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Phenotypic Variability of c.436delC *DCAF17* Gene Mutation in Woodhouse-Sakati Syndrome

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Case series
Patients: 38, female • 28, female • 41, female • 18, female • 23, male
Final Diagnosis: Woodhouse-Sakati syndrome
Symptoms: Hypogonadism • dystonia • alopecia • hearing loss • diabetes
Medication: —
Clinical Procedure: —
Specialty: Endocrinology and Metabolic

Objective: Rare disease

Background: Woodhouse-Sakati syndrome (WSS) is a rare autosomal recessive genetic condition that was first described in 1983. Since its original description, approximately 50 cases have been reported with various clinical signs and symptoms. Characteristics include progressive neurologic deterioration with extrapyramidal involvement and polyendocrinopathy most notable for hypogonadism starting in early adolescence. Clinical presentation is variable, and a subset of patients may have additional features, such as premature aging, alopecia, distinctive facial features, cognitive impairment, or deafness.

Case Report: We illustrate the phenotypic variability of 5 patients with WSS due to the previously reported homozygous single nucleotide deletion c.436delC in the *DCAF17* gene, identified in 2008. Despite identical genetic alteration, our 5 patients had various clinical features among them and compared with previously reported cases with the same pathogenic mutation.

Conclusions: The phenotypic variability of WSS due to c.436delC founder mutation may have a wider range than previously recognized.

MeSH Keywords: Alopecia • Dystonic Disorders • Hypogonadism • Leukoencephalopathies

Abbreviations: **DM** – diabetes mellitus; **ECG** – electrocardiography; **MRI** – magnetic resonance imaging; **WSS** – Woodhouse-Sakati syndrome

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Background

Woodhouse-Sakati syndrome (WSS) is a rare, multisystem genetic condition with autosomal recessive inheritance. The neurologic and endocrine systems are most commonly affected. Neurologic symptoms and signs involve progressive cognitive decline, extrapyramidal symptoms (i.e., dysarthria, dystonia, chorea, and gait abnormality), sensorineural hearing loss, and magnetic resonance imaging (MRI) abnormalities consistent with leukoencephalopathy. Endocrine symptoms are characterized by diabetes mellitus (DM), primary hypogonadism (i.e., testicular or ovarian failure, and rudimentary internal genitalia), and hypothyroidism. Other signs include alopecia, premature aging, hypodontia, distinctive facial features (e.g., elongated triangular face, prominent ears, prominent nasal root), electrocardiography (ECG) changes (nonspecific T-wave abnormalities), and laboratory abnormalities (i.e., increased follicle-stimulating hormone and decreased serum insulin-like growth factor 1, estradiol, and testosterone). This syndrome is caused by homozygous or compound heterozygous mutations in the *DCAF17* gene that encodes a nucleolar protein with poorly understood function. The pathogenic mechanism underlying WSS is not known, but hypothetically, the syndrome may result from defective ribosome biogenesis or other nucleolar dysfunction affecting cell cycle regulation or cellular aging [1]. Many of the reported cases originate from the Middle East and may result from a common ancestral mutation.

Herein, we describe 5 patients from the Middle East with a diagnosis of WSS due to a common founder mutation. To determine the spectrum of clinical features associated with this pathogenic variant, we characterize and compare their clinical manifestations with patients reported previously with the same mutation.

DNA analysis showed a homozygous single nucleotide deletion (c.436delC) in exon 4 of the *DCAF17* gene of all 5 patients. This frameshift pathogenic variant results in protein truncation and was originally reported in a Saudi-origin family by Alazami et al. [2].

Case Report

We performed a retrospective chart review searching for patients with a diagnosis of WSS due to c.436delC mutation and who were evaluated in the Department of Clinical Genomics at Mayo Clinic's campus in Rochester, Minnesota, USA, within the past 10 years. Five patients from 3 families were identified and their clinical features characterized. Their clinical data are summarized in Table 1.

Patient 1 (Family 1)

Our first patient was a 38-year-old woman from Kuwait who was referred for evaluation of alopecia, amenorrhea, absent secondary sexual characteristics, dystonia, and gait difficulty. The patient was born to parents in a consanguineous union and of an uncomplicated pregnancy. She had normal development until 12 years of age, when progressive alopecia was first noted, and dystonia developed, described as an upward eye-rolling on attempting to talk. She was noted to have amenorrhea and absence of secondary sexual characteristics from 12 years of age forward. A previous pelvic MRI showed a hypoplastic uterus.

