1990–1999	497 (24)	304 (24)	193 (24)	4970 (24)	635 (25)	543 (25)	92 (27)	6350 (25)
2000–2010	409 (19)	235 (18)	174 (22)	4090 (19)	174 (7)	140 (6)	34 (10)	1740 (7)
Type of phacomatosis, n (%)								
Tuberous sclerosis complex	–	–	–	–	376	292 (78)	84 (22)	–
von Hippel–Lindau disease	–	–	–	–	84	36 (43)	48 (57)	–
Ataxia telangiectasia	–	–	–	–	31	22 (71)	9 (29)	–
Others	–	–	–	–	2045	1845 (90)	200 (10)	–

Notes: ^aLow = elementary school; ^bIntermediate = high school or apprenticeship; ^cHigh = university or postgraduate university (parental education was defined by the highest household education level); ^dParental country of birth was considered as Nordic countries if the country of birth of either of the parents was defined as Nordic.

Abbreviation: NF, neurofibromatosis.

Table 3 Odds ratios of familial and nonfamilial neurofibromatosis in offspring according to parental age at birth

Parental age (years)	Nonfamilial neurofibromatosis				Familial neurofibromatosis								
	Number of cases	Number of controls	Crude OR	95% CI	Adjusted OR ^a	95% CI	Number of cases	Number of controls	Crude OR	95% CI	Adjusted OR ^a	95% CI	
Paternal age													
<25	132	1582	0.98	0.79–1.21 (Reference)	0.99	0.79–1.26 (Reference)	88	952	0.89	0.69–1.16 (Reference)	0.79	0.59–1.05 (Reference)	
25–29	326	3849	1.13	0.97–1.32	1.11	0.94–1.31	242	2342	1.05	0.87–1.26	1.18	0.96–1.44	
30–34	371	3921	1.44	1.21–1.71	1.43	1.16–1.74	271	2501	0.87	0.69–1.09	0.99	0.77–1.29	
35–39	258	2143	1.72	1.42–2.08	1.74	1.38–2.19	125	1400	0.89	0.68–1.17	1.03	0.74–1.43	
≥ 40	196	1335	1.03	1.02–1.04	1.03	1.02–1.05	80	865	0.99	0.98–1.01	1.01	0.99–1.03	
Continuous	1283	12830					806	8060					
Maternal age													
< 25	279	3234	0.89	0.75–1.04 (Reference)	0.94	0.78–1.13 (Reference)	211	1920	1.08	0.89–1.31 (Reference)	1.06	0.85–1.32 (Reference)	
25–29	420	4391	1.15	0.99–1.34	1.00	0.85–1.18	286	2806	0.92	0.76–1.12	0.95	0.77–1.16	
30–34	369	3365	1.23	1.02–1.49	0.92	0.74–1.14	203	2147	0.86	0.66–1.11	0.92	0.68–1.24	
35–39	173	1486	1.20	0.85–1.69	0.79	0.55–1.16	84	953	0.91	0.58–1.44	0.97	0.58–1.60	
≥ 40	42	354	1.02	1.01–1.03	0.99	0.97–1.00	22	234	0.99	0.97–1.00	0.99	0.97–1.01	
Continuous	1283	12830					806	8060					

Note: ^aAdjusted for maternal and paternal education, parental country of birth, and mutually adjusted for paternal and maternal ages.

Table 4 Odds ratios of familial and nonfamilial other phacomatoses combined in offspring according to parental age at birth

Parental age (years)	Nonfamilial other phacomatoses				Familial other phacomatoses								
	Number of cases	Number of controls	Crude OR	95% CI	Adjusted OR ^a	95% CI	Number of cases	Number of controls	Crude OR	95% CI	Adjusted OR ^a	95% CI	
Paternal age													
<25	265	2778	0.99	0.85–1.15 (Reference)	0.91	0.78–1.07 (Reference)	40	428	0.81	0.55–1.19 (Reference)	0.79	0.53–1.19 (Reference)	
25–29	651	6753	1.02	0.91–1.14	1.06	0.93–1.19	116	1003	0.76	0.57–1.01	0.74	0.55–1.01	
30–34	660	6738	1.11	0.97–1.27	1.16	0.99–1.35	95	1074	0.83	0.59–1.17	0.81	0.54–1.20	
35–39	393	3678	1.18	1.00–1.38	1.23	1.01–1.50	56	571	0.88	0.59–1.32	0.89	0.54–1.46	
≥40	226	2003	1.01	1.00–1.02	1.01	1.00–1.02	34	334	0.99	0.98–1.01	0.99	0.97–1.02	
Continuous	2536	25360					341	3410					
Maternal age													
<25	599	5720	1.13	1.01–1.27 (Reference)	1.21	1.06–1.37 (Reference)	88	857	1.04	0.78–1.39 (Reference)	1.01	0.73–1.40 (Reference)	
25–29	734	7915	1.09	0.98–1.23	1.04	0.92–1.17	119	1202	1.01	0.76–1.34	1.09	0.80–1.49	
30–34	567	5563	1.16	0.99–1.35	1.03	0.86–1.23	34	343	1.00	0.67–1.49	1.06	0.66–1.71	
35–39	239	2235	1.17	0.88–1.56	1.01	0.74–1.38	7	86	0.82	0.37–1.81	0.83	0.35–1.99	
≥40	56	517	1.00	0.99–1.01	0.99	0.98–1.01	341	3410	0.99	0.98–1.02	1.00	0.97–1.04	
Continuous	2536	25360					341	3410					

