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Alopecia and Hypotrichosis as Characteristic Findings in Woodhouse-Sakati Syndrome: Report of a Family with Mutation in the *C2orf37* Gene

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Abstract: **Woodhouse-Sakati syndrome (WSS) is a rare autosomal recessive disorder characterized by alopecia, hypogonadism, diabetes mellitus, intellectual disability, sensorineural deafness, extrapyramidal signs, and low insulinlike growth factor 1 levels. Inter- and intrafamilial phenotypic variability have been reported. Mutations in the *C2orf37* gene cause WSS. The present report describes the clinical signs and symptoms of three affected siblings from a consanguineous Bedouin family from Kuwait. Direct sequencing of the *C2orf37* gene revealed that the c.436delC (p.Ala147Hisfs*9) mutation was present in a homozygous state in all affected siblings and in a heterozygous state in the parents and a healthy sister. Nine *C2orf37* mutations causing WSS have been identified. This family shared the mutation reported earlier in Saudi families and families of Bedouin tribes from Qatar and Israel. No phenotypic or genotypic correlation has been observed. Despite the great phenotypic variability of WSS, hypotrichosis has been observed in all individuals with WSS reported. This condition has not been reported in the dermatologic literature. WSS should be included in the differential diagnosis of syndromic congenital hypotrichosis.**

Woodhouse-Sakati syndrome (WSS; Mendelian Inheritance in Man 241080) is a rare, autosomal recessive, neuroendocrine ectodermal disorder characterized by alopecia, hypogonadism, diabetes mellitus, intellectual disability, sensorineural deafness, and extrapyramidal signs. WSS was first described in 1983 (1). Approximately 30 families with fewer than 75 affected patients have subsequently

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been reported (2–15). Most of these families are of Middle Eastern origin (2–10), and the majority are from Saudi Arabia. Cases have also been observed in northern and eastern Europe (11,12), Turkey (13), India (14), and Pakistan (15). The gene responsible for WSS is *C2orf37*, which maps to chromosome 2q22.3-q35 (7). All reported Saudi families have been found to carry the same mutation (c.436delC), highlighting a founder effect (7,8), although *C2orf37* mutations other than c.436delC have been reported in families from other countries (7,8,11,15).

Individuals with WSS present with a wide range of inter- and intrafamilial phenotypic variability (5,8,10). Most patients present with intellectual impairment and delayed puberty. Alopecia or hypotrichosis is observed in all patients and ranges from the complete absence of scalp hair, eyebrows, and eyelashes in some to the presence of sparse, fine, and short hair in most. No scarring and no structural hair abnormalities have been reported (1–14). Diabetes mellitus and extrapyramidal signs may develop during the second or third decade (5,8,10). Facial dysmorphism and abnormalities of the cardiovascular and musculoskeletal systems, eyes, teeth, and thyroid have been reported in a small number of cases (1,3–6,11,14,15).

Although congenital alopecia is a cardinal sign of WSS, the disorder has not been reported in the dermatologic literature, with most published reports in genetic journals. We now describe WSS in three siblings from a consanguineous Bedouin family from Kuwait who were referred for evaluation of congenital hypotrichosis.

CASE REPORTS

The affected siblings are three of 10 children born to consanguineous parents (Fig. 1A). Patient 1 is a 19-year-old man (Fig. 1A [IV:4] and 1B). He was delivered at full-term with a birthweight of 4 kg. Sparse hair was present at birth that subsequently