The patient's condition progressed, and she had oral dystonia, which resulted in dysphagia and difficulty with speech, as well as upper extremity dystonia. Dystonia then affected her gait, which progressively deteriorated, and by age 32 years, she required assistance to ambulate. She had no cognitive dysfunction. A hearing screening showed bilateral sensorineural hearing loss. The parents of this patient were first cousins. Of 7 siblings, 2 younger sisters and 1 younger brother had similar symptoms of progressive gait difficulty, dystonia, hearing loss, alopecia, and hypogonadism.

Physical examination was notable for alopecia, sparse eyebrows, retrognathia, and Tanner stage 1 breast tissue development. Neurologic examination showed strained and dysphonic speech. The patient's muscle strength appeared to be mildly affected, with greater distal weakness than proximally in all 4 limbs. Her deep tendon reflexes were hypoactive with bilateral ankle areflexia and flexor plantar responses. Proprioception was absent at the toes, with preserved sensation to light and deep touch. The finger-to-nose test showed no evidence of dysmetria. Alternate motion rate in the upper extremities was severely impaired. She could not stand unassisted, had gait instability, and had a mild degree of gait freezing with shortened stride.

Increased follicle-stimulating hormone and low-normal estradiol levels were suggestive of primary ovarian failure. A brain MRI showed bilateral symmetrical confluent white matter T2 hyperintensities (Figure 1A, 1B) and susceptibility signal in the bilateral globus pallidi and substantia nigra pars reticulata suggestive of iron accumulation (Figure 1C, 1D).

Patient 2 (Family 1)

The second patient was the 28-year-old younger sister of Patient 1. She first realized cognitive and gait decline around age 18 years. She had dystonia of all 4 extremities, and her main report was stiffness all over her body. At evaluation, she was wheelchair dependent. The patient had mixed

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Table 1. Clinical characteristics of patients with Woodhouse-Sakati syndrome and the c.436delC mutation.

Characteristic	Patient No.					Location, No. (%)	
	1	2	3	4	5	Mayo Clinic	Outside Medical Centera
Age, years	38	28	41	18	23		
Sex	F	F	F	F	M		F 5 and M 6
Endocrine							
Alopecia	+	+	+	+	+	5/5 (100)	11/11 (100)
Hypogonadism	+	+	+	+	+	5/5 (100)	11/11 (100)
Hypoplastic uterus	+	+	+	+	N/A	4/4 (100)	5/5 (100)
Diabetes mellitus	+	+	+	+	+	5/5 (100)	5/11 (45)
Hypothyroidism	–	+	+	+		3/5 (60)	0/5 (0)
Neurologic							
ID	–	+	+	–	–	2/5 (40)	11/11 (100)
Extrapyramidal involvement	+	+	+	+	+	5/5 (100)	1/11 (9)
Dysarthria	+	+	+	–	+	4/5 (80)	1/11 (9)
Dysphagia	+	–	+	–	+	3/5 (60)	0/7 (0)
Upper extremity dystonia	+	+	+	+	–	4/5 (80)	0/11 (0)
Gait (lower extremity dystonia)	+	+	+	–	–	3/5 (60)	1/11 (9)
MRI abnormalities consistent with leukoencephalopathy	+	+	+	–	–	3/5 (60)	1/3 (33)
Sensorineural hearing loss	+	+	+	–	–	3/5 (60)	4/10 (40)
Pyramidal	–	N/A	–	–	–	0/4 (0)	0/7 (0)
Cerebellar	–	N/A	–	–	–	0/4 (0)	0/7 (0)
Cardiovascular							
ECG abnormality	+	N/A	+	+	+	4/4 (100)	0/4 (0)
Hyperlipidemia	+	+	+	–	–	3/5 (60)	4/5 (80)
Dysmorphism, long face	+	–	+	–	–	2/3 (67)	11/11 (100)
Adontia	N/A	N/A	+	–	–	1/3 (33)	
Premature aging	N/A	N/A	+	–	–	1/3 (33)	
Other	N/A	ESRD, bilateral cataracts	Seizures	N/A	N/A		
Age of onset, y	12	18	12	9	9	Range, 9–18	Range, 6–16
Presenting symptom	Alopecia dystonia	ID, gait	Alopecia	Alopecia	Alopecia		

