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Woodhouse-Sakati Syndrome

Synonym: Hypogonadism, Alopecia, Diabetes Mellitus, Intellectual Disability, and Extrapyramidal Syndrome

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Summary

Clinical characteristics

Virtually all individuals with Woodhouse-Sakati syndrome (WSS) have the endocrine findings of hypogonadism (evident at puberty) and progressive childhood-onset hair thinning that often progresses to alopecia totalis in adulthood. More than half of individuals have the neurologic findings of progressive extrapyramidal movements (dystonic spasms with dystonic posturing with dysarthria and dysphagia), moderate bilateral postlingual sensorineural hearing loss, and mild intellectual disability. To date, more than 40 families (including 33 with a molecularly confirmed diagnosis) with a total of 88 affected individuals have been reported in the literature.

Diagnosis/testing

The diagnosis of WSS is established in a proband with suggestive clinical, neuroimaging, and neurophysiologic findings by identification of biallelic pathogenic variants in *DCAF17* on molecular genetic testing.

Management

Treatment of manifestations: Treatment is symptomatic and should be managed by a multidisciplinary team. Hypogonadism requires hormone replacement therapy to induce secondary sex characteristics and promote bone health at the usual age of puberty. Alopecia is treated symptomatically for cosmetic reasons only. Treatment for dystonia is routine; oral medications are tried first and followed in some instances by botulinum toxin injection and/or deep-brain stimulation. Dysarthria often benefits from consultation with a speech therapist. Those with dysphagia often require measures to reduce oral secretions, use of thickened liquids and pureed foods to avoid aspiration, and eventually a gastrostomy to help maintain caloric intake. Standard treatment for diabetes mellitus, hypothyroidism, hearing loss, and intellectual disability.

Surveillance: Monitoring for endocrine abnormalities is recommended at the following ages: hypogonadism beginning at age 12-14 years; diabetes mellitus and hypothyroidism beginning at age 20 years; serum IGF-1

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every three to five years following diagnosis; annual neurologic assessment for dystonia; speech and language assessment for dysarthria and dysphagia as needed; annual developmental assessment throughout childhood; annual audiology evaluation.

Agents/circumstances to avoid: Persons with dystonia should avoid situations in which the risk of falling is increased.

Evaluation of relatives at risk: Molecular genetic testing for the *DCAF17* pathogenic variants identified in the proband is appropriate for evaluation of apparently asymptomatic older and younger sibs to identify as early as possible those who would benefit from early identification and treatment of potential complications.

Genetic counseling

WSS is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Once the pathogenic *DCAF17* variants have been identified in an affected family member, carrier testing for at-risk relatives, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing are possible.

Diagnosis

No consensus clinical diagnostic criteria for Woodhouse-Sakati syndrome (WSS) have been published.

Suggestive Findings

WSS **should be suspected** in individuals with any combination of the following clinical, family history, neuroimaging, and neurophysiology findings.

Endocrine

- Hypogonadism (100% of individuals), hypogonadotropic in males and hypergonadotropic in females
  - Primary amenorrhea in females
  - Lack of development of secondary sexual characteristics in males and females
- Low insulin-like growth factor 1 (IGF-1) (100%)
- Adolescent- to young adult-onset diabetes mellitus (66%)
- Hypothyroidism (30%)

Alopecia. Hair loss beginning in childhood or adolescence, resulting in partial-to-complete loss of scalp hair and eyelashes (100%) (Figure 1A, 1H)

Neurologic

- Adolescent to young-adult onset of extrapyramidal findings including focal (later generalized) dystonia (65%), chorea, dysarthria, and dysphagia
- Sensorineural hearing loss (SNHL) with onset in childhood (62%)
- Intellectual disability (58%)

Family history is consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis.

Supportive Findings

Neuroimaging findings on brain MRI

- Partially empty sella and a small pituitary gland (Figure 2A) [Abusrair et al 2018]

