A novel DCAF17 homozygous mutation in a girl with Woodhouse-Sakati syndrome and its role in the endocrine glands

Erdal Kurnaz[1], Ayberk Türkyılmaz[2], Oğuzhan Yaralı[2], Berrin Demir[3], Atilla Çayır[1]

[1]Erzurum Regional Research and Training Hospital, Department of Pediatric Endocrinology Erzurum, Turkey
[2]Erzurum Regional Research and Training Hospital, Department of Medical Genetics, Erzurum, Turkey
[3]Department of Radiology, Palandöken Hospital, Erzurum, Turkey

İntroduction

Woodhouse-Sakati syndrome (WSS) (OMIM#241080) has an autosomal recessive inheritance pattern. Ectodermal system findings, such as alopecia and changes in facial skin, endocrinological problems including hypogonadism, hypothyroidism, diabetes mellitus (DM), and decreased levels of insulin-like growth factor I (IGF-I), neurological disorders such as hearing loss and progressive extrapyramidal involvement, and non-specific T-wave changes at electrocardiography can all be detected. Alopecia and loss of hearing are generally present before puberty. Puberty is delayed in all cases, and primary amenorrhea is typically present in girls, while delayed development of secondary sexual characteristics is seen on physical examination in both genders. Hypothyroidism and diabetes mellitus may be added to the manifestation after puberty, and neurological disorders in later decades.

The nature of hypogonadism in WSS is often difficult to characterize since both hypergonadotropic and hypogonadotropic hypogonadism (hh) occur. However, hypergonadotropic hypogonadism (Hh) is generally determined in girls, while male patients have moderate testosterone depression and inappropriately low gonadotropins, compatibly with hh . The role of the pituitary gland in the etiogenesis of hypogonadism is unclear, since some WSS patients present with Hh, while normal levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) may be determined in others.

C2orf37 mutations were reported to be responsible for WSS in 2008. This gene was subsequently renamed *DCAF17*. Recent research has shown that the *DCAF17* gene is involved in gonad development and functions in both sexes.

In our case, whole exome sequencing (WES) analysis revealed a novel homozygous variant c.1091+1G>A in the *DCAF17* gene in a patient presenting with primary amenorrhea and with Hh-type hypogonadism. This case is discussed together with a review of previously reported cases and of the characteristics of WSS.

Case Report

A 16-year-old girl presented with absence of breast development and amenorrhea. Third-degree consanguinity was present between the parents. The patient had six sisters and was the youngest member of the family. Delayed menstruation or secondary sexual characteristics were not present in other family members. On physical examination, the weight was 55 kg (-0.38 SDS), the height 169.5 cm (1.14 SDS) and arterial blood pressure 100/70 mm Hg. Breast and pubic development were both Tanner stage 1, and no axillary hair development was observed. No other significant dysmorphic finding was present.

Complete blood count and biochemical parameters were normal at time of diagnosis. Thyroid function tests revealed TSH: 11 µIU/ml (0.35-4.94), sT4: 0.72 ng/dl (0.7-1.48), Anti-TPO: <0.18 U/ ml (<5.61), anti-TG antibody: <0.6 U/ml (<4.11). Other biochemical results were serum FSH: 79.4 mIU/mL (1.8-11.2), LH: 19.4 mIU/mL (2-9), estrogen 2: <10 pg/mL (30-100), cortisol: 14 µg/dL (1.34-2.65 µg/dL); and adrenocorticotropic hormone: 22.4 pg/mL (0–46). Suprapubic ultrasonography (USG) showed that the uterus was 25x10x10 mm in size, and that the ovaries could not be clearly visualized. The patient was started on low-dose sex steroid replacement (1/4 tablet Estrofem®) and L-thyroxine therapy. At the follow-up, the Estrofem® dose was increased to one tablet.

