Expanding on the phenotypic spectrum of Woodhouse-Sakati syndrome due to founder pathogenic variant in DCAF17: Report of 58 additional patients from Qatar and literature review

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Abstract
Woodhouse-Sakati syndrome (WSS) is a rare autosomal recessive neuroendocrine and ectodermal disorder caused by variants in the DCAF17 gene. In Qatar, the c.436delC variant has been reported as a possible founder pathogenic variant with striking phenotypic heterogeneity. In this retrospective study, we report on the clinical and molecular characteristics of additional 58 Qatari patients with WSS and compare them to international counterparts’ findings. A total of 58 patients with WSS from 32 consanguineous families were identified. Ectodermal and endocrine (primary hypogonadism) manifestations were the most common presentations (100%), followed by diabetes mellitus (46%) and hypothyroidism (36%). Neurological manifestations were overlapping among patients with intellectual disability (ID) being the most common (75%), followed by sensorineural hearing loss (43%) and both ID and aggressive behavior (10%). Distinctive facial features were noted in all patients and extrapyramidal manifestations were uncommon (8.6%). This study is the largest to date on Qatari patients with WSS and highlights the high incidence and clinical heterogeneity of WSS in Qatar due to a founder variant c.436delC in the DCAF17 gene. Early suspicion of WSS among Qatari patients with hypogonadism and ID, even in the absence of other manifestations, would shorten the diagnostic odyssey, guide early and appropriate management, and avoid potential complications.

KEYWORDS
c.436delC, DCAF17 gene, founder pathogenic variant, Qatar, variable clinical manifestations, Woodhouse-Sakati syndrome
1 | INTRODUCTION

Woodhouse-Sakati syndrome (WSS) (OMIM 241080) is a rare autosomal recessive multisystem disorder characterized by hypogonadism, diabetes mellitus, alopecia, intellectual disability, and deafness. It was initially described by Woodhouse and Sakati in the mid of 1983 (Agopiantz et al., 2014; Woodhouse & Sakati, 1983b). As of today, 32 families with a total of 76 affected individuals have been reported, mainly from the Middle East, with a possible founder pathogenic variant c.436delC in the DCAF17 gene (S. A. Bohlega & Alkuraya, 2016). Other cases were reported from Europe, Turkey, Japan, Portugal, and the Indian sub-continent with different pathogenic variants (Abdulla et al., 2015; Agopiantz et al., 2014; A. Alazami et al., 2010; Alazami et al., 2008; Ali et al., 2016; S. A. Bohlega & Alkuraya, 2016; Crandall et al., 1973; Devriendt et al., 1996; Gül et al., 2000; Habib et al., 2011; Koshy et al., 2008; Kurnaz et al., 2019; Louro et al., 2019; Matsuno et al., 2017; Medica et al., 2007; Sendur et al., 2019; Shah et al., 2020; Tatar et al., 2009).

WSS is known for its clinical heterogeneity even among members of the same family, which leads to challenges and delays in reaching a diagnosis (S. A. Bohlega & Alkuraya, 2016). A study of the clinical features of 76 individuals with WSS from 32 families (23 were molecularly diagnosed) showed that almost all cases have endocrine findings such as hypogonadism at the time of puberty and progressive childhood-onset and adolescents, thinning that frequently develops to alopecia in adulthood. Almost all WSS cases have low insulin-like growth factor 1 (IGF-1), around two-thirds have adolescent-onset to young adult-onset diabetes mellitus, and more than a quarter have hypothyroidism. From a neurological point of view, more than half of the cases have progressive extrapyramidal movements such as dystonic spasms with dystonic posturing, dysarthria, and dysphagia, moderate bilateral post-lingual sensorineural hearing loss, and mild intellectual disability (Ben-Orman et al., 2011; Gül et al., 2000; Habib et al., 2011; Koshy et al., 2008; Matsuno et al., 2017; Medica et al., 2007; Steindl et al., 2010).

At the genetic level, the DCAF17 gene, located on chromosome 2q22.3-q35 and formerly known as C2orf37, is responsible for WSS. The DCAF17 gene was first documented in 2008 and nine pathogenic variants have been described in the literature to date (Alazami et al., 2008).

In 2011, we reported seven Qatari patients with a milder phenotype of WSS from two consanguineous families from a highly endogamous tribe. These patients showed intrafamilial phenotypic variability with the spectrum of clinical characteristics previously seen in WSS but with no evidence of extrapyramidal symptoms. That study also suggested that WSS is common in Qatar and the Arab region due to a possible founder effect in the DCAF17 c.436delC variant (Ben-Orman et al., 2011). The current retrospective study was carried out to describe and delineate the diversity of clinical phenotypes among 58 patients with WSS residing in Qatar who carry the same founder pathogenic variant c.436delC in the DCAF17 gene and to compare them with international findings from both a clinical and a molecular perspective.

2 | METHODS

A single-center study (Ault and Pediatric Medical Genetics, Hamad Medical Corporation, Doha, Qatar) was performed between October 1, 2020, and October 1, 2021, in patients with WSS. Detailed clinical and molecular data were retrospectively collected.

Information collected for each patient included: demographic data, clinical manifestations based on the most commonly involved system such as endocrinological, neurological, and ectodermal. In addition, molecular findings, family history, and consanguinity were collected.

An extensive review of the literature using the PubMed database and Google Scholar was performed. A full list of cases was recorded by searching PubMed and Google Scholar with the following keywords: Woodhouse-Sakati, C2orf37, DCAF17, hypogonadism and alopecia, hypogonadism and dystonia, and hypogonadism and IGF1. All patients clinically diagnosed with WSS were included in the review of this study. Cases who did not meet the inclusion criteria were not eligible in the review.

2.1 | Variant analysis

The patients’ genomic DNA was extracted. Exon 4 of the DCAF17 gene was PCR amplified and capillary sequencing was performed in the clinical setting for all patients except one who presented with neck dystonia and for whom whole exome sequencing (WES) was performed. Bi-directional sequence was assembled, aligned to reference gene sequences based on human genome build GRCh37/UCSC hg19, and analyzed for known familial sequence variant(s). Sequence alterations were reported according to the Human Genome Variation Society (HGVS) nomenclature guidelines.

Common haplotype analysis on this variant was also conducted to prove the founder effect as described before (Burns et al., 2018).

2.2 | Statistical analysis

Descriptive statistics in the form of mean, range, and frequency, with percentages, were calculated.