Note: ^aAdjusted for maternal and paternal education, parental country of birth, and mutually adjusted for paternal and maternal ages.

aged ≥ 40 years, compared with offspring of fathers aged 25–29 years, the crude OR was estimated at 1.18 (95% CI 1.00–1.38), whereas the adjusted OR was estimated at 1.23 (95% CI 1.01–1.50). An elevated risk estimate was also observed for offspring of mothers aged < 25 years (crude OR = 1.13 [95% CI 1.01–1.27]; adjusted OR = 1.21 [95% CI 1.06–1.37]), but with no consistent trend. We found no indication of associations between advanced paternal or maternal age and risk of other familial phacomatoses.

Table S1 summarizes the demographic characteristics of cases and controls included in the sensitivity analyses performed on the subjects born in 1987 or later for whom we expect a complete identification of familial cases. The associations between advanced paternal age and risk of nonfamilial neurofibromatosis, as well as other nonfamilial phacomatoses, were more pronounced in analyses restricted to subjects born since 1987 (Tables S2 and S3). As in the main analyses, no association was observed between advanced paternal age and risk of familial neurofibromatosis or other familial phacomatoses. Moreover, no association was observed with advanced maternal age in adjusted results, whereas an indication was found in crude analyses for nonfamilial neurofibromatosis (Tables S2 and S3).

Discussion

The results of this study demonstrate that advanced paternal age is associated with an increased risk of nonfamilial phacomatoses in children, with a clear trend with increasing paternal age. The estimated effect was more pronounced for neurofibromatosis than for other types of phacomatoses. For nonfamilial neurofibromatosis, no association was observed with maternal age, but there was an indication that offspring of young mothers had an increased risk of nonfamilial phacomatoses other than neurofibromatosis, but with no consistent trend with maternal age. No association was observed between parental age and familial phacomatoses in offspring.

Germ cell mutations result from errors in DNA replication, and, compared with oogenesis, spermatogenesis consists of more cell divisions and consequently more DNA replications. Therefore, the de novo mutation rate in the male germ line is higher than that in the female germ line, and the mutation frequency increases with advancing age.^{19–21} In addition, there is evidence that the majority of de novo *NF1* and *NF2* mutations are of paternal origin,^{22,23} which supports our findings of an increased risk of de novo neurofibromatosis associated with advanced paternal, but not maternal, age. Our findings are consistent with an increasing rate of de novo mutations in the *NF1* and *NF2* genes in spermatozoa of older fathers.

Moreover, most of the germ line mutations involved in various subtypes of phacomatosis belong to the Ras pathway genes, which are hypothesized to confer a selective advantage in terms of de novo mutations for the male gamete.²⁴ However, it has also been reported that young maternal age is related to some genetic abnormalities and congenital malformations, which could be due to disturbances during oocyte maturation.^{25–27} Moreover, there is evidence that the origin of de novo whole-gene deletion of *NF1* is predominantly maternal.²⁸

Our findings for neurofibromatosis are in line with the results of the study by Liu et al,⁸ although their substantially smaller study did not clearly distinguish between effects of paternal and maternal ages. A few previous smaller studies also support these findings.^{7,10,11,29–31} For other subtypes of phacomatoses, very few data are available and these do not indicate an effect of parental age. However, these studies included few subjects, and analyses were limited to comparison of the mean paternal and maternal ages.^{32–34} Our study represents the largest phacomatosis population to date and includes various subtypes of phacomatoses. We used population-based register data for both case and control recruitment, as well as for collection of information about familial conditions, parental age, and potential confounding factors, which limits selection and recall bias. Parental education and parental country of birth were included in the analyses as potential confounders, as well as mutual adjustment for maternal and paternal ages, respectively, which was not done in most of the previous studies. As such, we minimized the possibility that the observed associations were due to confounding by these factors.