Alopecia in the bilateral frontotemporal regions and sparse eyebrows were observed at physical examination at the final visit, two years after the initial examination. A long, triangular facial appearance was also observed. Thyroid functions were euthyroid with L-thyroxine therapy, with IGF1: 118 ng/ml (<-2 SDS). Fasting blood sugar was 92 mg/dl and Hba1c: 5.4%. Serum lipid levels were normal, and hearing test was also normal. Motor and cognitive developments were appropriate for age, but she is currently experiencing learning disabilities. In terms of IQ, her verbal score was 46, performance score 62, and total intelligence score was 51, suggestive of borderline intellectual disability. Under sex steroid replacement, the pubertal stage was Tanner stage 4. Suprapubic USG revealed a uterus size of 51x13 mm, endometrial thickness of 4.7 mm, right ovary size of 12.5x9.7x14 mm, and left ovary size of 16.2x7x15 mm, and four anechoic follicular cysts were reported in both ovaries.

Genetic testing: The patient's karyotype was 46,XX. WES was used to identify the underlying genetic etiology of hypogonadism. Molecular study revealed a novel homozygous splice-site variant (NM_025000.3: c.1091+1G>A) in intron 10 of the *DCAF17* gene. The consanguineous parents were sequenced, and both were heterozygous for the same mutation. A novel homozygous splice-site variant (NM_025000.3: c.1091+1G>A) in intron 10 of the *DCAF17* gene was identified in our patient (Figure 1).

Table 1. Description of the principal symptoms described by parents and causal mutations in all WSS cases.