ECG – electrocardiography; ESRD – end-stage renal disease; F – female; ID – intellectual disability; M – male; MRI – magnetic resonance imaging; N/A – not applicable.

hyperkinetic-hypokinetic dysarthria with particular difficulty when initiating speaking; in addition, she had hearing loss and alopecia. Other pertinent diagnoses included DM, hypothyroidism, and hyperlipidemia. Absent ovaries and uterus were reported. On general examination, secondary sexual characteristics were lacking, and she had considerable alopecia. Neurologic examination also showed moderate difficulty with comprehension; she was able to follow only 1-step instructions. An MRI of the brain showed white matter T2 signal change that appeared to have progressed over 8 years based on imaging performed at an outside facility.

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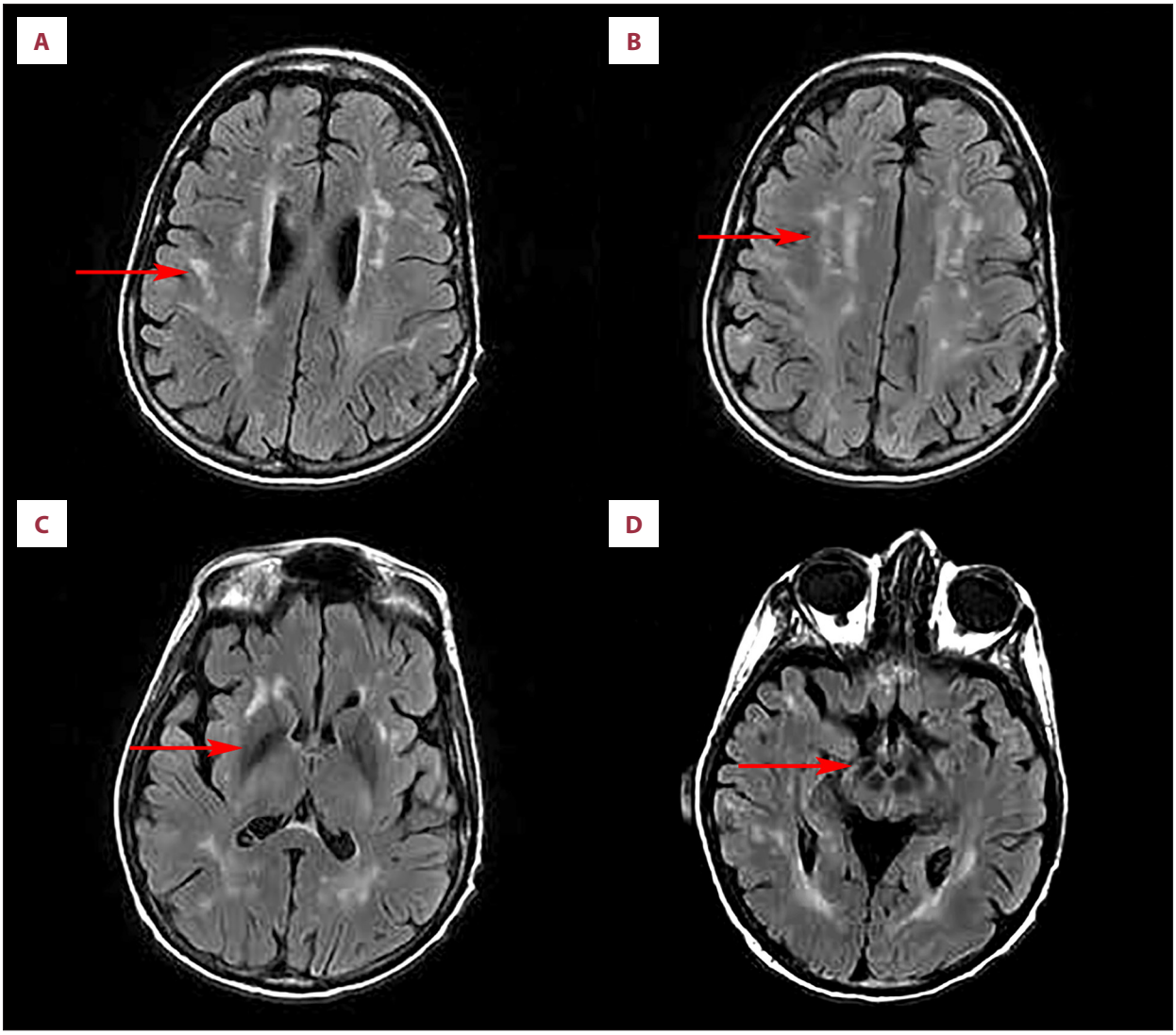

