Case Report

A novel c.885+1G>A splicing variant in exon 9 of the NF2 gene shows a delayed mild presentation with a predilection for spinal ependymomas

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ABSTRACT

Neurofibromatosis Type 2 (NF2) is a rare autosomal dominant disease caused by pathological variants of the tumor suppressor gene NF2 classically manifesting as bilateral vestibular schwannoma, intracranial and spinal neoplasms such as meningoima and ependymoma, and posterior subcapsular and cortical wedge lens opacities, with an average onset of 18-24 years of age. Approximately 50% of patients inherit the disorder from an affected parent with the remainder resulting from de novo mutations or genetic mosaicism. The most common variants of NF2 are due to C>T transitions resulting in nonsense pathological variants. Individuals with splice-site variants of NF2 display varied phenotypes. Here we present a family with NF2 as the result of an apparently de novo c.885+1G>A splicing variant in exon 9 of the NF2 gene not previously described in the literature. This variant appears to be associated with an extremely mild phenotype with regards to vestibular schwannomas, other schwannoma disease and meningioma, instead exhibiting a delayed presentation with a predilection for ependymomas. The non-classical presentation of this NF2 splicing variant illustrates the importance of keeping NF2 in the differential diagnosis in patients with multiple spinal ependymomas with delayed onset and may warrant genetic testing for NF2 variants in such patients.

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Introduction

Neurofibromatosis Type 2 (NF2; OMIM 101000) is a rare autosomal dominant disease which is caused by pathogenic variants of the tumor suppressor gene NF2, found on chromosome 22q12.2, which produces the protein known as merlin or schwannomin [1]. Diagnosis of NF2 is based on the Manchester Criteria which utilizes a combination of clinical and neuroaxis imaging findings [2]. Affected individuals most commonly develop bilateral vestibular schwannomas (VS) affecting the vestibular branch of the eighth cranial nerve [3]. They may also develop schwannomas, meningoima, ependymomas, and posterior subcapsular and cortical wedge lens opacities. Common presenting symptoms include hearing loss, tinnitus, vestibular dysfunction, and headache [4]. In the setting of spinal involvement, back pain, myelopathy, neuropathy, and sensory disturbances have also been reported.

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The current estimated disease prevalence of NF2 is 1 in 60,000 [1]. The average age of onset is 18-24 years old with almost all affected individuals developing bilateral vestibular schwannomas by age 30 years. Approximately 50% of individuals with NF2 inherit the disease from an affected parent and the remainder are the result of de novo mutations in the NF2 gene [5]. Truncating variants of the NF2 gene are the most common which lead to a smaller non-functional or possibly dominant negative protein product [5]. Approximately 30% of cases are thought to be the result of genetic mosaicism and result in a milder phenotype [6]. Individuals with splice-site variants of NF2 display varied phenotypes [7].

Here we present a family with NF2 which the result of is an apparently de novo splice-site variant not previously described

Case Report

History and Examination

The proband, a 79-year-old male, presented with a 5-year history of foot drop and progressive bilateral lower limb weakness leading to the inability to bear weight. He reported no significant family history but noted hearing deterioration later in life. His neuroaxis MRI scan showed evidence of bilateral small intra-canicular vestibular schwannomas, the right side with some cisternal component and the left measuring 7mm (Figure 1). Additionally, trigeminal and lower cranial nerve schwannomas were noted. His MRI spine showed multiple ependymomas, the largest at thoracic levels T2-T6 with multiple small non-compressive cauda equina schwannomas. He subsequently underwent resection of his large ependymoma.

Figure 1: Neuroaxis Imaging

(A) Brain T1 contrast enhanced MRI of proband showing bilateral intra-canicular vestibular schwannomas, the right side with some cisternal component and the left measuring 7 mm. Trigeminal and lower cranial nerve schwannomas are noted. (B, C, D) Spinal T1 and T2 contrast enhanced MRI images of the proband showing multiple ependymomas, the largest at thoracic levels T2-T6 with additional multiple small non-compressive cauda equina schwannomas. (E, F, G) Brain (T1) and spine (T1 and T2) contrast enhanced MRI imaging of the first son, age 41, showed a large spinal ependymoma at thoracic level T11-T12 and a 2 mm unilateral left vestibular schwannoma. (H, I) T1 contrast enhanced MRI of the second son, aged 40, did not show any evidence of VS, ependymoma, or any other abnormality on scans.