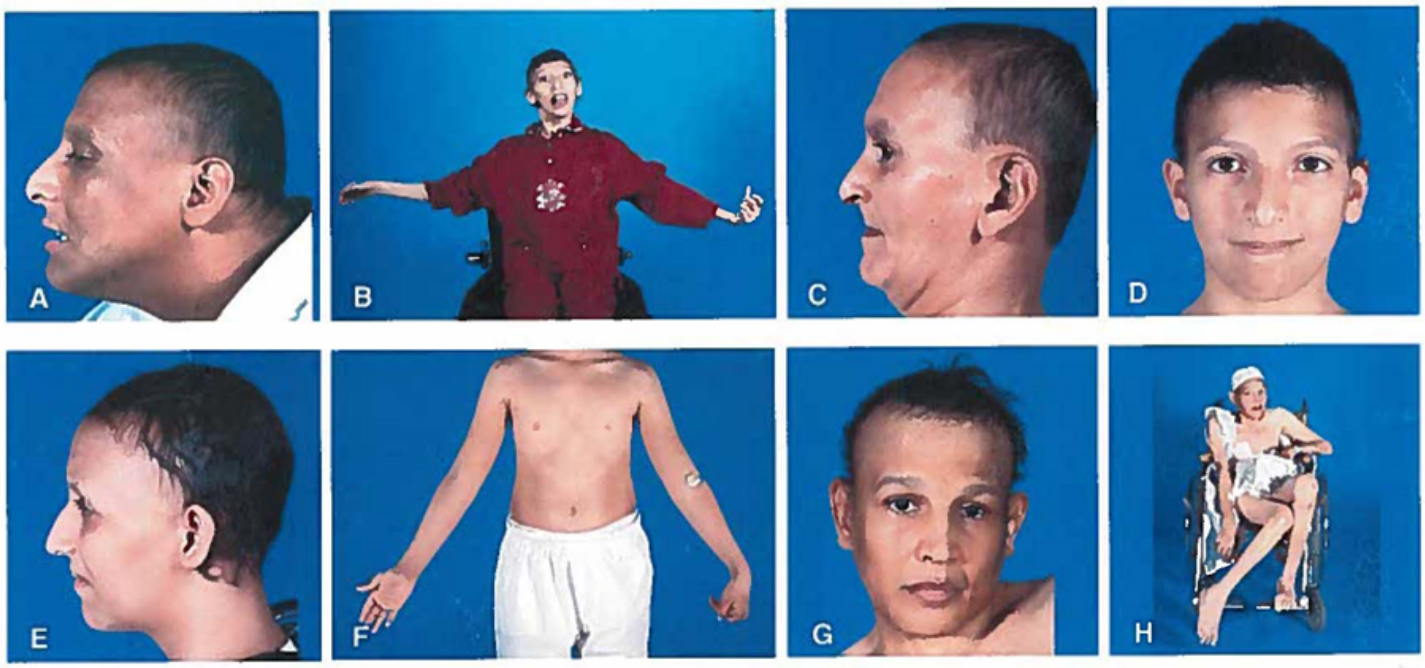

Figure 1. Affected individuals from different families with WSS who have variable degrees of alopecia or hair loss and neurologic involvement

A. Male age 23 with flat occiput; temporal and frontal alopecia

B. Female age 19 with dystonia involving neck, face, mouth, and tongue, arms, and hands

C. Female age 35 with sparse, short hair, flat occiput, low-set ears, and retrocollis

D. Male age 14 with sparse hair

E. Female age 25 with alopecia and wasting of the facial and temporal muscles

F. Male age 17 with dystonic posturing and lack of breast tissue

G. Male age 21 with sparse hair with temporal hair loss; long face

H. Male age 32 with severe generalized dystonia with alopecia totalis

- Progressive frontoparietal/periventricular white matter lesions (Figure 2B, 2C) [Abusrair et al 2018, Lehéricy et al 2020]
- Iron deposition in the globus pallidus (Figure 2D), and to a lesser extent, in the substantia nigra and red nucleus [Abusrair et al 2018, Lee et al 2020]
- Rarely, prominent perivascular spaces and diffusion restriction involving the splenium of the corpus callosum (Figure 2E, 2F) [Abusrair et al 2018]

Neurophysiology findings on evoked-potential (EP) analysis [Abusrair et al 2020]

- Prolonged P100 latencies on pattern reversal visual EPs
- Prolonged cortical N19 response on median somatosensory EPs
- Absent or prolonged P37 cortical response on tibial somatosensory EPs

Establishing the Diagnosis

The diagnosis of WSS **is established** in a proband with suggestive clinical, neuroimaging, and neurophysiologic findings by identification of biallelic pathogenic variants in *DCAF17* on molecular genetic testing (see Table 1).