Figure 1. Magnetic resonance imaging axial T2 fluid attenuated inversion recovery. (**A, B**) Innumerable areas of T2 hyperintensity in the subcortical and deep white matter of both cerebral hemispheres. (**C, D**) Susceptibility signal in the bilateral globus pallidi and substantia nigra pars reticulata, suggestive of iron accumulation.

Patient 3 (Family 2)

Our third patient was a 41-year-old woman from Qatar who presented with a history of alopecia, intellectual disability, hearing loss, hypoplastic uterus, hypothyroidism, hyperlipidemia, and DM that resulted in end-stage renal disease. She also had T-wave abnormalities on ECG.

The patient had normal early childhood development but subsequently had cognitive decline. During pubertal age, she had primary amenorrhea and no development of secondary sexual characteristics. She started losing her hair at age 14 years. The patient then received a diagnosis of hypothyroidism. At age 36, hearing loss and DM type 2 developed. She then had progressive gait deterioration and became wheelchair dependent at 37 years of age. At about the same age, epilepsy developed.

A brain MRI showed diffuse bilateral white matter signal abnormalities and cerebral atrophy. An ophthalmologic evaluation showed bilateral cataracts. The patient's family history was clinically significant for consanguinity. She had 9 siblings, of whom 3 were similarly affected: Two younger brothers and 1 sister were described to have learning delays, DM, and hearing loss. On physical examination, the patient had a general appearance of slight premature aging, adontia, alopecia, and sparse eyebrows. She had distinctive facial features, including a triangular face, prominent nasal root, and prominent ears. Her speech was mildly dysarthric. Her mental capacity could not be fully ascertained because of a language barrier.

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Deep tendon reflexes were hypoactive, and no evidence was convincing of pyramidal tract involvement. Continuous movements of her mouth were thought to represent a part of an extrapyramidal syndrome. She was able to stand unassisted but to walk only with assistance because her gait was unsteady.

Patient 4 (Family 3)

The fourth patient was an 18-year-old woman from Bahrain who was referred for evaluation of multiple endocrine problems and dystonia. She had noted hair loss when she was 9 years old. At age 12, she received a diagnosis of hypothyroidism and DM. She did not have spontaneous menstruation or secondary female characteristics because of primary ovarian failure. Pelvic ultrasonography showed a normal sized uterus, but the ovaries lacked ovarian follicles. Despite hormone replacement therapy, breast development stayed at Tanner stage 1, and at age 16 years, she had focal hand dystonia (so-called writer's cramp). MRI of the brain showed a small pituitary gland but no other abnormalities. Family history was clinically significant for consanguinity and a similarly affected her older brother. Neurologic examination showed normal gait, normoactive deep tendon reflexes, and no evidence of cerebellar or pyramidal signs.

Patient 5 (Family 3)

Our final patient was a 23-year-old man, the brother of Patient 4. Thinning of hair started at age 9 years. His development was normal until puberty, when he received a diagnosis of hypogonadotropic hypogonadism with associated azoospermia and sparse facial hair. The patient had a diagnosis of DM at age 16 and hypothyroidism at age 17. Also at age 16 years, extrapyramidal syndrome developed, which resulted in hypophonia, dysarthria, and difficulty with tongue movements when chewing. The patient had normal cognition and normal gait. A brain MRI showed a small pituitary gland and a hypoplastic optic chiasm. Physical examination was notable for hypertelorism, downslanting palpebral fissures, periorbital edema, mild gynecomastia, and small testicular size.