3 | RESULTS

3.1 | Demographic features and clinical characteristics

We studied 58 patients (24 males, 34 females, mean and range of current age 20, 8–37 years) with WSS from 32 families. The mean and range of age at diagnosis were 14.2 and 3–31 years, respectively. A total of 29 patients were children (0 to ≤14 years), 14 were adolescents (14 to ≤18 years), and 15 were adults (19–59 years).
All patients were of Qatari ethnic background with 100% of the families reporting parental consanguinity and 50% reporting a positive family history of similar illness (Table 1).

3.2 | Clinical characteristics and age of onset

All of the 58 (100%) patients had endocrine manifestations in the form of hypogonadism, 27 (46%) had diabetes mellitus, and 21 (36%) had hypothyroidism. The endocrine findings such as hypogonadism and diabetes mellitus were found to be evident at puberty, that is, from adolescent-onset to young adult-onset (Tables 2–4).

Ectodermal manifestations were also documented in 58 (100%) patients who all had alopecia while one (1.7%) had anodontia. A progressive childhood-onset hair thinning often progressed to alopecia in adulthood (Tables 2–4).

In addition, neurological involvements were also documented. ID was found in 44 (75%) patients, sensorineural hearing loss was found in 25 (43%) patients, and six (10%) had both ID and aggressive behavior.

Extrapyramidal manifestations were detected only in five (8.6%) patients, three (5.1%) with dystonia, and two (3.5%) with dysarthria. The onset of neurological manifestations was found to be in childhood (Tables 2–4).

A total of 20 patients had brain MRI, of which 11 (55%) had normal studies, five (25%) showed a picture of iron deposition within the globus pallidus and the substantia nigra, two (10%) had an atrophied anterior pituitary, and two (10%) had nonspecific hyperintensity in the form of bilateral periventricular and subcortical white matter changes (WMCs).

Distinctive facial features were noted in all patients: long triangular face, prominent nasal bridge, widely spaced eyes, and sparse eyebrows. The onset of facial deformities was found to be in childhood (Tables 2–4).

Eye examinations were performed on 24 patients. Keratoconus was noted in 22 (92%) patients and resulted in myopia in 20 (90%) and astigmatism in two (10%).

3.3 | Laboratory findings

A total of 21 (52%) of 50 had a high Hb1Ac (mean: 8.60%, range: 6.4–14.6); 13 (52%) of 27 had a high IGF-1 (mean: 125.9 mcg/L, range: 83–185); 26 (50.9%) of 51 had a low TSH (mean: 8.6 mIU/L, range: 5–49.6); 23 (45.1%) of 51 had a high T4 (mean: 10.84 mIU/L, range: 8.6–12.0); nine (82%) of 11 had a low growth hormone (mean: 0.61 ng/ml.

### Table 1 | Patient demographics for 58 WSS cases

| Group                  | Sub-group | Number (%) |
|------------------------|-----------|------------|
| Gender                 | Male      | 24 (41)    |
|                        | Female    | 34 (59)    |
| Age at diagnosis       | 0 to ≤14 years | 29 (51)    |
|                        | 14 to ≤18 years | 14 (24)    |
|                        | >18 years  | 15 (25)    |
| Nationality            | Qatari    | 58 (100)   |
| Parental consanguinity | Yes       | 32 (100)   |
| Family history         | Positive  | 16/32 (50) |
|                        | Negative  | 16/32 (50) |

### Table 2 | Our patient's clinical features compared to clinically diagnosed cases in Bohlega & Alkuraya, 2016

| Clinical presentations | % of WSS patients (Bohlega & Alkuraya, 2016) |
|------------------------|---------------------------------------------|
| Endocrinial manifestations |                                           |
| Hypogonadism           | 100                                         |
| Failure or delayed of secondary sexual characters development | 45 |
| Diabetes mellitus      | 52                                          |
| Hypothyroidism         | 50.9                                        |
| Ectodermal appendages  |                                             |
| Alopecia               | 100                                         |
| Anodontia              | 1.7                                         |
| Ocular findings        |                                             |
| Keratoconus            | 92                                          |
| Myopia                 | 90                                          |
| Astigmatism            | 10                                          |
| Neurological manifestations |                                           |
| Deafness (sensorineural hearing loss) | 43 | 62 |
| Cognitive impairiment ID | 75 | 58 |
| Both ID and aggressive behavior | 10 |
| MRI brain              |                                             |
| White matter changes   | 10                                          |
| Iron disposition       | 25                                          |
| Atrophied anterior pituitary | 10 |
| Extrapyramidal features | 8.6 | 56 |
| Dystonia               | 5.1                                         |
| Blepharospasm          | 3.5                                         |
| Choreoathetosis        | 3.5                                         |
| Dysarthria             | 3.5                                         |
| Dysphagia              | 3.5                                         |
| Dyspastic quadriplegia |                                             |
| Facial dysmorphic features |                                             |
| including triangular elongated lower face, hypertelorism, and prominent nasal bridge | 100 |

*aEye examinations were done for 24 patients.

*bMRI brain was done for 20 patients.*
range: 0.01–0.62); six (15.8%) of 38 had a low FSH (mean: 0.53 IU/L, range: 0.5–0.7); 11 (33%) of 33 had a low testosterone (mean: 33.3%, range: 0.18–10.25); and none of 13 who had been investigated for insulin had a low level of insulin (Table S1).

### 3.4 Molecular findings

All patients had genetic testing and were confirmed to have the homozygous founder pathogenic variant c.436delC in the DCAF17 gene. The c.436delC variant causes a frameshift starting with codon Alanine 147, changes this amino acid to a Histidine residue, creates a premature stop codon at Position 9 of the new reading frame, and is denoted p.A147HfsX9. This variant is predicted to cause loss of normal protein function either through protein truncation or nonsense-mediated mRNA decay. All parents were confirmed to be heterozygous carriers of this DCAF17 founder pathogenic variant via parental testing.

Haplotype analysis on this variant showed shared runs of homozygosity at chr2:172180771-174230991, spanning 2.32cM, corresponding to 43 generations (or meioses) since the pathogenic variant occurred (at ~25 years/generation that means ~1075 years ago) (Burns et al., 2018).