Molecular testing approaches can include **gene-targeted testing** (single-gene testing or multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

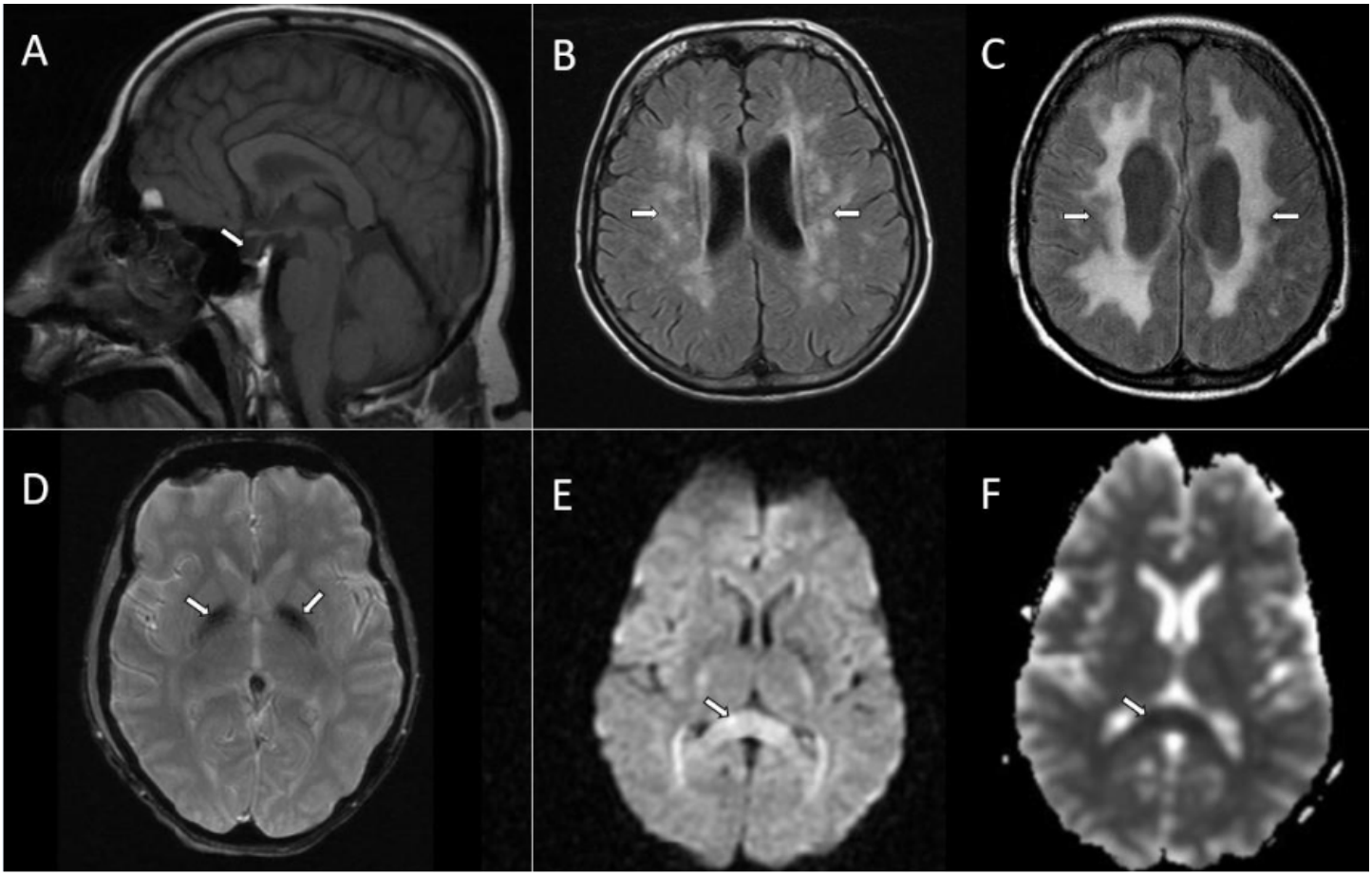

Figure 2. Brain MRI of individuals with WSS. Arrows indicate the following findings:

A. Sagittal T_1-weighted image, showing small pituitary gland and partially empty sella.

B-C. Fluid-attenuated inversion recovery (FLAIR) demonstrating variable degrees of white matter signal intensities at different stages of the disease.

D. T_2*-weighted MRI showing iron deposition in the globus pallidus.

E-F. Diffusion-weighted imaging (DWI) showing diffusion restriction involving the splenium of the corpus callosum.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of WSS has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

Single-gene testing. Sequence analysis of *DCAF17* identifies biallelic pathogenic variants in all individuals with typical findings of WSS. *DCAF17* exon and whole-gene deletion/duplication variants have not been reported. However, gene-targeted deletion/duplication analysis may be useful to confirm homozygosity of a pathogenic variant detected by sequence analysis when parental DNA is not available (see Molecular Genetics).