Discussion

The *DCAF17* gene was first identified as the underlying cause of WSS in 2008 [3]. Since this discovery, 16 confirmed cases have been reported to result from a homozygous c.436delC mutation, including our 5 patients. However, this number is likely higher given that 26 additional Saudi patients with a diagnosis of WSS have yet to be molecularly characterized [4,5]. Alazami et al. [2] first found this pathogenic variant in members from 7 Saudi Arabian families, indicating it is a founder mutation in this population. Before the identification of the causative gene, Al-Semari and Bohlega [6] described 26 patients from Saudi Arabia. Therefore, the 26 affected persons described in the original publication may also carry the same homozygous nucleotide deletion. Approximately 60 patients with WSS are described in the literature. The fact that more than one-half of the reported cases are due to this founder mutation underlies the importance of determining whether genotype-phenotype correlations exist, to improve family counseling and better define health surveillance guidelines.

DCAF17 has 2 main transcripts with undetermined function in the human cell cycle and both localizing to the nucleolus. Both transcripts are ubiquitously expressed in adult human tissues, and therefore the predilection to neurologic, endocrine, and ectodermal involvement in WSS is not clear. The c.436delC mutation affects only 1 isoform, but other mutations were predicted to affect both isoforms [2]. Several loss-of-function mutations have been depicted, including a splice site resulting in reduced splicing efficiency, nucleotide deletions, and substitutions resulting in protein truncation. Nevertheless, the pathogenic mechanism underlying the clinical variability associated with different mutations has not been explored extensively.

WSS is a phenotypically distinct genetic syndrome with some degree of phenotypic variability of a subset of multisystemic characteristics. It may be defined as a progressive neuroendocrine disorder accompanied by alopecia. The distinct endocrine abnormality is hypogonadism, characterized by testicular or ovarian failure resulting in underdevelopment of secondary sexual characteristics at puberty. Dystonia is a distinguishing neurologic symptom leading to dysarthria, gait abnormality, and in some patients, dysphagia. Most patients have progressive intellectual decline.

We analyzed clinical characteristics of our 5 cases, the other 11 cases with the same homozygous single nucleotide deletion in the *DCAF17* gene (c.436delC), and the cases described by Ali et al. [3]. We compared them with all other WSS cases of different mutations, in an attempt to determine whether this mutation is associated with specific phenotypic correlations (Tables 1, 2).

All patients had normal early childhood development and most commonly presented with alopecia at about 10 years of age, followed by evident signs of hypogonadism during puberty. All patients had DM, nonspecific T-wave abnormalities on ECG, and an extrapyramidal syndrome, but the presence of hypothyroidism, sensorineural hearing loss, intellectual disability, and hyperlipidemia was variable.

Dystonia was present in our 5 patients but in contrast was found in a sole patient of the other 11 patients with the c.436delC mutation. This contrast was not explained by a

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Table 2. Comparison of clinical characteristics of the 16 patients who have Woodhouse-Sakati syndrome and the c.436delC mutation with patients with a different mutation.

Characteristic	Patients with mutation c.436delC, %	Patients with different mutation, No. (%)
Endocrine		
Alopecia	100	35/35 (100)
Hypogonadism	97	35/35 (100)
Hypoplastic uterus	84	7/9 (78)
Diabetes mellitus	61	17/22 (77)
Hypothyroidism	38	2/14 (14)
Neurologic		
ID	84	20/22 (91)
Extrapyramidal	51	7/11 (64)
MRI leukoencephalopathy	49	N/A
SNHL	65	19/24 (79)
Pyramidal/cerebellar	0	N/A
Cardiovascular		
ECG abnormalities	50	9/11 (82)
Hyperlipidemia	70	N/A

ECG – electrocardiography; ID – intellectual disability; MRI – magnetic resonance imaging; N/A – not applicable; SNHL – sensorineural hearing loss.

difference in severity according to age of onset (range, 9–18 years in our cohort *vs.* 6–16 years in 7 of the 11 other patients with a known age at presentation). Our patient population was slightly older: Mean age at presentation was 30 years (range 18–41 years) compared with 17 years (range 8–23 years) in the other founder mutation cases. Therefore, dystonia may develop later in the disease course, which is consistent with the observation of dystonia as a presenting feature in only 1 of our patients. Ali et al. [3] reported dystonia in two-thirds of their Saudi patient population, similar to the frequency of dystonia (64%) in patients with other mutations. Therefore, this particular mutation may not be associated with greater frequency of extrapyramidal symptoms.