### 3.5 Literature findings

A total of 122 WSS cases from 53 families have been described in the literature so far from different populations around the world. Molecular diagnoses have been confirmed in 114 WSS cases. The first WSS cases were clinically described in 1973 in Italy (Crandall et al., 1973). Later, several clinically similar cases were reported around the world. A total of eight WSS cases were clinically described in Lebanon in 1979 (Slti & Salem, 1979) and six WSS cases from two different families were clinically diagnosed in Saudi Arabia in 1983 (Woodhouse & Sakati, 1983). In 1985, five more WSS cases were clinically diagnosed in Kuwait (Al-Awadi et al., 1985). From the early 1990s to the beginning of the 21st century, a total of nine WSS cases were further clinically described: four, two, one, and two WSS cases were clinically diagnosed in Myanmar, Belgium, Turkey, and Lebanon, respectively (Devriendt et al., 1996; Gül et al., 2000; Mégarbané et al., 2003; Oerter et al., 1992) (Table S1).

After the discovery of the DCAF17 gene as the gene responsible for WSS, different pathogenic variants were characterized in the DCAF17 gene and the molecular diagnosis of these pathogenic variants was confirmed in almost all the WSS cases that were subsequently reported.

In 2007 and 2008, Al-Semari and Bohlega and Alazami, et al. additionally reported an Arab founder pathogenic variant c.436delC in the DCAF17 gene in 23 WSS cases from 12 Saudi Arabian families (Alazami et al., 2008; Al-Semari & Bohlega, 2007) (Table S1). Further, different pathogenic variants in the DCAF17 gene were reported in different populations. One WSS case was diagnosed with a c.50delC in Slovenia (Medica et al., 2007).

A couple WSS cases were diagnosed with a c.1091+6T>G pathogenic variant in a Middle Eastern family and a Portuguese family (Kumaz et al., 2019; Louro et al., 2019).

In India, molecular diagnosis with a c.1422+5G>T pathogenic variant was confirmed in three members of the same family (Koshy et al., 2008) (Table S1). Furthermore, three Indian cases were molecularly diagnosed with a c.459-7_499del,c.1238delA pathogenic variant in the DCAF17 gene (Abdulla et al., 2015).
| Family | No. of patients | Sex | Hypogonadism | Alopecia | Intellectual disability | Dystonia | Deafness | Diabetes mellitus | Hypothyroidism |
|--------|----------------|-----|--------------|----------|-------------------------|----------|----------|------------------|---------------|
| 1      | 3              | 3M  | Y 3 (100%)   | Y 3 (100%)| N 3 (100%)             | N 2 (67%)| N 1 (33%)| Y 2 (75%)        | Y 2 (75%)     |
| 2      | 1              | 1F  | Y 1 (100%)   | Y 1 (100%)| N 1 (100%)             | Y 1 (100%)| N 2 (67%)| Y 2 (75%)        | N 1 (25%)     |
| 3      | 4              | 1M/3F| Y 4 (100%)   | Y 4 (100%)| N 4 (100%)             | N 4 (100%)| N 4 (100%)| Y 3 (75%)        | N 1 (25%)     |
| 4      | 2              | 1M/1F| Y 2 (100%)   | Y 2 (100%)| N 2 (100%)             | N 2 (100%)| N 2 (100%)| Y 2 (100%)       | N 1 (100%)    |
| 5      | 2              | 2F  | Y 2 (100%)   | Y 1 (50%) | N 2 (100%)             | Y 4 (100%)| N 2 (100%)| N 1 (50%)        | Y 1 (100%)    |
| 6      | 3              | 2M/1F| Y 3 (100%)   | Y 3 (100%)| N 3 (100%)             | Y 2 (67%)| Y 1 (33%)| N 2 (67%)        | N 1 (50%)     |
| 7      | 1              | 1M  | Y 1 (100%)   | Y 1 (100%)| N 1 (100%)             | Y 1 (100%)| N 1 (100%)| Y 1 (100%)       | Y 1 (100%)    |
| 8      | 4              | 2M/2F| Y 4 (100%)   | Y 2 (50%) | NA 2 (50%)             | Y 2 (50%)| Y 2 (50%)| N 1 (50%)        | Y 1 (50%)     |
| 9      | 1              | 1F  | Y 1 (100%)   | Y 1 (100%)| N 1 (100%)             | Y 1 (100%)| N 1 (100%)| Y 1 (100%)       | Y 1 (100%)    |
| 10     | 3              | 3M  | Y 3 (100%)   | Y 3 (100%)| N 3 (100%)             | Y 3 (100%)| N 3 (100%)| Y 1 (100%)       | N 3 (100%)    |
| 11     | 1              | 1F  | Y 1 (100%)   | Y 1 (100%)| N 1 (100%)             | Y 1 (100%)| N 1 (100%)| Y 1 (100%)       | N 1 (100%)    |
| 12     | 1              | 1M  | Y 1 (100%)   | Y 1 (100%)| N 1 (100%)             | Y 1 (100%)| N 1 (100%)| Y 1 (100%)       | N 1 (100%)    |
| 13     | 1              | 1M  | Y 1 (100%)   | Y 1 (100%)| N 1 (100%)             | Y 1 (100%)| N 1 (100%)| Y 1 (100%)       | Y 1 (100%)    |
| 14     | 2              | 2M  | Y 2 (100%)   | Y 2 (100%)| N 2 (100%)             | N 1 (50%)| NA 1 (50%)| Y 2 (100%)       | N 1 (50%)     |
| 15     | 4              | 4F  | Y 4 (100%)   | Y 4 (100%)| Y 2 (50%)              | N 3 (75%)| N 3 (75%)| Y 2 (50%)        | Y 1 (100%)    |
| 16     | 1              | 1M  | Y 1 (100%)   | Y 1 (100%)| N 1 (100%)             | N 1 (100%)| N 1 (100%)| Y 1 (100%)       | Y 1 (100%)    |
| 17     | 1              | 1F  | Y 1 (100%)   | Y 1 (100%)| N 1 (100%)             | Y 1 (100%)| N 1 (100%)| Y 1 (100%)       | Y 1 (100%)    |
| 18     | 2              | 2F  | Y 2 (100%)   | Y 2 (100%)| N 2 (100%)             | Y 1 (50%)| NA 1 (50%)| Y 2 (100%)       | N 1 (50%)     |
| 19     | 1              | 1F  | Y 1 (100%)   | Y 1 (100%)| Y 1 (100%)             | Y 1 (100%)| N 1 (100%)| Y 1 (100%)       | N 1 (100%)    |
| 20     | 1              | 1F  | Y 1 (100%)   | Y 1 (100%)| N 1 (100%)             | Y 1 (100%)| N 1 (100%)| Y 1 (100%)       | N 1 (100%)    |
| 21     | 1              | 1F  | Y 1 (100%)   | Y 1 (100%)| N 1 (100%)             | Y 1 (100%)| N 1 (100%)| Y 1 (100%)       | Y 1 (100%)    |
| 22     | 1              | 1M  | Y 1 (100%)   | Y 1 (100%)| Y 1 (100%)             | Y 1 (100%)| N 1 (100%)| Y 1 (100%)       | NA 1 (100%)   |
| 23     | 2              | 1M/1F| Y 2 (100%)   | Y 2 (100%)| N 2 (100%)             | NA 2 (100%)| N 2 (100%)| Y 1 (100%)       | N 1 (50%)     |
| 24     | 3              | 3F  | Y 3 (100%)   | Y 3 (100%)| NA 2 (67%)             | N 3 (100%)| NA 2 (67%)| Y 2 (67%)        | Y 2 (67%)     |
| 25     | 2              | 1M/1F| Y 2 (100%)   | Y 2 (100%)| N 2 (100%)             | Y 1 (50%)| NA 1 (50%)| Y 2 (100%)       | NA 1 (50%)    |
| 26     | 1              | 1M  | Y 1 (100%)   | Y 1 (100%)| N 1 (100%)             | N 1 (100%)| N 1 (100%)| Y 1 (100%)       | Y 1 (100%)    |
| 27     | 1              | 1F  | Y 1 (100%)   | Y 1 (100%)| N 1 (100%)             | N 1 (100%)| N 1 (100%)| Y 1 (100%)       | Y 1 (100%)    |
| 28     | 1              | 1M  | Y 1 (100%)   | Y 1 (100%)| N 1 (100%)             | N 1 (100%)| N 1 (100%)| Y 1 (100%)       | Y 1 (100%)    |
| 29     | 2              | 2F  | Y 2 (100%)   | Y 2 (100%)| NA 2 (100%)             | NA 2 (100%)| NA 2 (100%)| NA 2 (100%)      | NA 2 (100%)   |
| 30     | 1              | 1F  | Y 1 (100%)   | Y 1 (100%)| NA 1 (100%)             | NA 1 (100%)| NA 1 (100%)| NA 1 (100%)      | NA 1 (100%)   |
| 31*    | 3              | 1M/2F| Y 3 (100%)   | Y 3 (100%)| NA 2 (67%)             | NA 2 (67%)| NA 2 (67%)| NA 2 (67%)       | NA 2 (67%)    |
| 32     | 1              | 1F  | Y 1 (100%)   | Y 1 (100%)| NA                 | NA                 | NA                 | NA                 | NA                 |