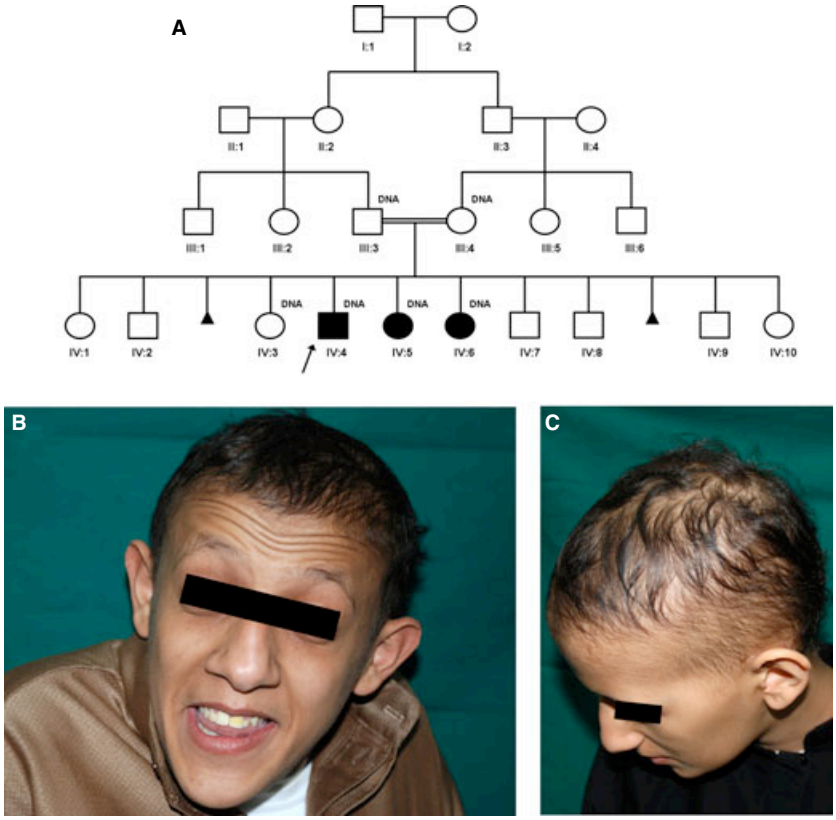

Figure 1. Pedigree structure and clinical pictures of individuals with Woodhouse-Sakati syndrome. (**A**) Family pedigree of a four-generation Bedouin family originating from Kuwait. A double line depicts the consanguineous marriage. Affected family members are shown in black; circles and squares denote females and males, respectively. The index patient is marked by an arrow. The triangular symbols indicate miscarriages. (**B**) The index patient (IV:4) is a 19-year-old man with a triangular-shaped face, prominent forehead, large ears, dystonia, and hypotrichosis. His hair does not grow beyond a length of 4 to 5 cm. (**C**) Patient 2 (IV:5) is a 15-year-old girl with a triangular-shaped face with large, low-set ears. Her scalp hair is sparse and short, and hypotrichosis has been reported since birth. Her eyebrows and eyelashes are sparse as well.

failed to grow beyond a length of 4 to 5 cm. His early development was normal. At the age of 10 years, focal choreoathetoid and dystonic movements were noted. Progressive gait abnormalities, dysarthria, and intellectual disability then developed. Before presenting to dermatology he had consulted a pediatrician, endocrinologist, and neurologist. His height and weight (at age 17 years) were assessed to be below the 5th percentile. Although his Tanner puberty stage rating for the genitalia was IV, no facial, axillary, or pubic hair was present. Neurologic assessment revealed moderate intellectual impairment, choreoathetoid movements, and difficulty walking. He was diagnosed with cerebral palsy with extrapyramidal signs and symptoms, delayed puberty, growth retardation, and hypothyroidism, but the diagnosis of WSS was not considered. On physical examination he was noted to have a triangular-shaped face, a prominent forehead, a flat occiput, large ears, and mild hypotrichosis of the scalp hair that followed a frontotemporal distribution. Ophthalmologic examination revealed an uncorrected visual acuity of 6/60 in both eyes. Laboratory investigations revealed low insulinlike growth factor 1 (IGF-1) (19 μM, normal range 36–73 μM), high thyroid-stimulating hormone (57.97 mIU/L, normal range 0.27–4.20 mIU/L), and low free thyroxine (5.57 pM, normal range 12–21 pM). Radiological examination of the spine showed mild scoliosis. The results of all other investigations, including serum testosterone, adrenocorticotrophic hormone, luteinizing hormone, follicle-stimulating hormone, prolactin, fasting blood sugar, glucose tolerance test, serum biochemistry, complete blood count, antithyroid antibodies, electromyogram, and magnetic resonance imaging (MRI) of his head, were normal. Chromosomal analysis revealed a normal male karyotype (46,XY).