Genetic Analysis of Proband

Genetic analysis of the proband’s tumor sample revealed loss of heterozygosity of NF2. Screening lymphocytic DNA genetic testing revealed a heterozygous c.885+1G>A splicing variant in exon 9 of the NF2 gene (Figure 2). This is a novel variant not previously seen in Manchester nor reported in the literature. There was no evidence of deletion or duplication for any NF2 exons. RNA analysis demonstrated an in-frame exclusion of exon 9. This variant is therefore predicted to disrupt normal splicing of the NF2 gene and consequently be pathogenic. No tumor tissue was available for immunohistochemical analysis, but preliminary protein analysis showed production of a recombinant protein from a gene expression construct.

Screening of Offspring

Both children of the proband underwent genomic analysis which revealed each had inherited the same c.885+1G>A splicing variant (Figure 2). At the time of this manuscript, both children remain clinically asymptomatic. Screening neuroaxis MRIs were obtained for both children (Figure 1). On imaging, the first son, age 41, showed a large spinal ependymoma at T11-T12 and a unilateral left VS measuring 2 mm. His hearing was normal. The second son, age 40, did not show any evidence of VS, ependymoma, or any other abnormality on scans.

Discussion

NF2 is a rare genetic disease that is classically associated with bilateral vestibular schwannomas, other schwannoma disease, and meningioma, with clinical symptoms typically presenting in affected individuals between age 18-24 [1]. The recognition of additional phenotypes associated with NF2 variants has led the development and subsequent expansion of the Manchester Criteria for NF2 diagnosis [2]. The most common variants of NF2 are due to C>T transitions resulting in nonsense pathogenic variants [8]. Most mild cases of NF2 are thought to be the result of genetic mosaicism [6].

This case describes a previously undescribed c.885+1G>A splicing pathogenic variant which is capable of producing Neurofibromatosis Type 2. While splice-site variants have been described with various disease severity, this variant appears to be associated with an extremely mild phenotype with regards to vestibular schwannomas, other schwannoma disease and meningioma, producing only one VS between the two sons aged 40 and 41. Instead, this variant shows a greater predilection for the development of spinal ependymomas. While the majority of NF2 variants display nearly 100% penetrance, only 1 of 2 affected offspring in this family has demonstrated any pathologic phenotype [1]. The onset of symptoms in this variant displays a later clinical time course than is typically described in full constitutional NF2 [5]. Given the delayed onset of symptoms in the proband at approximately age 74, further surveillance is warranted in the offspring with this variant of NF2. Prolonged surveillance may be advisable in all patients found to harbor a c.885+1G>A splicing variant of NF2.

The current treatment of patients with NF2 is focused on specialty centers with a multidisciplinary team of surgeons, geneticists, neurologists, and neuro-radiologists with expertise in NF2 [9]. Individualized treatment plans focus on preservation of neurologic function with the balanced use of microsurgery, radiotherapy, and observation [10, 11]. Current research aimed at future NF2 treatments has focused on modulating the downstream signaling pathways of the NF2 protein and identifying genetic loci for targeted treatment [12-15]. In frame exclusion of exon 9 results in a very mild disease and skipping of exon 9 using an antisense RNA approach has the potential to be used to treat those with truncating variants in exon 9, particularly if it can be confined to Schwann cells.
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Figure 2: cDNA Sequencing and Pedigree

(A) Screening lymphocytic DNA genetic testing revealed a heterozygous c.885+1G>A splicing variant in exon 9 of the NF2 gene. (B) Both children of the proband underwent genomic analysis which revealed each had inherited the same c.885+1G>A splicing variant.

The non-classical presentation of this NF2 splicing variant illustrates the importance of keeping NF2 in the differential diagnosis in patients with multiple spinal ependymomas with delayed onset and may warrant genetic testing for NF2 variants in such patients.

Author Contributorship

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Acquisition of data: Smith
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Critically revising the article: All authors.
Approval of the final version of the article on behalf of all authors: Shoakazemi
Study Supervision: Evans

Competing Interests

None declared.

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Data Sharing

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Patient Consent

Obtained.

Ethical Approval

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