Reported Year	Family	Patient	Age	Sex	Hypogonadism	Type of hypogonadism	Alopecia	Intellectual deficiency	Dystonia	Deafness	Diabetes	Type of Diabetes	IGF1	Hypothyroidism	Mutation of DCAF17
2007, 2008	I	1	M	41	Yes	Nh	Yes	Yes	Yes	Yes	Yes	NIDDM	Low	No	c.436delC
		2	M	40	Yes	Nh	Yes	Yes	Yes	Yes	Yes	IDDM	Low	No	c.436delC
		3	F	30	Yes	Nh	Yes	No	Yes	-	Yes	IDDM	Low	Yes	c.436delC
		4	F	38	Yes	Hh	Yes	Yes	-	Yes	Yes	NIDDM	NR	No	c.436delC
		5	F	43	Yes	Hh	Yes	Yes	Yes	Yes	Yes	NIDDM	NR	Yes	c.436delC
		6	F	24	Yes	Nh	Yes	Yes	No	-	Yes	NIDDM	Low	No	c.436delC
2007, 2008	II	7	F	52	Yes	Hh	Yes	Yes	Yes	Yes	Yes	Unknown	NR	Yes	c.50delC
2008	III	8	M	36	NR	-	Yes	Yes	Yes	Yes	Yes	NIDDM	NR	No	c.1091+6T>G
		9	F	22	Yes	Hh	Yes	Yes	Yes	Yes	Yes	Unknown	NR	NR	c.1091+6T>G
2008	IV	10	F	20	Yes	Hh	Yes	Yes	No	Yes	Yes	NIDDM	NR	NR	c.1422+5G>T
		11	F	23	Yes	Hh	Yes	Yes	No	Yes	Yes	Unknown	NR	NR	c.1422+5G>T
		12	M	19	Yes	Hh	Yes	Yes	No	Yes	Yes	Unknown	NR	NR	c.1422+5G>T
2010, 2014	V	13	M	36	Yes	Hh	Yes	Yes	Yes	Yes	No		Low	Yes	c.127-3delTAGinsAA
2010	VI	14	F	41	Yes	Unknown	Yes	Yes	No	Yes	Yes	IDDM	NR	NR	c.341C>A
2010	VII	15	M	15	Yes	Hh	Yes	Yes	No	Yes	No		NR	NR	c.387G>A
		16	F	13	Yes	Hh	Yes	No	No	No	No		NR	NR	c.387G>A
		17	F	12	Yes	Hh	Yes	No	No	No	No		NR	NR	c.387G>A
2010	VIII	18	M	58	Yes	Unknown	Yes	Yes	Yes	Yes	Yes	IDDM	NR	NR	c.906 G>A
		19	F	46	Yes	Unknown	Yes	Yes	NR	NR	NR		NR	NR	c.906 G>A
		20	F	47	Yes	Unknown	Yes	Yes	Yes	Yes	Yes	IDDM	NR	NR	c.906 G>A
2011	IX	21	F	16	Yes	Hh	Yes	Yes	No	No	Yes	Unknown	Low	NR	c.436 delC
		22	F	24	Yes	Hh	Yes	Yes	No	No	Yes	Unknown	Low	NR	c.436 delC
		23	M	36	Yes	Hh	Yes	Yes	NR	No	Yes	Unknown	Low	NR	c.436 delC
		24	M	43	Yes	Hh	Yes	Yes	Yes	Yes	Yes	Unknown	Low	NR	c.436 delC
2011	X	25	M	23	Yes	Nh	Yes	Yes	No	Yes	No		Low	No	c.436 delC
		26	F	20	Yes	Nh	Yes	Yes	No	Yes	No		Low	No	c.436 delC
		27	F	17	Yes	Nh	Yes	Yes	No	Yes	No		Low	No	c.436 delC
	XI	28	F	19	Yes	Nh	Yes	Yes	No	Yes	Yes	Unknown	Low	No	c.436 delC
		29	M	17	Yes	Hh	Yes	Yes	No	No	No		Low	No	c.436 delC
		30	M	15	Yes	Hh	Yes	Yes	No	No	No		Low	No	c.436 delC
		31	M	8	Not related	-	Yes	Yes	No	No	No		Low		c.436 delC
2011	XII	32	F	22	Yes	Unknown	Yes	Yes	Yes	Yes	NR		NR	NR	c.321+ 1 G>A
		33	F	16	Yes	Unknown	Yes	Yes	Yes	Yes	NR		NR	NR	c.321+ 1 G>A
		34	M	23	Yes	Hh	Yes	Yes	Yes	Yes	No		Low	NR	c.321+ 1 G>A
		35	M	18	Yes	Hh	Yes	Yes	Yes	Yes	No		Low	NR	c.321+ 1 G>A
		36	F	17	Yes	Unknown	Yes	Yes	No	Yes	NR		NR	NR	c.321+ 1 G>A
		37	M	14	Yes	Unknown	Yes	Yes	No	Yes	NR		NR	NR	c.321+ 1 G>A
2014	XIII	38	F	32	Yes	Hh	Yes	Yes	Yes	Yes	Yes	NIDDM	Low	NR	c.127-3delTAGinsAA
		39	F	27	Yes	Hh	Yes	Yes	Yes	No	Yes	NIDDM	Low	NR	c.127-3delTAGinsAA
2014	XIV	40	M	19	Yes	Nh	Yes	Yes	Yes	NR	No		Low	Yes	c.436delC
		41	F	15	Yes	Hh	Yes	Yes	No	NR	No		Low	Yes	c.436delC
		42	F	NR	NR	Unknown	Yes	Yes	Yes	NR	NR		Low	NR	c.436delC
2015	XV	43	F	40	Yes	Nh	Yes	Yes	No	Yes	Yes	Unknown	NR	NR	c.459- 7_499del, c.1238delA
		44	F	>34	Yes	Unknown	Yes	NR	NR	Yes	Yes	Unknown	NR	NR	c.459- 7_499del, c.1238delA
		45	M	>32	Yes	Unknown	Yes	Yes	NR	Yes	Yes	Unknown	NR	NR	c.459- 7_499del, c.1238delA
2015	XVI	46	M	17.3	Yes	Hh	Yes	Yes	NR	NR	NR		NR	NR	c.436delC
		47	F	19	Yes	Hh	Yes	No	NR	NR	NR		NR	NR	c.436delC
2016	XVII	48	M	50	Yes	Unknown	Yes	No	No	Yes	No		Low	No	c.270delA
		49	F	48	Yes	Unknown	Yes	No	No	Yes	NR		NR	NR	c.270delA
		50	M	14	Yes	Unknown	Yes	No	No	No	No		N	No	c.270delA
		51	F	13	Yes	Hh	Yes	No	No	No	No		NR	No	c.270delA
2016	XVIII	52	F	25	Yes	Hh	Yes	Yes	Yes	No	Yes	Unknown	NR	No	c.436delC
		53	F	30	Yes	Unknown	Yes	Yes	Yes	No	Yes	Unknown	NR	NR	c.436delC
2018	XIX	54	F	38	Yes	Hh	Yes	No	Yes	Yes	Yes	Unknown	NR	No	c.436delC
		55	F	28	Yes	Unknown	Yes	Yes	Yes	Yes	Yes	Unknown	NR	Yes	c.436delC
	XX	56	F	41	Yes	Unknown	Yes	Yes	Yes	Yes	Yes	Unknown	NR	Yes	c.436delC
	XXI	57	F	18	Yes	Unknown	Yes	No	Yes	No	Yes	Unknown	NR	Yes	c.436delC
		58	M	23	Yes	Unknown	Yes	No	No	No	Yes	Unknown	NR	NR	c.436delC
2018	XXII	59	F	12	Yes	Hh	Yes	No	NR	NR	No		Nl	No	c.127-1G>C
		60	F	13	Yes	Hh	Yes	No	NR	NR	No		N	No	c.127-1G>C
	XXIII	61	F	16	Yes	Nh	Yes	Yes	NR	NR	Yes	NIDDM	NR	NR	c.C535T , c.G906A
2018	XXIV	62	M	7	Not related		NR	NR	NR	NR	NR	NR	NR	Yes	c.256T>C, c.1519T>C
2018	XXV	63	M	28	Yes	Hh	NR	NR	NR	NR	NR	NR	NR	NR	c.933_935delGAA
	XXVI	64	M	22	Yes	Hh	NR	NR	NR	NR	NR	NR	NR	NR	c.579C>A
This study	XXVII	65	F	16	Yes	Hh	Yes	Yes	No	No	No	No	Low	Yes	c.1091+1G>A