This study has also some limitations. It was not possible to distinguish between specific phacomatosis subtypes for almost half of the cases due to limitations in the ICD coding system used in the Patient Register. The coding allowed us to identify neurofibromatosis, but we could not separate the specific subtypes of neurofibromatosis, although the majority is likely to be *NF1* (~95%). Moreover, cases were considered familial if their relatives were diagnosed with any type of genetic syndromes, again due to the difficulties in specifying the phacomatosis subtypes. Access to diagnostic information from hospital discharges and outpatient visits gave us a unique opportunity to study these rare outcomes in a large population with sufficient statistical power and to determine whether a case was familial or sporadic. There is, however, a possibility that some phacomatosis patients could not be identified, especially in the early study period when the Patient Register was not yet implemented nationwide. This would lead to nondifferential misclassification of the outcome, which could bias the risk estimates toward the null. However, the

studied outcomes are very rare; thus, the magnitude of such bias is likely to be negligible. Of more concern is the potential misclassification of familial cases as nonfamilial, which would dilute the estimates of the effect of paternal age on the sporadic occurrence of phacomatoses. Restricting the analyses to cases born since the coverage of the Patient Register had become nationwide resulted in slightly stronger risk estimates associated with paternal age. Thus, our findings are likely to be conservative estimates of the effect of paternal age.

Conclusion

In conclusion, the present study provides strong evidence that advanced paternal age is associated, in the offspring, with a higher prevalence of nonfamilial phacomatoses that are predisposing to nervous system tumors, with the strongest effects observed for neurofibromatosis. Our findings did not indicate any effect of advanced maternal age on these outcomes.

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

Table S1 Descriptive characteristics of study participants born since 1987

Characteristics	NF	Nonfamilial NF	Familial NF	NF-matched controls	Other phacomatoses combined	Nonfamilial phacomatoses	Familial phacomatoses	Other phacomatoses-matched controls
Number of participants (%)	1074	644 (60)	430 (40)	10740	1169	1010 (86)	159 (14)	11690
Paternal age in years, mean, SD	33.14, 0.19	33.84, 0.27	32.09, 0.28	32.42, 0.06	32.48, 0.18	32.45, 0.19	32.67, 0.49	32.00, 0.06
Maternal age in years, mean, SD	29.69, 0.16	30.16, 0.21	28.97, 0.24	29.65, 0.05	29.31, 0.15	29.26, 0.16	29.59, 0.39	29.09, 0.05
Sex, n (%)								
Male	578 (54)	365 (57)	213 (50)	5780 (54)	643 (55)	559 (55)	84 (53)	6430 (55)
Female	496 (46)	279 (43)	217 (50)	4960 (46)	526 (45)	451 (45)	75 (47)	5260 (45)
Parental education level, n (%)								
Low ^a	69 (6)	38 (6)	31 (7)	402 (4)	54 (5)	48 (5)	6 (4)	471 (4)
Intermediate ^b	547 (51)	278 (43)	269 (63)	4757 (44)	522 (45)	447 (44)	75 (47)	5399 (46)
High ^c	456 (43)	326 (51)	130 (30)	5570 (52)	592 (51)	514 (51)	78 (49)	5801 (50)
Missing	2 (0)	2 (0)	–	11 (0)	1 (0)	1 (0)	–	19 (0)
Parental country of birth, ^d n (%)								
Nordic countries	878 (82)	515 (80)	363 (84)	8855 (82)	990 (85)	863 (85)	127 (80)	9879 (85)
Non-Nordic countries	196 (18)	129 (20)	67 (16)	1885 (18)	179 (15)	147 (15)	32(20)	1811 (15)
Birth year, n (%)								
1987–1989	168 (16)	105 (16)	63 (15)	1680 (16)	360 (31)	327 (32)	33 (21)	3600 (31)
1990–1999	497 (46)	304 (47)	193 (45)	4970 (46)	635 (54)	543 (54)	92 (58)	6350 (54)
2000–2010	409 (38)	235 (37)	174 (40)	4090 (38)	174 (15)	140 (14)	34 (21)	1740 (15)
Type of phacomatoses, n (%)								
Tuberous sclerosis complex	–	–	–	–	220	164 (75)	56 (25)	–
von Hippel–Lindau disease	–	–	–	–	29	6 (21)	23 (79)	–
Ataxia telangiectasia	–	–	–	–	12	7 (58)	5 (42)	–
Others	–	–	–	–	908	833 (92)	75 (8)	–

Notes: ^aLow, elementary school; ^bIntermediate, high school or apprenticeship; ^cHigh, university or postgraduate university (parental education was defined by the highest household education level); ^dParental country of birth was considered as Nordic countries if the country of birth of either of the parents was defined as Nordic.

