

Albinism and Developmental Delay: The Need to Test for 15q11-q13 Deletion

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We report on a 17-month-old African girl with cutaneous and ophthalmologic features of oculocutaneous albinism type 2 as well as microcephaly, absent speech, and tremulous movements. Mutations of the *P* gene within the Angelman/Prader-Willi syndrome critical region at 15q11-q13 cause oculocutaneous albinism type 2. Comorbid oculocutaneous albinism and Angelman syndrome were suspected and confirmed by cytogenetics. Phenotypic features of Angelman syndrome or Prader-Willi syndrome in a patient with albinism should prompt further investigation. © 2007 by Elsevier Inc. All rights reserved.

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Introduction

Oculocutaneous albinism is a genetically heterogeneous autosomal-recessive disorder, categorized into four subtypes. Regardless of subtype, oculocutaneous albinism is not associated with developmental delay or seizures. Oculocutaneous albinism type 2, the focus of this report, is caused by point mutations or deletions of the *P* gene, located within the Angelman syndrome and Prader-Willi syndrome critical region of 15q11-q13 [1]. Oculocutane-

ous albinism type 2 is the most common form of albinism worldwide, and is characterized by reduced pigmentation of the skin, hair, iris, and retina. Individuals with oculocutaneous albinism type 2 are born with minimal to near-normal cutaneous pigmentation. A lack of normal melanin increases the risk of squamous-cell and basal-cell skin carcinoma. Hair color ranges from light yellow to brown, and iris color from blue to brown [2]. Skin, hair, and eye color can darken with age as yellow/orange pheomelanin accumulates over time. A lack of pigmentation in the eye results in foveal hypoplasia, horizontal nystagmus, visual impairment, photophobia, and a misrouting of the optic nerves which manifests as esotropic strabismus. Nystagmus may be congenital, or may develop within the first 3-4 months, and persists throughout life. Visual acuity varies from 20/30 to 20/400, and usually stabilizes during childhood without further deterioration [2].

Oculocutaneous albinism type 2 is particularly common in Africans, with a frequency of 1/1000-1/7900 [3,4], and in African-Americans with a frequency of 1/10,000 [4,5]. In contrast, the frequency of oculocutaneous albinism type 2 in Caucasian-Americans is estimated at 1/36,000 [4]. A homozygous deletion of exon 7 of the *P* gene is the predominant cause of oculocutaneous albinism type 2 in Africans and African-Americans [6]. This 2.7-kb deletion causes a frameshift mutation, resulting in a truncated null allele.

Angelman Syndrome and Prader-Willi Syndrome

Angelman syndrome is characterized by severe speech impairment, developmental delay, gait ataxia, or tremulous movements and behavioral features that include frequent laughing, a happy demeanor, and an excitable personality. Microcephaly by age 2 years and seizure activity are also frequent. Following a typically normal pregnancy, birth, physical appearance, and biochemical test results, Angelman syndrome is not suspected until 6-12 or more months of age, when the child develops seizures and global delay [7]. Usually the brain is also structurally normal, though there may be mild cortical atrophy or dysmyelination [7].

The types of seizure in Angelman syndrome can be varied, and include both major and minor motor types. Most often, the seizures are myoclonic [8]. Electroen-

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cephalograms demonstrate characteristic changes consisting of high-amplitude, 2-3-Hz delta activity with intermittent spike and slow-wave discharges, runs of rhythmic theta activity over a wide area, and runs of rhythmic, sharp theta activity of 5-6 per second over the posterior third of the head, forming complexes with small spikes [9]. Seizures can be difficult to treat in infancy, but their severity decreases significantly in later childhood [8]. Anticonvulsant medications such as valproic acid, topiramate, clonazepam, lamotrigine, and ethosuximide are commonly used [10]. Moreover, benzodiazepines in combination with valproic acid or topiramate have been particularly effective [8]. Vigabatrin and tiagabine, which increase levels of Gamma-aminobutyric acid in the brain, should be avoided because of the postulated influence of abnormal Gamma-aminobutyric acid in Angelman syndrome seizures [7].

Prader-Willi syndrome is a neurobehavioral disorder distinct from Angelman syndrome. In the neonatal period, Prader-Willi syndrome is characterized by failure to thrive with significant feeding problems and hypotonia. These signs are followed by hyperphagia and obesity in childhood, mild to moderate mental retardation, persistent hypotonia, motor delay, short stature, and hypogonadism. In both isolated Angelman syndrome or Prader-Willi syndrome, hypopigmentation is reported; however, it is typically much less severe than in oculocutaneous albinism [11,12].

