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SHORT COMMUNICATION

Parent-of-origin in individuals with familial neurofibromatosis type 1 and optic pathway gliomas

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Abstract Neurofibromatosis type 1 (NF1) is one of the most common autosomal dominant cancer syndromes worldwide. Individuals with NF1 have a wide variety of clinical features including a strongly increased risk for pediatric brain tumors. The etiology of pediatric brain tumor development in NF1 is largely unknown. Recent studies have highlighted the contribution of parent-of-origin effects to tumorigenesis in sporadic cancers and cancer predisposition syndromes; however, there is limited data on this effect for cancers arising in NF1. To increase our understanding of brain tumor development in NF1, we conducted a multi-center retrospective chart review of 240 individuals with familial NF1 who were diagnosed with a pediatric brain tumor (optic pathway glioma; OPG) to determine whether a parent-of-origin effect exists overall or by the patient's sex. Overall, 50 % of individuals with familial NF1 and an OPG inherited the *NF1* gene from their mother. Similarly, by sex, both males and females were as likely to inherit the *NF1* gene from their mother as from their father, with 52 % and 48 % of females and males with OPGs inheriting the *NF1* gene from their mother. In conclusion, in contrast to findings from other studies of sporadic cancers and cancer predisposition syndromes, our results indicate no parent-of-origin effect overall or by patient sex for OPGs in NF1.

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Introduction

Neurofibromatosis type 1 (NF1) is one of the most common familial cancer syndromes worldwide with reported incidences ranging from 1/3,000 to 1/4,000 (reviewed in Lynch and Gutmann [1]). NF1 is an autosomal dominant disorder characterized by germline mutations in the *NF1* tumor suppressor gene. An estimated 56 % of North American and European NF1 cases occur in the context of familial inheritance, while the rest are sporadic [2]. Individuals with NF1 are at an elevated risk for the development of several different tumors, including brain tumors. In this regard, ~15 % of children with NF1 harbor a low-grade glial neoplasm of the optic pathway (OPG), which can lead to vision loss and hypothalamic dysfunction [1, 3, 4]. The etiology of pediatric brain tumors in NF1 is largely unknown, which poses a significant barrier to clinicians caring for children with NF1 and necessitates regular vision and radiologic examinations for all young patients. Understanding the genetic mechanisms underlying OPG development in individuals with NF1 may help to identify high risk populations and improve clinical risk prediction of brain tumor formation and outcome.

A few recent studies have suggested that the influence of cancer predisposition variants on cancer development in the offspring may depend on their parent-of-origin [5–7]. A parent-of-origin effect was recently reported in a study of individuals with Lynch syndrome, a colorectal cancer (CRC) syndrome characterized by germline mutations in DNA mismatch repair genes. In this study, both parent-of-origin and patient sex influenced CRC with maternally-inherited mutations conferring a larger increase in risk for CRC in males than paternally-inherited mutations [5]. In addition, parent-of-origin effects have been demonstrated for common susceptibility variants residing near imprinted genomic loci for breast cancer and basal cell carcinoma in an Icelandic population [6]. Studies of familial cases of pheochromocytoma/paraganglioma in association with germline succinate–ubiquinone oxidoreductase succinate dehydrogenase subunit D *(SDHD)* mutations have also showed a parent-of-origin effect with tumors predominantly occurring in patients inheriting *SDHD* mutations from their fathers [7, 8]. With respect to NF1, a few previous studies examined parent-of-origin effects on NF1 disease severity with inconsistent results [9–12]. Three of these studies examined parent-of-origin effects on OPGs specifically; however the number of OPG cases was small in each study (fewer than 25 individuals). In addition, none of these studies evaluated parent-of-origin effects on OPGs by the sex of the offspring [9, 11, 12].

The objective of this large multi-center retrospective chart review study was to determine whether a parent-of-origin effect exists for OPGs in children with familial NF1 and whether this effect is influenced by patient sex.

Methods

Study population

We obtained anonymized data on sex and parent-of-origin from 240 familial NF1 cases (122 females and 118 males) with OPG from seven established NF1 clinical programs in the United States, Canada, and Australia. All procedures used for this study were in accordance with the ethical standards of the Washington University in St. Louis Institutional Review Board.

Statistical analysis

We conducted a two-tailed binomial test for proportions to determine whether the proportion of cases that inherited the *NF1* germline mutation from their mother versus their father was significantly different from the expected value of 50 %. We also calculated the statistical significance of the association between sex of the child and parent-of-origin using contingency tables and fisher's exact test to determine if patient sex influenced potential parent-of-origin effects. Finally, we examined whether there were any differences in parent-of-origin patterns in patients with OPGs by NF1 clinical program, since some programs routinely screen all their NF1 patients by magnetic resonance imaging (MRIs) to detect OPGs while others rely on ophthalmologic evaluations to identify those who will be referred for MRI. p values ≤ 0.05 were considered statistically significant.