Note: Targeted analysis for individuals who are Saudi Arabian or Qatari may be performed first. To date, all affected individuals in these populations have been homozygous for the same founder pathogenic variant, c.436delC [Alazami et al 2008, Ben-Omran et al 2011].

A multigene panel that includes *DCAF17* and other genes of interest (see Differential Diagnosis) may also be considered. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Woodhouse-Sakati Syndrome

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
DCAF17	Sequence analysis [3]	100%
	Gene-targeted deletion/duplication analysis [4]	None reported

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

Clinical Characteristics

Clinical Description

Woodhouse-Sakati syndrome (WSS) is characterized by the endocrine findings of hypogonadism, diabetes mellitus, and hypothyroidism and progressive childhood-onset alopecia along with neurologic findings of progressive extrapyramidal movements, sensorineural hearing loss, and intellectual disability. To date, 88 individuals from more than 40 families have been reported [Steindl et al 2010, Nanda et al 2014, Abdulla et al 2015, Bohlega et al 2019].

Two clinical types of WSS have been described [Bohlega et al 2019] with variable prognosis. However, intrafamilial variability is common and both types can occur within a family:

- **Type 1.** Severe and progressive neurologic disability at a younger age (range 9-17 years) causing significant impairment of the quality of life and activities of daily living. Manifestations include severe intellectual disability and dystonia.
- **Type 2.** Absent or mild neurologic involvements that do not affect activities of daily living

Endocrine

Hypogonadism, present in all affected individuals, manifests as delayed puberty with lack of secondary sexual characteristics. The nature of hypogonadism has been difficult to characterize as both hypergonadotropic and hypogonadotropic hypogonadism have been described [Agopiantz et al 2014]; in about 30% of affected individuals the hormonal profile does not neatly fit either group. Sense of smell is normal.

Women typically have primary amenorrhea. Detailed endocrine investigation in more than 50 of the women described in the literature typically revealed severely reduced or absent estradiol and high FSH and LH, consistent with hypergonadotropic hypogonadism. There appears to be decreased hypothalamic-pituitary responsiveness, as the FSH and LH are not as high as expected for the degree of ovarian failure [Woodhouse & Sakati 1983, Rachmiel et al 2011, Agopiantz et al 2014].

The ovaries are streak or underdeveloped, and not visualized by laparotomy, laparoscopy, or autopsy [Al-Semari & Bohlega 2007, Ben-Omran et al 2011, Rachmiel et al 2011]. Ovarian biopsy showed fibrous tissue with no identifiable oocysts [Woodhouse & Sakati 1983, Agopiantz et al 2014].

Men have moderately low testosterone and – in contrast to women – inappropriately low gonadotropins, consistent with hypogonadotropic hypogonadism, which may be of central or central and peripheral etiology. Semen analysis may show azoospermia [Agopiantz et al 2014, Ali et al 2016]. One male had cryptorchidism [Rachmiel et al 2011].

Although the testes are of normal size, testicular biopsy reveals reduced spermatogenesis with predominance of Sertoli cells and few Leydig cells [Agopiantz et al 2014].

Low insulin-like growth factor 1 (IGF-1) is present in all individuals [Ali et al 2016]. Reduction of IGF-1 is more pronounced in females [Al-Semari & Bohlega 2007, Ben-Omran et al 2011]. The low IGF-1 levels may reflect low sex steroids resulting from hypogonadism.

The growth pattern is normal and growth hormone levels are usually normal; short stature is not a part of this syndrome [Agopiantz et al 2014].

Diabetes mellitus. Type 2 diabetes (either insulin dependent or non-insulin dependent) was reported in 66% of all individuals and 96% of those older than age 25 years [Al-Semari & Bohlega 2007, Agopiantz et al 2014].

Hypothyroidism of peripheral origin (primary but without evidence of autoimmunity) was found in 30% of individuals, typically around age 20 years [Al-Semari & Bohlega 2007].

Other. No abnormalities of the corticotropic axis or prolactin [Al-Semari & Bohlega 2007, Agopiantz et al 2014] have been reported.