The Angelman syndrome/Prader-Willi syndrome critical region is located at 15q11-q13. This region is subject to genomic imprinting, the process by which certain genes are activated or inactivated, depending on their parent of origin. Different diseases can be caused by abnormal imprinting at the same locus seen in Angelman syndrome and Prader-Willi syndrome. Failure of expression of the Angelman gene, *UBE3A*, on the maternally inherited allele results in Angelman syndrome. This failure of expression is caused by a maternal deletion of this locus (in 65-75% of cases), a point mutation in *UBE3A* (in 10% of cases), uniparental disomy of two paternal chromosomes 15 (in 5% of cases), or an imprinting defect (in 5% of cases) [13]. In 5-10% of patients with a clinical diagnosis of Angelman syndrome, no genetic etiology is currently known. In Prader-Willi syndrome, the diagnosis is established by the absence of an active paternal allele via deletion (in 65-75% of cases), uniparental maternal disomy (in 20-30% of cases), or a nondeletion or nonuniparental disomy defect (in ~5% of cases) [13].

We report on a patient with characteristic cutaneous and ophthalmologic features of oculocutaneous albinism type 2, and features not attributable to albinism, including microcephaly, absent speech, global developmental delay, tremulous jerky movements, and seizures. A subsequent evaluation revealed comorbid conditions of oculocutaneous albinism type 2 and Angelman syndrome.

Case Report

The proband, a 17-month-old African girl, was born at 39 weeks of gestation to unrelated, healthy Yoruba Nigerian parents. The previous two pregnancies resulted in a 3-year-old healthy boy and a 10-week spontaneous abortion. The mother received standard prenatal care, and there were no maternal illnesses or exposure to alcohol, cigarettes, or illicit substances. There was no family history of albinism, mental retardation, developmental delay, or seizures.

Cutaneous diffuse depigmentation, nystagmus, and retinal and iris depigmentation were noted immediately after birth. The patient was referred for a developmental assessment at age 15 months because of global delay (sat at age 12 months, not pulling to stand, absent verbalization and speech, and no pincer grasp). An evaluation of her hearing and magnetic resonance imaging of the brain produced normal results.

At age 17 months, she was generally fussy and sleepy, and had lost the ability to sit independently after a 1-2-minute febrile seizure episode. Her skin was pale and her hair was coarse. Nystagmus and gray irides with translucent red areas were present (Fig 1). Her head circumference was 44.5 cm (<5% for age 50th percentile for a 9-month-old), her length was 87 cm (>95% for age), and her weight was 10 kg (25% for age). She smiled spontaneously, but was otherwise noninteractive. Movements in her extremities were volitional, but jerky and tremulous.

At age 19 months, over the course of a day, she developed multiple unprovoked and nonfocal generalized tonic-clonic seizures. These were described as a synchronous jerking of all extremities for 15-20 seconds, followed by sleepiness and a difficulty to arouse. An electroencephalogram produced markedly abnormal results, with diffuse slow activity and sharp activity posteriorly, suggesting epileptiform activity. She was discharged on topiramate, which has significantly reduced, but not eliminated, the seizures.

Her clinical presentation was consistent with albinism and African descent, but was also suspicious for comorbid Angelman syndrome, on the basis of microcephaly, absent speech, jerky tremulous movements, seizures, and global delay.



Figure 1. The patient at age 17 months. Note the depigmentation of her skin compared with her mother, who is holding her, and the coarse, depigmented hair consistent with both albinism and her African descent.

Materials and Methods

Cytogenetics

A cytogenetic analysis was performed on thymidine-synchronized peripheral blood lymphocytes. Chromosome preparations and Giemsa-banding followed standard procedures. Fluorescence in situ hybridization was performed using the small nuclear ribonucleoprotein-associated polypeptide N probe for the Angelman syndrome/Prader-Willi syndrome region on chromosome 15 that includes control probes for the centromere, chromosome enumeration probe15, and for promyelocytic leukemia probe on 15q22, and for subtelomeres (Vysis, Inc., Des Plaines, IL).

Molecular Analysis and the P Gene

Genomic DNA was prepared from peripheral blood leukocytes (proband and mother) [14] or a mouthwash specimen (father) (Puregene DNA Purification Kit, Gentra Systems, Minneapolis, MN). Polymerase chain reaction-based screening for the 2.7-kb deletion of the *P* exon 7 was performed as described by Durham-Pierre et al. [6] (Fig 2A).

Results

Chromosome analysis revealed a microscopically visible deletion on one chromosome 15, with breakpoints at q11.2 and q13. Fluorescence in situ hybridization with the small nuclear ribonucleoprotein-associated polypeptide N probe confirmed the deletion, indicating an absence of material within the Angelman syndrome/Prader-Willi syndrome critical region. The patient's karyotype

was 46,XX,del(15)(q11.2q13).ish del(15)(q11.2q11.2) (SNRPN-). Fluorescence in situ hybridization with subtelomere probes revealed normal hybridization (results not shown).