Patients 2 and 3 first presented to dermatologists with primary complaint of frontotemporal hypotrichosis noticed since birth. Patient 2 was a 15-year-old girl (Fig. 1A [IV:5] and 1C). Like her brother, she had sparse hair at birth that subsequently failed to grow beyond a length of 4 to 5 cm. Her early development was reported as having been normal except for being a "slow learner" in school. By age 15 years she had not reached menarche. Her height and weight were below the 5th percentile and she had an intelligence quotient of 69. She had a triangular-shaped face with large, low-set ears; sparse, short scalp hair; and sparse eyebrows and eyelashes. She was referred to a pediatric endocrinologist. Laboratory investigations revealed very low IGF-1 (5.8 nM, normal range 36–73 μM), high follicle-stimulating hormone (73 IU/L, normal range 4.7–21.5 IU/L), high thyroid-stimulating hormone (13.54 mIU/L), low free thyroxine (7.53 pM), high antithyroglobulin (1,243 IU/mL, normal range 75–250 IU/mL), high antithyroid peroxidase (231 U/mL, normal <35 U/mL), and low vitamin D3 (10 nM, normal range 75–250 nM). MRI of the pelvis revealed a hypoplastic uterus and the absence of both ovaries. MRI of the pituitary glands showed a small pituitary gland (3 mm) with upward concavity. Ophthalmologic examination revealed uncorrected visual acuity of 6/60 and a myopic fundus in both eyes. The results of all other investigations, including fasting blood sugar, glucose tolerance test, serum luteinizing hormone, prolactin, testosterone, adrenocorticotrophic hormone, growth hormone, complete blood count, serum biochemistry, serum ferritin, serum insulin, and a skeletal survey, were within the normal ranges. Chromosomal analysis revealed a normal female karyotype (46,XX).

WSS was suspected in the three siblings on the basis of hypotrichosis and the other clinical symptoms, in particular the hypogonadism, intellectual disability, low IGF-1 levels, and the extrapyramidal symptoms. The findings in the third sibling were similar and are presented in Table S1.

MOLECULAR GENETIC ANALYSIS

Blood samples were obtained from the three affected siblings, their parents (Fig. 1A [III:3 and III:4]), and one healthy sister (Fig. 1A [IV:3]) after the provision of written informed consent. DNA was extracted from peripheral leukocytes according to standard procedures. For the index patient (Fig. 1A [IV:4]), all coding exons of the *C2orf37* gene were amplified using polymerase chain reaction (PCR). The PCR products were purified and directly sequenced (BigDye Terminator v1.1 Cycle Sequencing Kit; Applied Biosystems, Darmstadt, Germany) on a genetic analyzer (ABI 3100; Applied Biosystems). The Ethics Committee of the Medical Faculty of the University of Bonn approved the study.

Sequencing analysis revealed the homozygous mutation c.436delC (p.Ala147Hisfs*9) in exon 4 of the *C2orf37* gene in the index patient. Further analyses revealed that this 1 bp deletion was also present in a homozygous state in the two affected siblings and in a heterozygous state in the parents and the healthy sister (Fig. 1A). No other family members were available for molecular genetic studies.

DISCUSSION

Although well characterized in the genetic literature, to our knowledge WSS has not been reported previously in a dermatology specialty journal. Scalp alopecia or hypotrichosis has been observed in all individuals with WSS reported (1–15). The hair loss may be noticed soon after birth or in early childhood (5,11) and dermatologists may thus be the first physicians that affected patients consult. Steindl et al (11) have proposed that the presence of alopecia in individuals with WSS may be an indicator of a diagnosis of WSS if it shows a frontotemporal distribution and occurs with some of the aforementioned additional symptoms. Alopecia in WSS is usually partial, frontotemporal, and associated with the presence of normal to sparse eyebrows and eyelashes (5). Scalp hair is short and sparse and fails to grow to a normal length. In general, the most severe hair loss has been reported in older patients (1). In males, facial hair is usually absent, whereas in males and females, axillary and pubic hair is scant or completely lacking (3,5). No definite structural hair abnormalities have been described except longitudinal grooving in some hair (3) and pili annulati (13) in one report each.

After the identification of *C2orf37* mutations as the cause of WSS (7), Alazami et al studied the mutation spectrum of WSS in 15 families (7,8). Nine mutations for WSS have been identified (Table 1). Despite the great phenotypic variability of WSS, no phenotypic–genotypic correlation has been demonstrated.

Little is known about *C2orf37* and the pathogenesis of this multisystem disorder. High *C2orf37* expression was observed in the brain, liver, and skin of a mouse model, and low *C2orf37* expression was found in all examined human adult tissues (7). It was also shown that the nucleoli of the lymphoblasts of individuals with WSS had enhanced sensitivity to transcriptional blockade (7), thus defective ribosome biogenesis and other nucleolar processes may be implicated in the pathogenic mechanisms in WSS (7), although this hypothesis needs further experimental support.