Ectodermal

Alopecia. All affected individuals have predominantly frontotemporal alopecia with sparse, thin scalp hair. Hair loss begins in childhood and often progresses to alopecia totalis in the third or fourth decade or earlier. Eyelashes and eyebrows are absent or sparse. In men, facial hair is absent or underdeveloped.

Scanning electron microscopy of the hair shows longitudinal grooves with no specific abnormalities [Al-Semari & Bohlega 2007].

Facial skin is often wrinkled in advanced stages, conferring a progeroid appearance [Woodhouse & Sakati 1983, Al-Semari & Bohlega 2007, Agopiantz et al 2014].

Anodontia. Total loss of teeth is rare; when it occurs, it is usually seen at a later stage [Al-Semari & Bohlega 2007, Agopiantz et al 2014].

Nails appear to be normal.

Neurologic

Extrapyramidal abnormal movement was seen in more than 56% of reported individuals. In particular, dystonic spasms with dystonic posturing were seen in the majority, including segmental dystonia affecting the craniocervical region, oromandibular region, or one extremity. Often, the first neurologic manifestation is abnormal posturing movements that typically start insidiously in childhood or the early teens. Dysarthria (often with a high-pitched voice) and dysphagia are common.

In a majority of individuals, dystonia becomes generalized and disabling (Figure 1B, 1F, 1H). Progressive dystonia of the trunk may lead to severe dystonic scoliosis. As the dystonia progresses, gait difficulties ultimately lead to immobility.

Inter- and intrafamilial variability is common [Al-Semari & Bohlega 2007, Ben-Omran et al 2011, Ali et al 2016 , Bohlega et al 2019]. For example, families with the founder *DCAF17* pathogenic variant (c.436delC) can have dystonia [Al-Semari & Bohlega 2007] or not [Bohlega et al 2019]. Of note, although extrapyramidal features were not mentioned in the original report of Woodhouse and Sakati [1983], it was found that up to 65% of affected individuals develop variable degrees of dystonia at some point in the disease course (Figure 1H) [Bohlega et al 2019].

Sensorineural hearing loss (SNHL). Moderate bilateral SNHL was noted in 62% of reports. When present, deafness is invariably postlingual, usually starting in adolescence [Ben-Omran et al 2011].

Intellectual disability is described in 58% of individuals. It is typically mild and usually overshadowed by accompanying severe and disabling dystonia, dysarthria, and SNHL. The authors have observed ten individuals who were able to complete a college education and hold permanent manual occupations [Author, personal observation].

Other. Seizures with onset in early childhood, tremors, and mild Parkinsonism features have rarely been reported [Al-Semari & Bohlega 2007, Schneider & Bhatia 2008, Bohlega et al 2019].

Polyneuropathy with stocking glove sensory loss and diminished deep tendon reflexes but normal strength has been reported [Schneider & Bhatia 2008].

Other Findings

Dysmorphic facial features include a long triangular face, prominent nasal bridge, widely spaced eyes, and sparse eyebrows, creating a characteristic facial appearance (Figure 1D, 1E, 1G).

Bilateral keratoconus was reported in four individuals [Al-Swailem et al 2006, Schneider & Bhatia 2008, Ben-Omran et al 2011].

Electrocardiographic (EKG) abnormalities (lengthening of the ST segments and T-wave flattening) were described in the original report [Woodhouse & Sakati 1983] but rarely reported subsequently [Koshy et al 2008, Schneider & Bhatia 2008]. Of note, these EKG abnormalities were asymptomatic and individuals with WSS have no major cardiac manifestations.

Genotype-Phenotype Correlations

There is no clear genotype-phenotype correlation. Even individuals with the same Saudi Arabian founder *DCAF17* pathogenic variant (c.436delC) have displayed marked phenotypic variability.

Prevalence

To date, more than 40 families with an estimated 88 affected individuals have been reported. Of these, 51 individuals from 33 families have had the diagnosis confirmed molecularly.

The carrier frequency of the Saudi Arabian founder variant (c.436delC) is 0.00243309 [Abouelhoda et al 2016].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *DCAF17*.

