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Case Report

Nevoid Basal Cell Carcinoma Syndrome with Nystagmus and Immobile First Digit Interphalangeal Joints: Expanding the Phenotype of *PTCH1* Duplications

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Abstract

Nevoid basal cell carcinoma syndrome (NBCCS, Gorlin syndrome) is an autosomal dominant condition caused by mutations in the *PTCH1* gene. It is characterized by distinct skeletal and craniofacial anomalies with an increased risk for basal cell carcinomas. We present a 5-year-old male with a family history of NBCCS, found to have a previously unreported 2.7kb partial duplication in the *PTCH1* gene. The patient has several classical craniofacial findings of NBCCS (macrocephaly and frontal bossing), but he also displays additional manifestations of nystagmus and immobile first digit interphalangeal joints due to hypoplastic flexor muscles with underlying normal bony anatomy. Pathogenic mutations are typically protein truncating due to deletions or missense mutations; there have only been three previous reports of duplications in *PTCH1*. Although nystagmus is frequently listed as an eye anomaly associated with NBCC, it has been reported in just 3 members of the same family (all with rotary nystagmus). Hand abnormalities such as polydactyly, metacarpal shortening, and cutaneous 2,3 syndactyly have been reported, but thumb abnormalities are rare, and there are no reports of immobile thumbs due to hypoplastic flexor muscles. This patient's novel genetic duplication and combination of classical and uncommon features of NCBBS offer the opportunity for both expansion of the NBCCS phenotype and further genotype-phenotype correlations. This case also reiterates the importance of copy number analysis for both duplication and deletion events in the *PTCH1* gene.

ABBREVIATIONS

NBCCS: Nevoid Basal Cell Carcinoma Syndrome

INTRODUCTION

Nevoid basal cell carcinoma syndrome (NBCCS, Gorlin syndrome) is an autosomal dominant condition characterized by distinct skeletal and craniofacial anomalies with an increased risk for basal cell carcinomas. *PTCH1* at 9q22.32 is the only known gene in which mutations cause NBCCS and 70-80% of probands inherited the mutation from a parent [1].

The most recently proposed diagnostic criteria recommend two major or one major and two minor criteria. Major criteria are >2 basal cell carcinomas or one under the age of 20; odontogenic jaw keratocysts; three or more palmar or plantar pits; bilamellar calcification of the falx cerebri; bifid, fused, or markedly splayed ribs; or a first degree relative with NBCCS. Minor criteria include macrocephaly; congenital malformations such as cleft lip or palate, frontal bossing, coarse facial features, hypertelorism; skeletal abnormalities such as Sprengel deformity, marked pectus deformity, digit syndactyly; and radiographic abnormalities such as bridging of the sella turcica, vertebral anomalies, modeling

defects of the hands and feet, or flame-shaped lucencies of the hands and feet; ovarian fibromas; and medulloblastoma [2]. These do not account for newer genetic testing results, as some families with *PTCH1* mutations do not meet diagnostic criteria.

Early identification in the pediatric population is important, as patients should be advised to limit UV radiation and healthcare providers should limit medical radiation exposure. Management guidelines recommend baseline cardiac ultrasounds, dermatological exams, digital panorex of the jaw, spine films, and baseline ophthalmological exams, along with routine developmental, hearing, vision, and speech screenings [3]. Pediatric patients should also be screened with a yearly brain MRI until age 8 for medulloblastoma, which is of highest incidence in those less than 3 years of age [2,3].

CASE PRESENTATION

We present a 5-year-old male who initially presented to genetics clinic at 14 months of age for macrocephaly and developmental delay. His family history was notable for features of NBCCS (Figure 1), including his mother and maternal uncle with multiple basal call carcinomas, cleft lip and palate, and macrocephaly. Informed consent was obtained to share medical and familial information and images.

He was born at term via C-section to a 36-year-old G2P2, with no medication or drug exposures and no pregnancy complications. Birth weight was 4.2kg. He had gross motor delay, as he held his head up at 4 months, sat 11 months, pulled to stand at 13 months, and walked at age 20 months.

On physical exam, he has several classical craniofacial features of NBCCS including macrocephaly (occipitofrontal circumference 57.4cm, >>98%ile, >+3 standard deviations), frontal bossing, and widely set eyes (Figure 2). Other growth parameters were normal, including height (120.5cm, 90-95%ile) and weight (21kg, 50-75%ile). Prior OFC measurement at 13mo was 52cm, at 14mo was 52.6cm, and at 26mo was 55cm.

Nystagmus was noted since birth, and neurological and ophthalmological exams in early childhood displayed gaze-evoked nystagmus with lateral movements, which improved over time without intervention. A brain MRI at 10 months of age revealed mild ventriculomegaly of the lateral and third ventricles and prominence of the extra-axial CSF spaces, but no falxcerebri calcification. Frontal occipital horn ratio was increased at 0.5 (upper limit of normal is up to 0.37 at that age). There was clinical concern for optic atrophy, but brain MRI noted normal optic chiasm. He later developed myopia.