*New effected WWS members in the families reported before Ben-Omran et al. (2011).
Moreover, four Turkish WSS cases were diagnosed, three via clinical presentations, and one via presence of a c.127-3delTAGinsAA pathogenic variant (Tatar et al., 2009; Agopiantz et al., 2014), respectively.

In addition, two different types of pathogenic variants in the DCAF17 gene were additionally reported in the Turkish population: two cases with a c.127-1G>C pathogenic variant (Gurbuz et al., 2018), and one case with a c.270dup pathogenic variant (Sendur et al., 2019).

Four additional Italian WSS cases were diagnosed, one case with a c.341C>A pathogenic variant (A. Alazami et al., 2010) and three cases with a c.906G>A pathogenic variant in the DCAF17 gene (A. Alazami et al., 2010; Steindl et al., 2010). Additionally, three French WSS cases from the Gypsy population were molecularly diagnosed with a c.387G>A pathogenic variant on the DCAF17 gene (Matsuno et al., 2016). In addition to the Arab founder pathogenic variant, other WSS pathogenic variants were reported in the Arab population. Compound heterozygous pathogenic variants c.256T>C and c.1519T>C were reported in the DCAF17 gene in a single Saudi Arabian case (Zou et al., 2018) (Table S1).

More WSS cases with different types of pathogenic variants in the DCAF17 gene have continued to be reported in different populations around the world. For instance, three different pathogenic variants have been reported in the DCAF17 gene in three different Pakistani families: six Pakistani cases were diagnosed with a c.321+1G>A pathogenic variant (Habib et al., 2011), four cases were diagnosed with a c.270delA pathogenic variant (Ali et al., 2016), and three more cases with a c.1A>G pathogenic variant (Shah et al., 2020). Similarly, three different types of pathogenic variants in the DCAF17 gene were additionally reported in the Turkish population: three Turkish cases with a c.127-3delTAGinsAA pathogenic variant (Agopiantz et al., 2014), two cases with a c.127-1G>C pathogenic variant (Gurbuz et al., 2018), and one case with a c.270dup pathogenic variant (Sendur et al., 2019). One WSS case was reported in the USA with compound heterozygous pathogenic variants c.535T and c.9906A in the DCAF17 gene (Gurbuz et al., 2018). Two WSS cases were diagnosed in Japan with a c.796G>T pathogenic variant in the DCAF17 gene (Matsumo et al., 2017). Finally, a c.1091-12T>C pathogenic variant in the DCAF17 gene was reported in a Portuguese female diagnosed with WSS (Louro et al., 2019) (Table 5 and Figure 1).

### 3.6 Molecular findings

To date, 19 pathogenic variants are identified in DCAF17 gene, including frameshift and nonsense pathogenic variants as well as splice-site ablations. All these pathogenic variants result in a truncated protein (Table 6).

### 4 DISCUSSIONS

Consanguineous marriages and large family size are observed in most Middle Eastern populations including Qatar, in addition to a relatively limited access to and acceptance of prenatal diagnosis, carrier screening, and other preventative strategies, which all lead to an increased number of recessive disorders within these populations (Ben-Omran et al., 2019). In this article, we aimed to describe the largest reported WSS cohort with detailed clinical, molecular, and biochemical characterization to date. We previously reported on interfamilial phenotypic variability of seven patients with WSS who belong to two families from the same highly consanguineous Qatari tribe (Ben-Omran et al., 2011). However, this larger study presents more data and evidence on the clinical heterogeneity and biochemical profile of WSS in Qatar, especially in relation to the founder pathogenic variant c.436delC in the DCAF17 gene.

In this retrospective study, 100% of the patients belonged to highly consanguineous families from the same tribe and carried the same recurring pathogenic variant c.436delC in the DCAF17 gene, which was previously reported as a possible founder variant in Qatar. In this study, supportive proof using haplotype analysis was carried out, which showed that this variant has occurred approximately 43 generations ago (at 25 years/generation that means ~1075 years ago), signifying that c.436delC is an ancient and founder variant in our population. Recognizing that the reported tribe extends to adjacent countries, the founder DCAF17 pathogenic variant c.436delC might be a frequent founder variant in the Gulf region.