Abbreviation: NF, neurofibromatosis.

Table S2 Odds ratios of familial and nonfamilial neurofibromatosis in offspring born since 1987 according to parental age at birth

Parental age (years)	Nonfamilial neurofibromatosis				Familial neurofibromatosis								
	Number of cases	Number of controls	Crude OR	95% CI	Adjusted OR ^a	95% CI	Number of cases	Number of controls	Crude OR	95% CI	Adjusted OR ^a	95% CI	
Paternal age													
<25	39	500	0.96	0.66–1.39 (Reference)	0.99	0.67–1.47 (Reference)	32	318	0.94	0.63–1.42 (Reference)	0.76	0.49–1.19 (Reference)	
25–29	138	1701	1.13	0.90–1.42	1.09	0.86–1.40	118	1109	0.99	0.76–1.27	1.18	0.89–1.56	
30–34	198	2174	1.39	1.09–1.78	1.37	1.04–1.81	149	1419	0.85	0.63–1.15	1.13	0.80–1.59	
35–39	148	1312	1.98	1.53–2.57	1.94	1.42–2.65	81	891	0.83	0.59–1.18	1.21	0.80–1.83	
≥40	121	753	1.04	1.03–1.05	1.04	1.03–1.06	50	563	0.99	0.97–1.00	1.01	0.99–1.04	
Continuous	644	6440					430	4300					
Maternal age													
<25	87	1092	0.84	0.65–1.09 (Reference)	0.87	0.65–1.17 (Reference)	83	692	1.09	0.83–1.46 (Reference)	1.05	0.76–1.44 (Reference)	
25–29	202	2163	1.17	0.96–1.43	1.04	0.84–1.29	158	1446	0.83	0.65–1.07	0.86	0.66–1.12	
30–34	224	2055	1.19	0.92–1.53	0.89	0.67–1.19	124	1354	0.80	0.58–1.11	0.84	0.58–1.22	
35–39	103	940	1.61	1.05–2.47	1.04	0.65–1.66	57	644	0.44	0.21–0.91	0.46	0.21–1.00	
≥40	28	190	1.02	1.01–1.04	0.99	0.97–1.01	8	164	0.97	0.95–0.99	0.98	0.95–1.01	
Continuous	644	6440					430	4300					

Note: ^aAdjusted for maternal and paternal education, parental country of birth, and mutually adjusted for paternal and maternal ages.

Table S3 Odds ratios of familial and nonfamilial other phacomatoses combined in offspring born since 1987 according to parental age at birth

Parental age (years)	Nonfamilial phacomatoses				Familial phacomatoses								
	Number of cases	Number of controls	Crude OR	95% CI	Adjusted OR ^a	95% CI	Number of cases	Number of controls	Crude OR	95% CI	Adjusted OR ^a	95% CI	
Paternal age													
<25	75	925	0.86	0.66–1.13 (Reference)	0.80	0.60–1.06 (Reference)	6	133	0.39	0.17–0.94 (Reference)	0.37	0.15–0.91 (Reference)	
25–29	267	2845	1.05	0.89–1.25	1.11	0.92–1.33	51	443	0.85	0.56–1.28	0.87	0.56–1.35	
30–34	322	3246	1.18	0.97–1.42	1.25	0.99–1.55	50	514	0.85	0.53–1.37	0.86	0.50–1.49	
35–39	216	1964	1.24	0.99–1.54	1.32	1.01–1.72	31	318	1.00	0.58–1.72	0.95	0.49–1.85	
≥40	130	1120	1.01	1.00–1.02	1.02	1.00–1.03	21	182	1.01	0.99–1.04	1.01	0.97–1.04	
Continuous	1010	10100					159	1590					
Maternal age													
<25	203	2026	1.06	0.89–1.27 (Reference)	1.19	0.98–1.46 (Reference)	26	276	0.91	0.56–1.47 (Reference)	1.04	0.62–1.74 (Reference)	
25–29	339	3584	1.07	0.91–1.26	0.98	0.82–1.17	58	558	0.89	0.59–1.34	0.93	0.59–1.43	
30–34	297	2937	1.16	0.94–1.44	0.99	0.78–1.27	47	507	1.12	0.67–1.87	1.18	0.65–2.17	
35–39	138	1261	1.19	0.82–1.74	0.99	0.66–1.49	23	196	0.91	0.35–2.38	0.87	0.29–2.52	
≥40	33	292	1.01	0.99–1.02	0.99	0.98–1.01	5	53	1.01	0.98–1.04	1.01	0.96–1.05	
Continuous	1010	10100					159	1590					

Note: ^aAdjusted for maternal and paternal education, parental country of birth, and mutually adjusted for paternal and maternal ages.

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