An important observation is that dystonia most commonly affected the oral region initially, leading to dysarthria and, less often, to difficulty chewing or swallowing. Dystonia then progressed in a descending manner to involve the upper extremities and eventually affected the gait. As a result, 2 patients became wheelchair dependent in their 30s. The frequent occurrence of extrapyramidal symptoms corresponds to frequent signal abnormalities observed in the basal ganglia and substantia nigra on brain MRI (Figure 1C, 1D).

Intellectual disability was seen in most patients with this mutation, with a combined frequency of 84%, similar to the frequency (87%) previously described by Ali et al. [3]. However, compared with affected persons with other mutations (91%), intellectual disability was slightly more common in the other cases reported between 1973 and 2011 [2,7–16].

Similar to previously reported WSS cases, none of our patients had clinical evidence of pyramidal tract involvement. The MRI signal abnormalities were typically confined to the supratentorial white matter but spared the cerebellum. Hence, one may conclude that pyramidal or cerebellar tracts of the nervous system are not characteristically affected early in the disease course of WSS. Leukoencephalopathy was observed in approximately one-half of the patients with the founder mutation but was not uniformly described in other patient cohorts. Therefore, the presence of white matter signal abnormality on brain MRI is not required for diagnosis of WSS. However, this diagnosis should be considered among patients with leukoencephalopathy who also have hypogonadism and early-onset hair loss.

Of note, hypothyroidism was twice as common in our cohort (38%) as in other reported patients (14%), but the number of patients with reported thyroid function cascade (14%) was small. Based on these

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observations, we recommend performing a thyroid function screening for patients with the founder mutation and to consider thyroid function assessments for all patients with WSS. DM was less common in our cohort (51%) than for other patients (77%). This deletion/mutation may be more commonly associated with hypothyroidism and less commonly with DM than other pathogenic variants.

ECG changes, primarily consisting of nonspecific T-wave abnormalities, were half as frequently associated with this mutation (45% *vs.* 82% with other mutations) and were not associated with clinical symptoms; they were of uncertain clinical significance. None of the patients with WSS was known to have cardiac arrhythmia or cardiomyopathy. However, longitudinal data were not available to determine whether they had a risk of cardiac complications with disease progression. It may be prudent to monitor cardiac function with a clinical examination and ECG and address cardiac symptoms at each patient visit. Moreover, cardiovascular health may be affected by the occurrence of hyperlipidemia in more than two-thirds of patients with the founder mutation. A lipid screening was performed at an earlier age (mean age, 30 years) for our patients than recommended for the general population. Based on this observation, we recommend lipid screening and, if needed, treatment of hyperlipidemia to be conducted when the diagnosis of WSS is made and then monitored periodically thereafter.

Conclusions

WSS continues to be a rare genetic syndrome characterized by multisystem involvement and distinct clinical features, including adolescent onset of neuroendocrine abnormalities and alopecia, which are present in most cases. Dystonia is a distinct neurologic feature and seems to progress in a descending manner affecting speech, swallowing, or chewing early. It can lead to disability when it affects ambulation. Disability also may result from intellectual deterioration or complications of DM. Two patients with WSS and the Saudi Arabia founder mutation were reported to have nephropathy attributed to DM. Screening renal function regularly and including testing for proteinuria may facilitate both an understanding of the mechanism of nephropathy [5] and add to current data (Table 1).

Variability of clinical characteristics was observed mainly in intellectual function, hearing loss, hyperlipidemia, hypothyroidism, and brain MRI and ECG abnormalities. The Saudi Arabia founder mutation c.436delC was frequently associated with hyperlipidemia and hypothyroidism but less commonly with DM, deafness, or intellectual disability compared with patients who had other mutations.

The pathophysiologic factors of WSS have yet to be understood, and the mechanism by which multisystem involvement is possible has yet to be explained. Variability of clinical presentations may in part be explained by genotype-phenotype correlations. As other mutations are phenotypically characterized, our understanding of this syndrome may broaden, and the group of described features will likely continue to expand.

Acknowledgments

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Conflict of interest

None.

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