In this large study, we report on 58 Qatari patients who belong to 32 families with intrafamilial and interfamilial phenotypic variability despite harboring the same pathogenic variant c.436delC in the DCAF17 gene.

The heterogeneity of clinical presentations defined in our cohort of patients is comparatively distinctive to WSS. These include delayed puberty, primary amenorrhea, alopecia, and learning disabilities. Particular clinical manifestations such as diabetes mellitus, hypogonadism, and extrapyramidal symptoms were observed to have an older age of onset, making diagnosis challenging in childhood. For instance, less than half of the patients in our study had evidence of diabetes mellitus and less than 10% of the patients had extrapyramidal symptoms, which could be attributed to late onset of disease presentation. WSS would be suspected in the presence of both hypogonadism and alopecia; however, hypogonadism can be obvious at puberty and alopecia can be mild and become more progressive with age.

In our study, ID was found to be more common (75% vs. 58%) while deafness was found to be less common (43% vs. 62%) in our cohort of patients in comparison to other studies where the majority of cases were also from the Middle East (S. A. Bohle & Alkuraya, 2016). In addition, WMCs were found to be less frequent in our cohort in comparison to other studies.
| Origin       | Family | No. of patients | Sex    | Hypogonadism | Alopecia | Intellectual disability | Dystonia | Deafness | Diabetes mellitus | Hypothyroidism | DCAF17 mutation | References                               |
|--------------|--------|-----------------|--------|--------------|----------|-------------------------|----------|----------|------------------|----------------|-----------------|------------------------------------------|
| Italy        | 1      | 3               | 3M     | Y 3 (100%)   | Y 3 (100%)| NR                      | NR       | Y 3 (100%)| NR               | NR             | NR              | Crandall et al. (1973)                    |
| Lebanon      | 2      | 8               | 4M/4F  | Y 3 (100%)   | Y 3 (100%)| NR                      | NR       | NR       | NR               | NR             | NR              | Slti and Salem (1979)                     |
| Saudi Arabia | 3      | 4               | 2M/2F  | Y 4 (100%)   | Y 4 (100%)| Y 4 (100%)              | Y 4 (100%)| Y 4 (100%)| Y 4 (100%)       | NR             | NR              | Woodhouse and Sakati (1983)               |
| Kuwait       | 5      | 3               | 1M/2F  | Y 3 (100%)   | Y 3 (100%)| NR                      | NR       | NR       | NR               | NR             | NR              | Al-Awadi et al. (1985)                    |
| Lebanon      | 6      | 4               | 2M/2F  | Y 4 (100%)   | Y 4 (100%)| NR                      | Y 4 (100%)| NR       | NR               | NR             | NR              | Oerter et al. (1992)                      |
| Saudi Arabia | 7      | 2               | 1M/1F  | Y 2 (100%)   | Y 2 (100%)| Y 2 (50%)               | Y 1 (50%)| Y 1 (100%)| Y 1 (100%)       | NR             | NR              | Devriendt et al. (1996)                   |
| Turkey       | 8      | 1               | 1M     | Y 1 (100%)   | Y 1 (100%)| Y 1 (100%)              | NA       | Y 1 (100%)| NR               | NR             | NR              | Gül et al. (2000)                         |
| Kuwait       | 9      | 2               | 2F     | Y 2 (100%)   | Y 2 (100%)| NR                      | NR       | NR       | NR               | NR             | NR              | Mégarbané et al. (2003)                   |
| Saudi Arabia | 10     | 6               | 2M/4F  | Y 6 (100%)   | Y 5 (83%) | Y 4 (67%)               | Y 6 (67%)| Y 1 (33%)| Y 6 (100%)       | NR             | c.436delC | Al-Semari and Bohlega (2007), Alazami et al. (2008) |
|              | 11     | 2               | 1M/1F  | Y 2 (100%)   | Y 2 (100%)| Y 2 (100%)              | N 2 (100%)| N 2 (100%)| NA               | c.436delC | NA              |                                          |
|              | 12     | 3               | 3F     | Y 3 (100%)   | Y 2 (67%) | Y 2 (67%)               | Y 1 (33%)| N 2 (100%)| Y 3 (100%)       | NA             | c.436delC |                                          |
|              | 13     | 2               | 1M/1F  | Y 2 (100%)   | Y 2 (100%)| Y 2 (100%)              | Y 2 (100%)| Y 1 (50%)| N 1 (50%)        | NA             | c.436delC |                                          |
|              | 15     | 3               | 2M/1F  | Y 2 (67%)   | Y 3 (100%)| Y 2 (67%)               | Y 2 (100%)| N 2 (100%)| NA               | c.436delC | NA              |                                          |
|              | 16     | 1               | 1F     | Y 1 (100%)   | Y 1 (100%)| Y 1 (100%)              | NA       | Y 1 (100%)| Y 1 (100%)       | c.436delC | NA              |                                          |
|              | 17     | 1               | 1M     | Y 1 (100%)   | Y 1 (100%)| Y 1 (100%)              | NA       | Y 1 (100%)| NA               | c.436delC | NA              |                                          |
|              | 18     | 1               | 1M     | Y 1 (100%)   | NA        | Y 1 (100%)              | Y 1 (100%)| NA       | Y 1 (100%)       | c.436delC | NA              |                                          |
|              | 19     | 1               | 1M     | Y 1 (100%)   | Y 1 (100%)| Y 1 (100%)              | Y 1 (100%)| Y 1 (100%)| Y 1 (100%)       | c.436delC | NA              |                                          |
|              | 20     | 1               | 1M     | Y 1 (100%)   | Y 1 (100%)| Y 1 (100%)              | Y 1 (100%)| Y 1 (100%)| Y 1 (100%)       | c.436delC | NA              |                                          |
|              | 21     | 1               | 1M     | Y 1 (100%)   | Y 1 (100%)| Y 1 (100%)              | Y 1 (100%)| Y 1 (100%)| Y 1 (100%)       | c.436delC | NA              |                                          |
|              | 22     | 4               | 3M/1F  | Y 4 (100%)   | N 3 (75%) | N 3 (75%)               | Y 1 (25%)| Y 1 (25%)| Y 1 (25%)        | c.436delC | NA              |                                          |
| Slovenia     | 23     | 1               | 1F     | Y 1 (100%)   | Y 1 (100%)| Y 1 (100%)              | Y 1 (100%)| Y 1 (100%)| Y 1 (100%)       | c.50delC | NA              | Medica et al. (2007), Alazami et al. (2008) |
| Middle East  | 24     | 2               | 1M/1F  | Y 2 (100%)   | Y 2 (100%)| Y 2 (100%)              | Y 2 (100%)| Y 2 (100%)| N 1 (50%)        | c.1091 + 6T > G | ALI ET AL. | Alazami et al. (2008), Schneider and Bhatia (2008) |