Results

We found no significant deviations (either overall or by patient sex) from the expected 50 % frequency when comparing individuals with OPGs inheriting the *NF1* mutation from their mother versus their father. The proportion of OPG cases inheriting the *NF1* mutation from their mother (n = 121) versus their father (n = 119) was the same (~50 %). By sex, 52 % of female (n = 64) and 48 % of male (n = 57) OPG cases, respectively, inherited the *NF1* mutation from their mother. By clinic, none of the clinics revealed a statistically significant parent-of-origin effect overall; however, data from clinic 2 showed a

Table 1 Parent-of-origin of *NF1* mutations in individuals with OPG

Clinic	Males and females		Females	Males	
	Maternal inheritance [% (n)]	*p* value	Maternal inheritance [% (n)]	Maternal inheritance [% (n)]	*p* value
Pooled	50 (121)	0.95	52 (64)	48 (57)	0.61
1	52 (14)	1.0	64 (9)	31 (5)	0.13
2	52 (13)	1.0	69 (9)	15 (4)	0.02
3	68 (11)	0.2	45 (5)	40 (6)	1.0
4	52 (34)	0.8	47 (16)	52 (18)	0.81
5	48 (14)	1.0	64 (9)	66 (5)	1.0
6	44 (12)	0.7	33 (4)	47 (8)	0.83
7	46 (23)	0.7	41 (12)	52 (11)	0.60

statistically significant sex-specific effect of parent-of-origin with 69 % of female patients, but only 15 % of male patients inheriting NF1 from their mothers ($p = 0.02$, Table 1). A similar trend towards an interaction between patient sex and parent-of-origin was observed in data from clinic 1.

Discussion

The most likely mechanism for a parent-of-origin effect on cancer susceptibility is imprinting, where the expression of an imprinted gene depends on the parental allele inherited. However, for non-imprinted genomic loci, such as *NF1*, alternative mechanisms have been proposed. For example, in an *Nf1* mouse model it has been demonstrated that maternal inheritance of the mutated *Nf1* gene on chromosome 11 is associated with an increased frequency of astrocytoma formation compared to mice with a paternally-inherited *Nf1* mutant allele. The authors proposed that this effect could result from modulation of astrocytoma incidence by imprinted genes on chromosome 11 [13]; however, none have been conclusively identified to date [14]. Another mechanism that has been proposed for a maternal effect on disease severity in NF1 is that mothers with NF1 may produce factors, such as nerve-growth factor, that accelerate disease severity in her NF1 affected offspring [10]. However, our data do not support either of these mechanisms for OPG development in humans with NF1.

A maternal effect on disease severity in NF1 was first proposed in 1978 by Miller and Hall who conducted a case series of 62 patients whose NF1 was diagnosed during childhood. The authors developed a grading system that varied from 0 to 3 (0 = least severe, 3 = most severe) based on the severity of NF1 associated complications and evaluated whether the severity of the disease varied by the parent-of-origin of the *NF1* germline mutation. The authors reported that the mean severity of NF1 disease was three times as high in the offspring of affected mothers versus fathers [10]. Three subsequent published studies examined parent-of-origin effects on OPGs specifically, two of which included an overlapping set of familial OPG cases. None of these studies found a maternal effect on OPGs based on 11, 13, and 22 familial cases [9, 11, 12]. In our large multicenter study of 240 cases of OPGs, we did not find an overall parent-of-origin effect on OPG development in familial NF1, which is consistent with the smaller studies to date.

Our study has strengths and limitations. The main strength of our study is its large size that pooled data from seven different clinics in North America and Australia. A limitation of our study is that ascertainment of OPGs varies by clinic with some clinics diagnosing OPGs on the basis of symptoms followed by MRI confirmation and others routinely screening all of their patients (including those who are asymptomatic) by MRI. Differential clinical protocols for OPG detection could bias our results if a parent-of-origin effect differed by the presence or absence of symptoms; however, when we conducted analyses that excluded cases that were known to be detected on the basis of MRI screening alone, our overall results were similar (data not shown).

In conclusion, we did not find evidence for a parent-of-origin effect for OPGs in children with NF1. However, future prospective studies should implement uniform data collection criteria, which might demonstrate geographic genetic effects for parent-of-origin and patient sex. The influence of regional genetics might account for the observed interaction between patient sex and parent-of-origin observed in two of the eight centers included in this study. Finally, future directions should include examination of the potential roles of single nucleotide polymorphisms and copy number variations as potential OPG risk modifiers in this common brain tumor predisposition syndrome.

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