At a follow-up genetics clinic appointment at 5 years of age, mother noted concern that he is unable to bend his thumbs, which was first recognized when he was trying to learn how to write. Physical exam confirmed immobile first digit interphalangeal joints bilaterally with absent flexion creases (Figure 3A).

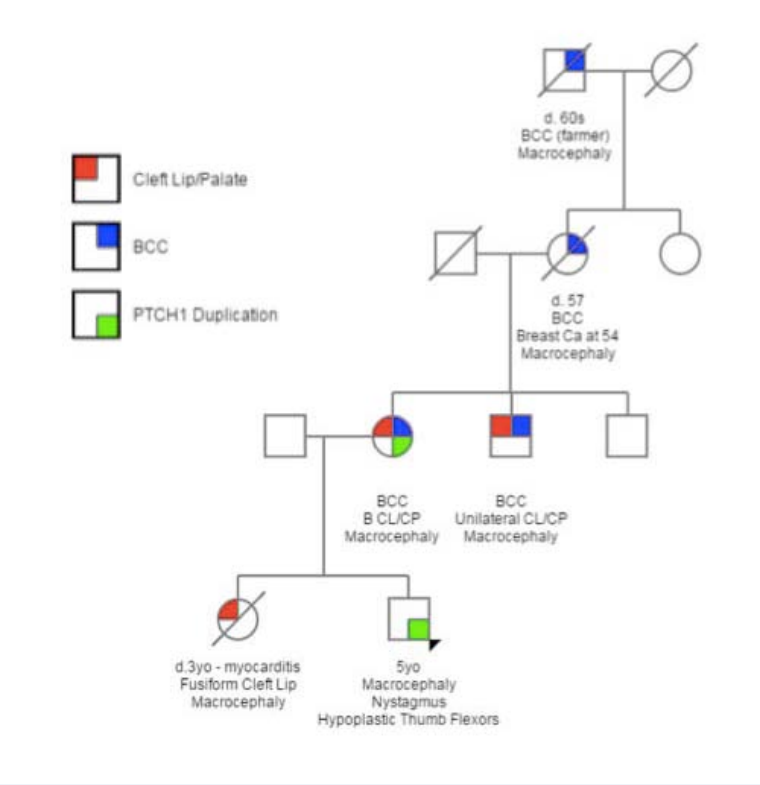

Figure 1 The family pedigree shows the proband's mother and maternal uncle were affected with multiple basal call carcinomas, cleft lip and palate, and macrocephaly. His sister had a fusiform cleft lip, macrocephaly, and died at 3 years of age due to viral myocarditis. His maternal grandmother (who died at age 54 of breast cancer) and great-grandfather were also reported to have multiple basal cell carcinomas and macrocephaly. great-grandfather was a farmer who was frequently sun-exposed.

Figure 2 Proband and his mother, who both tested positive for 2.7kb *PTCH1* duplication.

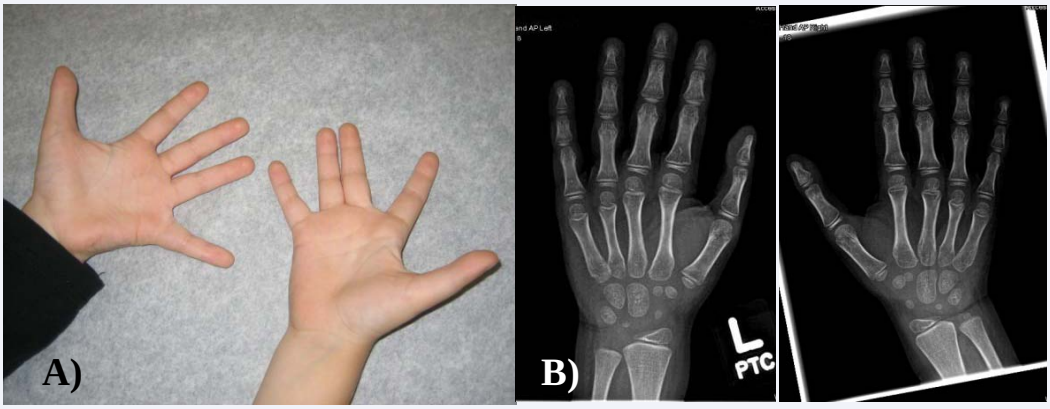

Figure 3 (A) Palmar view of the patient's hands. Note the absent flexor crease of the first digit interphalangeal joint bilaterally.(B) X-ray images of the patient's left and right hands, showing subtle shortening of the first digit and the first proximal phalange of digits 3, 4, and 5 bilaterally with normal bony morphology.

Orthopedics evaluation noted that his immobile first digit interphalangeal joints are due to hypoplastic flexor muscles with underlying normal bony anatomy (Figure 3B). They found no flexion in either thumb at the interphalangeal joint and no flexion creases, and he had normal extension at the metacarpophalangeal joint. Occupational therapy was recommended for strengthening and optimal utilization of residual function of the IP joint, specifically to work on handwriting.

Multiple thorough skin exams by a pediatric dermatologist showed no evidence of suspicious lesions. These visits reiterated the importance of strict sun protection and avoidance of unnecessary radiation.