| Origin | No. of patients | Sex | Hypogonadism | Alopecia | Intellectual disability | Dystonia | Deafness | Diabetes mellitus | Hypothyroidism | DCAF17 mutation | References |
|--------|----------------|-----|--------------|----------|-------------------------|----------|---------|-----------------|---------------|----------------|----------------|
| India  | 25             | 3M/2F | Y 3 (100%)  | Y 3 (100%) | N 3 (100%)              | Y 3 (100%) | Y 3 (100%) | Y 3 (100%)       | NR 3 (100%)   | c.1422 + 5G > T | Alazami et al. (2008), Koshy et al. (2008) |
| Turkey | 26             | 2F   | Y 2 (100%)  | Y 2 (100%) | NR 2 (100%)             | Y 1 (50%)  | NR 2 (100%) | NR 2 (100%)      | NR            |               | Tatar et al. (2009) |
| Turkey | 27             | 1M   | Y 1 (100%)  | Y 1 (100%) | N 1 (100%)              | Y 1 (100%) | N 1 (100%) | Y 1 (100%)       |               | c.127-3delTAGinsAA | Alazami et al. (2010), Agopiantz et al. (2014) |
| Italy  | 28             | 1F   | Y 1 (100%)  | Y 1 (100%) | N 1 (100%)              | Y 1 (100%) | N 1 (100%) | Y 1 (100%)       |               | c.341C > A     | Alazami et al. (2010) |
| France | 29             | 3M/2F | Y 3 (100%)  | Y 3 (100%) | N 3 (100%)              | Y 3 (100%) | N 3 (100%) | N 3 (100%)       |               | c.387G > A     | Alazami et al. (2010) |
| Italy  | 30             | 3M/2F | Y 3 (100%)  | Y 3 (100%) | Y 2 (66%)               | Y 2 (66%)  | Y 2 (66%) | NR 1 (33%)       | NR 3 (100%)   | c.906 G > A    | Alazami et al. (2010), Steindl et al. (2010) |
| Palestine | 31          | 1M/2F | Y 4 (100%)  | Y 4 (100%) | Y 1 (25%)               | Y 1 (25%)  | Y 1 (25%) | Y 4 (100%)       | NR 4 (100%)   | c.436 delC     | Rachmiel et al. (2011) |
| Qatar  | 32             | 3M/2F | Y 3 (100%)  | Y 3 (100%) | N 3 (100%)              | N 3 (100%) | N 3 (100%) |                 |               | c.436 delC     | Ben-Omran et al. (2011) |
| Pakistan | 34            | 3M/2F | Y 6 (100%)  | Y 6 (100%) | Y 4 (67%)               | Y 6 (100%) | Y 6 (100%) | N 2 (33%)        | NR 6 (100%)   | c.321 + 1 G > A | Habib et al. (2011) |
| Turkey | 36             | 1M/3F | Y 3 (100%)  | Y 3 (100%) | Y 3 (100%)              | Y 3 (100%) | Y 3 (100%) | Y 3 (100%)       | NR 3 (100%)   | c.127-3delTAGinsAA | Agopiantz et al. (2014) |
| Kuwait | 37             | 1M/2F | Y 2 (67%)   | Y 3 (100%) | Y 2 (67%)               | Y 2 (67%)  | Y 2 (67%) | Y 2 (67%)        | NR 1 (33%)    | c.436delC      | Nanda, Pasternack et al. (2014) |
| India  | 38             | 2M/1F | Y 3 (100%)  | Y 2 (67%)   | Y 2 (67%)               | Y 3 (100%) | N 1 (33%) | N 2 (66%)        | NR 1 (33%)    | c.459-7_499del,c.1238delA | Abdulla et al. (2015) |
| Qatar  | 39             | 1M/1F | Y 2 (100%)  | Y 2 (100%) | Y 2 (100%)              | Y 2 (100%) | Y 2 (100%) |                 |               | c.436 delC     | Sheridan et al. (2015) |
| Pakistan | 40            | 2M/2F | Y 4 (100%)  | Y 4 (100%) | Y 4 (100%)              | Y 2 (50%)  | N 2 (50%) | N 3 (66%)        | NR 1 (33%)    | c.270delA      | Ali et al. (2016) |
| Tunisian | 41            | 2F   | Y 2 (100%)  | Y 2 (100%) | Y 2 (100%)              | Y 2 (100%) | Y 2 (100%) | N 1 (50%)        | NR 1 (50%)    | c.436 delC     | Hdi et al. (2016) |
| Japan  | 42             | 1M   | Y 1 (100%)  | Y 1 (100%) | Y 1 (100%)              | Y 1 (100%) | Y 1 (100%) | Y 1 (100%)       |               | c.796 G>T      | Matsuno et al. (2017) |
| Origin     | Family | No. of patients | Sex | Hypogonadism | Alopecia | Intellectual disability | Dystonia | Deafness | Diabetes mellitus | Hypothyroidism | DCAF17 mutation | References            |
|------------|--------|-----------------|-----|--------------|----------|------------------------|----------|----------|------------------|----------------|------------------|----------------------|
| Kuwait     | 43     | 2               | 2F  | Y2 (100%)    | Y2 (100%)| Y1 (50%)               | Y2 (100%)| Y2 (100%)| Y1 (50%)         | N1 (50%)       | c.436 delC      | Almeqdadi et al. (2018) |
| Qatar      | 44     | 1               | 1F  | Y1 (100%)    | Y1 (100%)| Y1 (100%)               | Y1 (100%)| Y1 (100%)| Y1 (100%)         | N1 (100%)       | c.436 delC      |                     |
| Bahrain    | 45     | 2               | 1M/1F| Y2 (100%)    | N2 (100%)| Y1 (50%)               | N2 (100%)| Y2 (100%)| Y1 (50%)         | NR1 (50%)       | c.436 delC      |                     |
| Turkey     | 46     | 2               | 2F  | Y2 (100%)    | N2 (100%)| NR2 (100%)              | NR2 (100%)| N2 (100%)| NR1 (100%)       |                | c.127-1G > C    | Gurbuz et al. (2018)  |
| US         | 47     | 1               | 1F  | Y1 (100%)    | Y1 (100%)| NR1 (100%)              | NR1 (100%)| Y1 (100%)| NR1 (100%)       |                | c.C535T, c.G906A |                     |
| Saudi Arabia | 48   | 1               | 1M  | Y1 (100%)    | NR1 (100%)| NR1 (100%)              | NR1 (100%)| NR1 (100%)| Y1 (100%)         |                | c.256T > C, c.1519T > C | Zou et al. (2018)    |
| Turkey     | 50     | 1               | 1F  | Y1 (100%)    | Y1 (100%)| Y1 (100%)               | Y1 (100%)| Y1 (100%)| Y1 (100%)         |                | c.270dup        | Sendur et al. (2019)  |
| Portugal   | 51     | 1               | 1F  | Y1 (100%)    | Y1 (100%)| Y1 (100%)               | Y1 (100%)| Y1 (100%)| Y1 (100%)         |                | c.1091+2T>C     | Louro et al. (2019)   |
| Turkey     | 52     | 1               | 1F  | Y1 (100%)    | Y1 (100%)| N1 (100%)               | N1 (100%)| N1 (100%)| Y1 (100%)         |                | c.1091 + 1G > A | Kurnaz et al. (2019)  |
| Pakistan   | 53     | 3               | 3M  | Y3 (100%)    | NR3 (100%)| NR3 (100%)              | NR3 (100%)| NR3 (100%)| NR3 (100%)       |                | c.1A>G          | Shah et al. (2020)    |
(10% vs. 100%) in our cohort of patients in comparison to another study on individuals with the same DCAF17 founder pathogenic variant (Abusair et al., 2018). The onset of clinical presentations was found to be similar to other studies. For instance, endocrine manifestations of hypogonadism and diabetes mellitus showed adolescent-onset to young adult-onset, hypothyroidism showed onset from childhood to adolescence, hair loss started in childhood and often progressed to alopecia in adulthood, and neurological manifestations such as deafness and ID were found to be present in childhood while WMC appeared from adolescence to young adulthood (S. A. Bohlega & Alkuraya, 2016).