Differential Diagnosis

Table 2. Disorders/Phenotypes to Consider in the Differential Diagnosis of Woodhouse-Sakati Syndrome

Gene(s) / Genetic Mechanism	Disorder	MOI	Endocrine Findings	Alopecia	Neurologic Findings & MRI	Other
ANOS1 *CHD7* *FGFR1* *GNRHR* *IL17RD* *PROKR2* *SOX10* *TACR3* [1]	Isolated GnRH deficiency	XL AD AR	Idiopathic hypogonadotropic hypogonadism	–	Ataxia, epilepsy, & congenital paresis of cranial nerves III, IV, VI In IGD: typically, normal-appearing hypothalamus & pituitary on MRI. In KS: typically, aplasia or hypoplasia of the olfactory bulbs/sulci/tracts.	± Congenital olfactory deficit (KS)
ATP13A2 C19orf12 *COASY* CP FA2H FTL PANK2 PLA2G6 WDR45	Neurodegeneration w/ brain iron storage disorders	AR XL AD [2]			Dystonia w/postural instability; brain iron accumulation on MRI	Variable phenotype & variable age of onset
CLPP *ERAL1* *HARS2* *HSD17B4* *LARS2* *TWNK*	Perrault syndrome	AR			Early SNHL, learning difficulties, DD, cerebellar ataxia, motor & sensory peripheral neuropathy	Heterogeneous & variable; premature ovarian failure
ERCC6 *ERCC8*	Cockayne syndrome type III	AR		–		Short stature & appearance of premature aging

Table 2. continued from previous page.

Gene(s) / Genetic Mechanism	Disorder	MOI	Endocrine Findings	Alopecia	Neurologic Findings & MRI	Other
LMNA	Hutchinson-Gilford progeria syndrome	AD [3]	Affected persons do not become sexually mature. Insulin resistance w/o overt development of diabetes mellitus in ~50%	+	Normal motor & mental development	Aged-looking skin, joint abnormalities, & loss of subcutaneous fat; conductive hearing loss
RBM28	Alopecia, neuropathy, endocrinopathy syndrome (OMIM 612079) [4]	AR	Hypogonadotropic hypogonadism & adrenal insufficiency	+	Cognitive impairment	
RNF216 *PNPLA6* [5]	Gordon Holmes syndrome (OMIM 212840)	AR	Hypogonadotropic hypogonadism	–	Cerebellar ataxia & (to a variable degree) brisk reflexes; white matter lesions	
TIMM8A delXp22.1 [6]	Deafness-dystonia-optic neuronopathy syndrome	XL		–	Early-onset SNHL; movement disorder; dementia (onset age ~40 yrs); psychiatric symptoms may appear in childhood & progress.	Impaired vision & behavior problems; occurs almost exclusively in males.

– = not associated with this disorder; + = associated with this disorder; AD = autosomal dominant; AR = autosomal recessive; DD = developmental delay; GnRH gonadotropin-releasing hormone; IGD = isolated gonadotropin-releasing hormone deficiency; KS = Kallmann syndrome; MOI = mode of inheritance; SNHL = sensorineural hearing loss; XL = X-linked

1. Listed genes represent the most common genetic causes; see Isolated Gonadotropin-Releasing Hormone (GnRH) Deficiency for other, less commonly involved genes.

2. Eight of the ten genetically defined types of neurodegeneration with brain iron accumulation are inherited in an autosomal recessive manner. Exceptions are: beta-propeller protein-associated neurodegeneration, caused by *de novo* pathogenic variants in *WDR45*, which is inherited in an X-linked manner with suspected male lethality; and neuroferritinopathy, caused by pathogenic variants in *FTL*, which is inherited in an autosomal dominant manner.

3. Almost all individuals with Hutchinson-Gilford progeria syndrome have the disorder as the result of a *de novo* autosomal dominant pathogenic variant.

4. Only one family reported to date according to OMIM

5. See *PNPLA6*-Related Disorders.

6. The diagnosis of deafness-dystonia-optic neuronopathy is established in either a male proband who has a hemizygous *TIMM8A* pathogenic variant or a female proband who has a heterozygous *TIMM8A* pathogenic variant or a contiguous gene deletion of Xp22.1 involving *TIMM8A*.

Other disorders to consider in the differential diagnosis of Woodhouse-Sakati syndrome (WSS):

- **Hereditary dystonia.** Hereditary dystonia is associated with extensive clinical and genetic heterogeneity (see Hereditary Dystonia Overview). Unlike WSS, hypogonadism and alopecia are not known to be features associated with hereditary dystonia.
- **Hereditary hearing loss and deafness.** Nonsyndromic hereditary hearing loss is characterized by extreme genetic heterogeneity: to date, more than 6,000 causative variants have been identified in more than 110 genes. Syndromic hearing impairment is known to be associated with more than 400 genetic syndromes. (See Hereditary Hearing Loss and Deafness Overview.)