He required bilateral myringotomy with tympanostomy tube placement for chronic otitis media at age 6,but has otherwise been healthy. He had a normal echocardiogram, which was performed because NBCCS is associated with cardiac fibromas. We plan to begin regular orthopantograms to evaluate for odontogenic jaw cysts beginning at age 8, as per screening recommendations.

Genetic testing of the mother was initially recommended at the first genetics evaluation in 2010 (when patient was 14mo); however there were insurance difficulties and testing was deferred. Molecular analysis of the *PTCH1* gene performed in 2011 directly on the patient at 26mo revealed a previously unreported 2.7kb partial duplication that encompasses exons 13, 14, and part of exon 15. This was found through copy number analysis using targeted array comparative genomic hybridization (CGH) with exon-level resolution; it was confirmed with multiplex ligation-dependent probe amplification (MLPA). Sequence analysis was discontinued after identification of the duplication, as traditional sequencing methods often do not detect large deletions and duplication events. Further testing revealed the duplication was maternally inherited.

DISCUSSION

Here we report a male with a novel familial duplication in *PTCH1* who has a strong family history of NBCCS and displays classic findings of NBCCS along with additional features of nystagmus and immobile thumbs due to hypoplastic flexors.

Pathogenic germline mutations causing NBCCS are typically

protein truncating due to deletions or nonsense mutations (73%), followed by missense mutations (17%), and splice-site mutations (10%) [4]. Exonic, multiexonic, and whole-gene deletions account for up to 6% of cases [5], including microdeletions of the 9q22.3 region involving *PTCH1* [6]. There are no clear genotype-phenotype correlations [3]. Among patients who meet clinical criteria, approximately 73% have a positive mutation detected in *PTCH1* [3], and even though a clinical diagnosis can often be made, genetic testing is recommended to confirm a diagnosis in patients who have early signs but do not meet clinical criteria to allow for increased surveillance. Testing is also recommended for predictive testing in individuals with a positive family history or for those with a positive familial mutation who desire prenatal testing [3].

Sanger sequencing is the gold standard for detecting molecular sequence variants; however a known limitation is that this technique is not designed to detect deletions and duplication events, which can also be pathogenic. If a provider does not specifically order deletion/duplication analysis, a normal sequencing result may provide false reassurance and delay diagnostic confirmation.

While intragenic or whole-gene deletions are more common, duplications are rarely seen [7], and have been reported three times, although the previously reported duplications are either much smaller or much larger than the one found in our patient.

A study of six Japanese families with a clinical diagnosis of NBCCS found a single patient with multiple jaw keratocytes, macrocephaly, and characteristic facies had a 58-bp duplication in exon 8 (c.1138_1195dup) [8].

Another case study identified a 14-year-old male with odontogenic cysts, hypertelorism, macrocephaly and agenesis of the corpus callosum, and his 43-year-old mother had a 25-bp duplication in exon 10 (c.1375dupl25bp) [9]. Interestingly, while both patients had a clinical diagnosis of NBCCS, neither had a history of basal cell carcinomas.

A 14-year-old female with maxillary and mandibular cysts and a keratogenic odontogenic tumor prompted a clinical diagnosis of NBCCS. *PTCH1* studies revealed the first multi-exonic duplication (18kb) spanning exons 10-17 [10].

Nystagmus is frequently listed as an eye anomaly associated with NBCCS along with strabismus, cataracts, and pigmentary changes of the retinal epithelium as an eye anomaly associated with NBCCS [11,12]; however a review of the literature shows very few reports of patients who actually have this finding. A study of 72 people with NBCCS in the United Kingdom identified 3 members of the same family who all had rotary nystagmus out of the 18 cases with noted eye anomalies [13].

Hand abnormalities such as pre- and postaxial polydactyly, metacarpal shortening, and cutaneous syndactyly of the second and third fingers have been reported in patients with NBCCS [14], but thumb abnormalities are rare. One study reports 2 of 4 patients in the same family with NBCCS had a short terminal phalanx of the thumb [15]. A case report describes a boy with NBCCS who has bilateral hypoplastic thumbs [1].There are no reports of immobile thumbs to due hypoplastic flexor muscles.

Early diagnosis is important because delays of screening and treatment may greatly increase associated morbidity and mortality [3]. Screening guidelines exist for pediatric and adult patients, and suggest a yearly medical genetics evaluation to ensure all multidisciplinary issues are addressed and appropriate referrals are made. These include brain MRI yearly until age 8 (for medulloblastoma), baseline cardiac ultrasound (for cardiac fibromas), yearly dermatology exam (for basal cell carcinomas), yearly digital panorex of the jaw (for cysts), baseline spine films (for scoliosis) [3].

Families and healthcare providers should be encouraged to minimize ionizing radiation exposure and maximize protection. Radiographs are warranted for evaluation of valid medical problems, but non-ionizing or digital modalities are preferred when possible [3].

This patient's novel genetic duplication and combination of classical and uncommon features of NBCCS offer the opportunity for both expansion of the NBCCS phenotype and possible further genotype-phenotype correlations, which are not currently known. This case also reiterates the importance of copy number analysis – not just gene sequencing– for both duplication and deletion events in the *PTCH1* gene.

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