In a more recent study, S. Bohlega et al. (2019) assessed the neurological manifestations of 38 WSS patients with the same founder pathogenic variant c.436delC using the Neurological Impairment Scale (NIS) and delineated two distinct phenotypes. Almost half of the cases had NIS of 3–4 (Type 1 WSS) along with severe disability and rapid disease progression, while the other half had NIS of 0–1 (Type 2 WSS) and showed either absent or mild neurological involvement with preserved activities of daily living. In addition, neurological symptoms had an earlier mean age of onset in Type 1 WSS (12.6 ± 4.5 years) compared to Type 2 WSS (18.1 ± 4.3 years) and the rate of ID was significantly higher in Type 1 WSS (S. Bohlega et al., 2019).

Our search of the literature showed no clear indication of any correlation among diverse DCAF17 pathogenic variants and phenotypes. Even subjects with the Arab founder pathogenic variant c.436delC show distinct phenotypic variability. It is unclear how this clinical variability occurs despite the fact that patients in our cohort and other reported patients in the region carry the same c.436delC variant; however, modifier genes or epigenetics may be contributing.

The particular mechanisms behind hormonal abnormalities and the other signs and symptoms in WSS remain elusive. Also, in relation to the multiple endocrine manifestations, comprehending the role of DCAF17 gene in diabetes mellitus, hypogonadism, and hypothyroidism will offer unprecedented insights into the function of the pancreas, gonads, and the thyroid gland. This may also help to develop novel precision medicine therapies for patients with WSS.

Nonetheless, some of the molecular mechanisms of DCAF17 have been studied. For instance, more than 30 mRNA isoforms encoding the WSS protein have been identified. The two major isoforms are α and β that are expressed in equivalent abundance. Both α and β WSS protein were found to be ubiquitously expressed in all tissues with relatively higher expression in the brain, liver, and skin (Alazami et al., 2008). Interestingly, a novel third nuclear isoform of 80-kDa has been recently described and needs further investigation to understand its role (Blocka, 2018). The intracellular localization of both isoforms

**Figure 1** Summarizing the number and frequency of DCAF17 variants per ethnic group
was thought to be primarily nucleolus and to be colocalized with B23 (nucleophosmin), which is a known granular component of the nucleoli in both mice model/WSS patients. Other studies showed that α-WSS was found to be more abundantly in the nucleolus, whereas β-WSS within other subnuclear departments (A. M. Alazami et al., 2008). It was also suggested that wild-type WSS is only partially dependent on active transcription while the lymphoblasts of WSS patients show a hypersensitivity to transcriptional blockade, that is, in the WSS patient lymphoblasts, WSS protein (and B23) mobilized into the nucleoplasm at a lower dose of actinomycin D (RNA polymerase I inhibitor) while a higher dose was required for a displacement of C2orf37 in the control lymphoblasts (A. M. Alazami et al., 2008).

Regardless of their abundant expression, a lack of nucleolar proteins commonly appears to clinically affect a limited number of organs. This phenomenon has formerly been described in other syndromes and may suggest a redundancy of nucleolar proteins in the phenotypically unaffected tissues. For instance, Nousbeck et al. described a syndrome with alopecia, neurological symptoms, and endocrinopathy (ANE syndrome) caused by a reduced expression of RNA-binding motif 28 (RBM28)—a nucleolar protein associated with ribosome biogenesis (Nousbeck et al., 2008).

Nevertheless, it is still unknown whether the increased sensitivity to RNA polymerase I inhibitor is associated to a pathologic ribosome biogenesis as the fundamental cause of WSS. Besides the RNA polymerase I activity in blocking the rRNA transcription, it also inhibits the fusion of prernucleolar bodies (PNBs) and nucleolar organizer regions (NORs). Other nucleolar functions, such as snRNA processing, mRNA transport, cell cycle regulation, cell aging, and apoptosis, may subsequently be disrupted by RNA polymerase I blockade and consequently explain the underlying mechanisms of the WSS pathogenesis lymphoblasts (A. M. Alazami et al., 2008).

So far, the exact function of DCAF17 is still not fully understood apart from it being part of the ubiquitin ligase complex (DDB1-CUL4-ROC1 E3), particularly binding directly to DDB1 and serving as a substrate recruiter for E3. It could be possible that the DDB1-CUL4A E3 ubiquitin ligase pathway is disturbed in WSS patients, which plays an important role in protein degradation, cell cycle, transcription, as well as regulation of molecule trafficking (Pickart, 2004). Thus, studying DCA17 as part of the ubiquitin pathway will open numerous doors to comprehending the physiology of cell functioning, cell reaction and adaptation to stress factors, and consequences of disruption of these mechanisms.