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Woodhouse-Sakati syndrome (WSS), the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with Woodhouse-Sakati Syndrome

System/Concern	Evaluation	Comment
Endocrine	• Ask about menstrual cycle (women) or sexual dysfunction (men) to screen for hypogonadism. • Serum IGF-1 • Fasting glucose level, hemoglobin A1c, or oral glucose tolerance test • Thyroid function studies incl TSH & free T4	To evaluate for endocrine findings: hypogonadism, low IGF-1, diabetes mellitus, hypothyroidism
Ectodermal	Assessment of scalp hair	
Neurologic	Neurologic exam for evidence of dystonia (See Dystonia Overview.)	
	Speech & language assessment of dysarthria & dysphagia	
	Assessment of hearing (See Hereditary Hearing Loss and Deafness.)	
	Assessment of psychomotor development	In young children
	Assessment of intellectual ability	In persons age >6 yrs
Genetic counseling	By genetics professionals [1]	To inform patients & their families re nature, MOI, & implications of WSS in order to facilitate medical & personal decision making

MOI = mode of inheritance

1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

No specific treatment exists for WSS. Treatment is aimed at relieving symptoms [Albanese et al 2015].

Table 4. Treatment of Manifestations in Individuals with Woodhouse-Sakati Syndrome

Manifestation/ Concern	Treatment	Considerations/Other
Hypogonadism	Sex hormone replacement therapy at usual age of puberty to induce & maintain secondary sex characteristics & promote bone health.	Standard replacement hormonal treatment will not promote fertility. It may be possible to stimulate testes w/gonadotropins & harvest sperm w/assisted reproductive technology.
Low IGF-1	Treatment w/recombinant IGF-1 is not recommended: no evidence that it improves clinical features of WSS [Agopiantz et al 2014].	IGF-1 levels may ↑ w/sex hormone replacement therapy.
Diabetes mellitus	Standard treatment	
Hypothyroidism	L-thyroxine replacement therapy	
Sparse hair	Treatment is symptomatic & cosmetic only.	

Table 4. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Dystonia	**Oral medications** are usually tried first: • Anticholinergics (e.g., trihexyphenidyl) are moderately effective in 40%-50%. • Baclofen (Lioresal®) • Benzodiazepines, especially clonazepam • Other medications tried alone or in combination w/the above: levodopa, carbamazepine, & dopamine depleting agents (reserpine, tetrabenazine) **Botulinum toxin** injections directly into dystonic muscles are generally the treatment of choice for adult-onset focal dystonias. For those w/more widespread dystonia in whom specific muscle groups produce disabling symptoms, such injections may also be helpful & are often used in combination w/oral medications.	• Trihexyphenidyl can be titrated to high doses (~100 mg/day) in younger persons. • Anticholinergic side effects, esp cognitive effects, must be monitored closely. • If medications fail, surgery to enable deep-brain stimulation of the globus pallidus interna has been an effective treatment for some forms of medically refractory primary generalized dystonia [Crowell & Shah 2016]. Its use in WSS has not been documented.
Dysarthria	Consultation w/a speech therapist may be helpful.	
Dysphagia	• Oral secretions in those w/bulbar symptoms can be ↓ w/ tricylic antidepressants & anticholinergic agents, thus reducing need for suctioning. • Swallowing difficulties can be alleviated by thickening liquids & pureeing solid food, & eventually using a gastrostomy tube to help maintain caloric intake & hydration. • Nutritional mgmt by a knowledgeable nutritionist is helpful.	
Sensorineural hearing loss	See Hereditary Hearing Loss and Deafness for mgmt.	
Intellectual disability	Educational support services as needed	

Surveillance

Table 5. Recommended Surveillance for Individuals with Woodhouse-Sakati Syndrome

System/Concern	Evaluation	Frequency
Endocrine	Ask about menstrual cycle (women) or sexual dysfunction (men) to screen for hypogonadism.	Beginning at age 12-14 yrs
	Screening for type 2 diabetes mellitus by standard clinical assays incl fasting glucose level, hemoglobin A1c, or oral glucose tolerance test	Annually beginning at age 20 yrs
	Thyroid function studies to incl TSH & free T4	
	Serum IGF-1	Every 3-5 yrs
Neurologic	Assessment for dystonia	Annually
	Speech & language assessment for dysarthria & dysphagia	As needed
	Developmental assessment	Annually throughout childhood
	Audiology eval	Annually

Agents/Circumstances to Avoid

Persons with dystonia should avoid situations in which the risk of falling is increased.