The cases reported herein emphasize that hypotrichosis or scalp alopecia of variable severity has been observed in all reported individuals with WSS. As such, WSS should be included in the differential diagnosis of congenital hypotrichosis or alopecia. The presence of frontotemporal hair loss in association with other systemic signs and symptoms, particularly delayed puberty, hypogonadism, extrapyramidal signs, and low IGF-1 levels, are important clues to the diagnosis of WSS.

TABLE 1. *C2orf37* Mutations Reported in Individuals with WSS

Mutation	Ethnicity	References*
c.436delC (frameshift)	Saudi, Bedouin (from Qatar, Israel, and Kuwait)	(7,9,10, present report)
c.50delC (frameshift)	East European (Slovenia)	(7)
c.1422+5G>T (splice site)	Indian	(7)
c.1091+6T>G (splice site)	Middle Eastern	(7)
c.127-3delTAGinsAA (splice site)	Turkish	(8)
c.341C>A (nonsense)	Italian	(8)
c.387G>A (nonsense)	French Gypsy	(8)
c.906G>A (nonsense)	Italian	(8,11)
c.321+1G>A (splice site)	Pakistani	(15)

*References 1–6 and 12–14 do not contain any reported mutations because the causative gene was not known at the time of publication.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article:

Table S1. Comparison of the salient clinical features of the present WSS patients with those from earlier reports.

REFERENCES

1. Woodhouse NJ, Sakati NA. A syndrome of hypogonadism, alopecia, diabetes mellitus, mental retardation, deafness and ECG abnormalities. J Med Genet 1983;20:216–219.
2. Al-Awadi SA, Farag TI, Teebi AS et al. Primary hypogonadism and partial alopecia in three sibs with Müllerian hypoplasia in the affected females. Am J Med Genet 1985;22:619–622.
3. Mégarbané A, Gannagé-Yared MH, Khalifé AA et al. Primary hypergonadotrophic hypogonadism, partial alopecia, and Mullerian hypoplasia: report of a second family with additional findings. Am J Med Genet 2003;119:214–217.
4. Al-Swailem SA, Al-Assiri AA, Al-Torbak AA. Woodhouse-Sakati syndrome associated with bilateral keratoconus. Br J Ophthalmol 2006;90:116–117.

5. Al-Semari A, Bohlega S. Autosomal recessive syndrome with alopecia, hypogonadism, progressive extrapyramidal disorder, white matter disease, sensorineural deafness, diabetes mellitus, and low IGF1. Am J Med Genet A 2007;143:149–160.
6. Schneider SA, Bhatia KP. Dystonia in the Woodhouse Sakati syndrome: a new family and literature review. Mov Disord 2008;23:592–596.
7. Alazami AM, Al-Saif A, Al-Semari A et al. Mutations in C2orf37, encoding a nucleolar protein, cause hypogonadism, alopecia, diabetes mellitus, mental retardation and extrapyramidal syndrome. Am J Hum Genet 2008;83:684–691.
8. Alazami AM, Schneider SA, Bonneau D et al. C2orf37 mutational spectrum in Woodhouse-Sakati syndrome patients. Clin Genet 2010;78:585–590.
9. Rachmiel M, Bistritzer T, Hershkoviz E et al. Woodhouse-Sakati syndrome in an Israeli-Arab family presenting with youth-onset diabetes mellitus and delayed puberty. Horm Res Paediatr 2011;75:362–366.
10. Ben-Omran T, Ali R, Almureikhi M et al. Phenotypic heterogeneity in Woodhouse-Sakati syndrome: two new families with a mutation in the C2orf37 gene. Am J Med Genet A 2011;155:2647–2653.
11. Steindl K, Alazami AM, Bhatia KP et al. A novel C2orf37 mutation causes the first Italian cases of Woodhouse Sakati syndrome. Clin Genet 2010;78:594–597.
12. Medica I, Sepeić J, Peterlin B. Woodhouse-Sakati syndrome: case report and symptoms review. Genet Couns 2007;18:227–231.
13. Gül D, Ozata M, Mergen H et al. Woodhouse and Sakati syndrome (MIM 241080): report of a new patient. Clin Dysmorphol 2000;9:123–125.
14. Koshy G, Danda S, Thomas N et al. Three siblings with Woodhouse Sakati syndrome in an Indian family. Clin Dysmorphol 2008;17:57–60.
15. Habib R, Basit S, Khan S et al. A novel splice site mutation in gene C2orf37 underlying Woodhouse-Sakati syndrome (WSS) in a consanguineous family of Pakistan. Gene 2011;490:26–31.