Molecular analysis (Fig 2B) indicated that the proband is hemizygous for the exon 7 deletion inherited from her father, who is a carrier of this allele. The mother has normal *P* gene alleles.

The paternal exon 7 *P* gene deletion, in combination with a large de novo deletion of the Angelman syndrome critical region including the *P* gene from the maternal allele, is responsible for this compound phenotype.

Discussion

Approximately 1% of individuals with oculocutaneous albinism type 2 also present with clinical features of Prader-Willi syndrome or Angelman syndrome [15]. This comorbid situation arises when a deletion of the Angelman syndrome/Prader-Willi syndrome critical region of chromosome 15q11-q13 includes the *P* gene on one allele, and a *P* gene mutation or deletion on the other allele. Our patient manifested a paternally inherited deletion of exon 7 of the *P* gene and a large de novo deletion on the maternally inherited chromosome 15q that included the Angelman syndrome critical region and the *P* gene on that allele, causing this compound phenotype of oculocutaneous albinism and Angelman syndrome.

Unlike the relatively rare occurrence of oculocutaneous albinism type 2 in patients with either Angelman syndrome or Prader-Willi syndrome, up to 50% of patients with Angelman syndrome and Prader-Willi syndrome exhibit mild to moderate hypopigmentation [12]. Decreased pigmentation is most common in those patients with Angelman syndrome or Prader-Willi syndrome caused by a deletion [12]. Hemizygosity for the *P* gene within the Angelman syndrome/Prader-Willi syndrome critical region correlates significantly with the presence of hypopigmentation [12]. However, heterozygous carriers of *P* gene mutations alone do not have hypopigmentation. Hypotheses to explain this inconsistency include reduced expression of the intact *P* gene via an interaction with the larger 15q deletion, resulting in reduced pigmentation, or else another undiscovered gene exists in that region that, in haploinsufficiency, is not adequate to create normal pigment [12].

Although hypopigmentation, the primary feature of oculocutaneous albinism type 2, occurs in up to 50% of patients with Angelman syndrome or Prader-Willi syndrome, the severe speech impairment, seizure activity, gait and movement disorder, and characteristic behavioral manifestations of Angelman syndrome, or the psychomotor retardation, infantile hypotonicity, hyperphagia, obesity, and hypogonadism of Prader-Willi syndrome, should not be present in an individual with isolated oculocutaneous albinism type 2. In young infants with albinism who may not yet manifest the entire constellation of Angelman

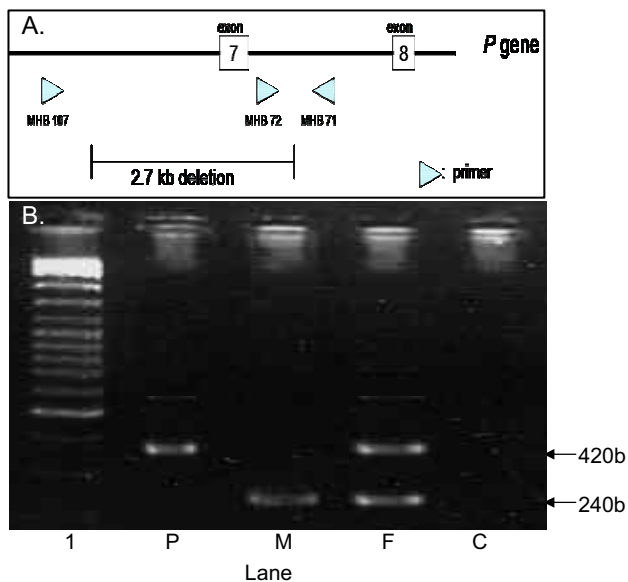


Figure 2. (A) Detection by polymerase chain reaction of deletion. Primers MHB 71, 72, and 107 were used in the polymerase chain reaction assays to amplify genomic DNA. Unaffected individuals have no deletion. Thus, a 240-bp fragment between MHB 71 and MHB 72 is amplified. The fragment for MHB 107 to MHB 71 is too large to amplify using our polymerase chain reaction conditions. Deletion of the 2.7-kb region of the *P* gene eliminates the primer sequence of MHB 72, resulting in amplification of a 420-bp fragment between MHB 71 and MHB 107. (B) Molecular analysis of the 2.7-kb deletion of the *P* gene revealed that the affected child (P) carries only the deleted allele (420-bp fragment), the mother (M) carries only the normal allele (240-bp fragment), and the father (F) carries one deleted allele and one normal allele. Lane 1 is the size marker; lane C is a negative control.

syndrome or Prader-Willi syndrome features, neurodevelopmental delay may be the first clue to this compound diagnosis. Thus, the present case demonstrates the necessity to investigate for concurrent Angelman syndrome and Prader-Willi syndrome in a patient with developmental delay and albinism.

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