Evaluation of Relatives at Risk

Molecular genetic testing for known familial *DCAF17* pathogenic variants is appropriate for the evaluation of apparently asymptomatic older and younger sibs of a proband in order to identify as early as possible those who will benefit from early identification and treatment of potential complications.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Woodhouse-Sakati syndrome (WSS) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected individual are obligate heterozygotes (i.e., presumed to be carriers of one *DCAF17* pathogenic variant based on family history).
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a *DCAF17* pathogenic variant and to allow reliable recurrence risk assessment. If a pathogenic variant is detected in only one parent, the following possibilities should be considered:
  - One of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017].
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for a *DCAF17* pathogenic variant, each sib of an affected individual has at conception a 25% chance of inheriting biallelic *DCAF17* pathogenic variants and being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- The neurologic phenotype in a sib who inherits biallelic pathogenic variants cannot be predicted based on the phenotype in the proband; an affected sib may have a neurologic phenotype ranging from normal to severe regardless of the neurologic features observed in the proband [Bohlega et al 2019].
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. Unless an individual with WSS has children with an affected individual or a carrier, his/her offspring will be obligate heterozygotes (carriers) for a pathogenic variant in *DCAF17*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *DCAF17* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *DCAF17* pathogenic variants in the family.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

Prenatal Testing and Preimplantation Genetic Testing

Once the *DCAF17* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for WSS are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **NBIA Disorders Association**
  www.nbiadisorders.org
- **Dystonia Medical Research Foundation**
  Phone: 312-755-0198; 800-377-DYST (3978)
  Email: dystonia@dystonia-foundation.org
  dystonia-foundation.org
- **Dystonia UK**
  United Kingdom
  Email: info@dystonia.org.uk
  dystonia.org.uk
- **NBIAcure**
  Center of Excellence for NBIA Clinical Care and Research
  International Registry for NBIA and Related Disorders
  Oregon Health & Science University

Email: info@nbiacure.org
www.nbiacure.org

- **Treat Iron-Related Childhood Onset Neurodegeneration (TIRCON)**
  Germany
  Email: TIRCON@med.uni-muenchen.de
  www.TIRCON.eu

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Woodhouse-Sakati Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
DCAF17	2q31.1	DDB1- and CUL4-associated factor 17	DCAF17 database	DCAF17	DCAF17

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Woodhouse-Sakati Syndrome (View All in OMIM)

241080	WOODHOUSE-SAKATI SYNDROME; WDSKS
612515	DDB1- AND CUL4-ASSOCIATED FACTOR 17; DCAF17

Molecular Pathogenesis

Alternate splicing of *DCAF17* results in multiple transcripts of variable length. The longest transcript, NM_025000.4, has 14 exons. In comparison another major transcript, NM_001164821.1, lacks two exons in the coding region for a total of 12 exons. Transcript NM_025000.4 encodes DDB1- and CUL4-associated factor 17, a 520 amino-acid protein known as the α isoform (NP_079276.2). This is a nucleolar protein of unknown function expressed in various tissues including brain, skin, and liver – which correlates to some extent with the multiorgan involvement in individuals with Woodhouse-Sakati syndrome (WSS).

Reported *DCAF17* pathogenic variants include small intragenic deletions, nonsense and splice site variants, and small indels [Alazami et al 2010, Habib et al 2011, Abdulla et al 2015, Ali et al 2016]. Pathogenic *DCAF17* missense variants have not been described.

Of the 33 families with molecularly confirmed WSS, biallelic compound heterozygous *DCAF17* pathogenic variants has been reported in only one [Ali et al 2016]. The remaining families were homozygous for *DCAF17* pathogenic variants. Gene-targeted deletion/duplication analysis may be useful to confirm apparent homozygosity of a pathogenic variant detected by sequence analysis when parental DNA samples are not available.

Mechanism of disease causation. The types of pathogenic variants known to result in WSS predict premature translation termination, missplicing, or nonsense-mediated decay, suggesting that WSS results from loss of DCAF17 function.

Table 6. Notable *DCAF17* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_025000.4 NP_079276.2	c.436delC [1]	p.Ala147HisfsTer9	Founder variant in Saudi Arabian & Qatari populations [Alazami et al 2008, Ben-Omran et al 2011]

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. This variant has the same nucleotide and protein change designations for either transcript variant NM_025000.4 or NM_001164821.1.

Chapter Notes

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