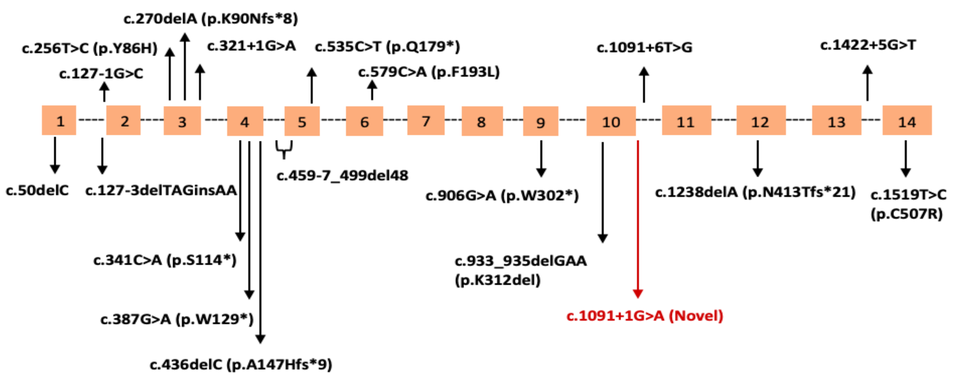

Figure 1. All boxes indicate exons of the *DCAF17* gene. The mutations in bold type were reported in previous studies. The mutation in the present case is novel homozygous c.1091+1G>A in the *DCAF17* gene

CONCLUSİON

An adolescent girl who presented with absence of secondary sex characteristics due to primary gonadal insufficiency and received the diagnosis of WSS after identification of a novel mutation in DCAF17 by a whole-exom sequencing analysis, was reported here. Whole-exom sequencing provided an important benefit for this patient in terms of receiving the definitive diagnosis before the onset of other systemic findings of the syndrome. Since various manifestations of WSS, such as alopecia, endocrine and neurological disorders do not emerge until later in life, it is difficult to make diagnose in pediatric cases. Alopecia can initially be mild and may become more remarkable by age. Similarly, diabetes and extrapyramidal findings usually emerge after adolescence or in early adulthood.

The responsible gene for WSS, DCAF17, was discovered in 2008, and many cases have since been reported in the literature. To the best of our knowledge, 42 cases of WSS were identified prior to 2008 but could not be subjected to genetic analysis . After that date, 64 cases from 26 families underwent genetic analysis . Including our case, hypogonadism was present in 61/65 cases (93.84%) (Table 1). When female patients are classified according to hypogonadism, Hh was reported 19 out of 39 cases, normogonadotropic hypogonadism (Nh) in seven, and hh in one. Hypogonadism was unknown in a further 12 cases. Among male patients, one case was Hh, four cases were Nh, 11 cases were hh, and six were unknown. The majority of female cases (48.7%) had hypogonadism in the form of Hh. In contrast, hypogonadism in the form of hh has been detected in the majority of male cases (68.18%). In addition, while the testis may be normal or subnormal, ovarian tissue in some of them could not be visualized at USG or magnetic resonance imaging. The nature of hypogonadism is not only peripheral, but also has a central and peripheral etiology, suggesting that DCAF17 play a role in the development of the pituitary gland or/and hypothalamus as well. Although iron deposition in the central nervous system (CNS) and extrapyramidal involvement have been reported, the role of DCAF17 in the CNS is still unknown.

The height of our patient was in normal range despite hypogonadism. Short stature is not an expected finding in this syndrome. IGF-1 levels were reported in 28/65 cases. IGF-1 was normal in three of these and low in 25. The low IGF-1 levels may reflect the low sex steroids resulting from hypogonadism. However, we detected a low IGF-1 level in our case following sex steroid replacement, suggesting that this derived from liver function in the DCAF17 gene, because this gene has previously been shown to be overexpressed in the liver.

Thyroid function tests were reported in 29/65 cases, and hypothyroidism was detected in 11 (37.9%) of these. As in the present case, subclinical or marked hypothyroidism may be observed. However, autoantibody levels in these cases are negative. This suggests a possible role in thyroid gland development similar to that in gonadal development. Although this patient and previous cases had hypothyroidism, suggesting that DCAF17 has an effect on thyroid gland development, further studies are needed to conclude this. Despite the impairment of the hypothalamic-pituitary-gonadal axis in some cases, no central hypothyroidism was observed.

Extrapyramidal findings such as dystonia, chorea, dysarthria, and dysphagia that commence focally and convert to the generalized form are seen in the advanced stages. In contrast, pyramidal and cerebral effects are not expected. Varying levels of intellectual disorder may be determined in cases. Mental capacity was also limited in our case, although no additional pathological finding developed at other neurological system examinations at follow-up. Severe gait disorder, scoliosis, and wheelchair confinement have been reported as a result of progressive impairment in the extrapyramidal system. Changes in periventricular white matter and iron accumulation in the globus pallidus may also be observed at MRI.

Seven missense/nonsense and four splice-site variants, five small deletions, one small indel and one gross deletion have been defined to date (Figure 1). All loss-of-function mutations have been associated with WSS, but two missense variants (p.Y86H and p.C507R) have been linked to thyroid dyshormonogenesis. The most common c.436delC mutation has been proved to constitute the founder mutation for the Arab population. Our scan of the literature revealed no evidence of any correlation between different DCAF17 mutations and phenotype. Even subjects with the same Saudi Arabian founder DCAF17 pathogenic variant (c.436delC) exhibit pronounced phenotypic variability.

In conclusion, previous studies revealed no obvious genetic-phenotype correlation in patients having DCAF17 mutations. WSS may be defined as a progressive neuroendocrinological disorder accompanied by alopecia. Particular attention should be paid to these additional findings, which may lead to early diagnosis and may reduce genetic analysis costs in patients with hypogonadism.

58ESPE P1-241

Multisystem endocrine disorders

Erdal Kurnaz

Poster presented at: ESPE 2019 VIENNA

PosterSessionOnline.com