Consanguineous marriages and endogamy could be factors in aggregating rare autosomal recessive syndromes such as WSS in the Arab countries and, based on our published reports, WSS is perhaps more common among the Arabs than assumed earlier. Based on the

### TABLE 6  Reported Mutations in DCAF17 gene

| Family origin       | Location of mutation | Type of mutation | References                                                                 |
|---------------------|----------------------|------------------|---------------------------------------------------------------------------|
| Qatari, Kuwaiti, Bahraini, Saudi Arabian, Palestinian, Tunisian | c.436delC         | Frameshift       | Al-Semari and Bohlega (2007), Alazami et al. (2008), Ben-Omran et al. (2011), Rachmiel et al. (2011), Nanda, Pasternack et al. (2014), Sheridan et al. (2015), Hdiji et al. (2016), Almeqdadi et al. (2018) |
| Saudi Arabian       | c.256T>C, c.1519T>C  | Compound heterozygous | Zou et al. (2018)                                                          |
| Middle Eastern      | c.1091+6T>G          | Splice-site       | Alazami et al. (2008), Schneider and Bhatia (2008)                        |
| Turkish             | c.127-3delTAInsAA    | Splice-site       | Alazami et al. (2010), Agopiantz et al. (2014)                            |
|                     | c.127-1G > C         | Frameshift        | Gurbuz et al. (2018)                                                      |
|                     | c.1091+1G > A        | Frameshift        | Kurnaz et al. (2019)                                                      |
|                     | c.270dup             |                  |                                                                           |
| Italian             | c.341C>A             | Nonsense          | Alazami et al. (2010)                                                    |
|                     | c.906G>A             |                  | Alazami et al. (2010), Steindl et al. (2010)                              |
| US                  | c.535T, c.G906A      | Compound heterozygous | Gurbuz et al. (2018)                                                     |
| Slovenia            | c.50 delC            | Frameshift        | Medica et al. (2007), Alazami et al. (2008)                               |
| French              | c.387G>A             | Nonsense          | Alazami et al. (2010)                                                    |
| Portuguese          | c.1091+2T>C          | Frameshift        | Louro et al. (2019)                                                      |
| Pakistani           | c.270delA            | Frameshift        | Ali et al. (2016)                                                         |
|                     | c.321-1G>A           | Splice-site       | Habib et al. (2011)                                                       |
|                     | c.1A>G               |                  | Shah et al. (2020)                                                        |
| Indian              | c.1422+5G>T          | Splice-site       | Alazami et al. (2008)                                                    |
|                     | c.459-7,499del       |                  | Alazami et al. (2015)                                                    |
|                     | c.1238delA           |                  | Abdulla et al. (2015)                                                    |
| Japanese            | c.796 G>T            |                  | Noris et al. (2017)                                                       |
evidence presented in this study regarding the high incidence, founder effect, and clinical heterogeneity of WSS in Qatar, it is important to raise awareness on the signs and symptoms of WSS and its clinical heterogeneity in order to reduce the diagnostic odyssey of patients and provide prompt interventions and management. In addition, we recommend that WSS be added in large screening programs such as premarital screening in Qatar in order to reduce the incidence of the disease. This may be achieved through the identification of carriers and at-risk couples and the provision of genetic counseling and guidance regarding reproductive options.

This retrospective study has one limitation: it could not characterize the rate of progression of the disease because all of the medical charts of WSS patients were reviewed at variable clinical stages of the disease.

5 | CONCLUSIONS

WSS is a multisystem disease with diverse clinical presentations. Interfamilial and intrafamilial phenotypic variability is present among patients with the same pathogenic variants, which could be due to potential role of both genetic or environmental modifying factors and interactions. We conclude that targeted testing for the DCAF17 founder variant c.436delC should be included in the clinical workup of patients with hypogonadism and intellectual disability, even in the absence of other typical syndromic characteristics, especially in individuals of Qatari and Middle Eastern ancestry. Our study also recommends having an early detection strategy through family screening or by adding WSS to the premarital screening program to reduce the incidence of the disease or at least to allow for early multidisciplinary management to avoid potential complications.

This report also highlights the importance of early suspicion of WSS among individuals of Middle Eastern ancestry and especially of Qatari origin with hypogonadism and intellectual disability, even when other typical syndromic characteristics are absent, which could shorten the diagnostic odyssey, guide early and appropriate multidisciplinary management, and prevent potential complications.

ACKNOWLEDGMENTS
The authors would like to thank all patients and their families for their outstanding collaboration. The authors thank their respective institutions for their continued support. The publication of this article was funded by the Qatar National Library, Doha, Qatar.

CONFLICT OF INTEREST
The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS
Nader Al-Dewik and Tawfeg Ben-Omran wrote the initial draft of article and research protocol, as well as performed literature review and supervised the data collection. Mahmud Elfituri, Sahar Agouba, and Shayma Mohammed did data collection. Sahar Agouba performed data analysis for laboratory findings and contributed to the literature findings. Rehab Ali, Nader Al-Dewik, Shayma Mohammed, Mahmud Elfituri, Sahar Agouba, Sara Musa, Laila Mahmoud, Mariam Almulla, Karen El-Akouri, Howaida Mohd, Reem Bux, Hajer Almulla, Amna Othman, Fatma Al-Mesaifri, Noora Shahbeck, Mariam Almuriikhi, Amal Khalifa, Reem Alsualaiman, and Tawfeg Ben-Omran provided the clinical data for WSS. All authors read and approved the final manuscript.

ETHICS STATEMENT
This project was approved by the Hamad Medical Corporation Research Ethics Committee—reference number (MRC-01-20-779).

DATA AVAILABILITY STATEMENT
This is a research article and all data generated or analyzed during this study are included in this published article. All enquiries should be directed to the corresponding author.

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**How to cite this article:** Ali, R., Al-Dewik, N., Mohammed, S., Elfituri, M., Agouba, S., Musa, S., Mahmoud, L., Almulla, M., El-Akouri, K., Mohd, H., Bux, R., Almulla, H., Othman, A., Al-Mesaifri, F., Shahbeck, N., Al-Muriekh, M., Khalifa, A., Al-Sulaiman, R., & Ben-Omran, T. (2021). Expanding on the phenotypic spectrum of Woodhouse-Sakati syndrome due to founder pathogenic variant in DCAF17: Report of 58 additional patients from Qatar and literature review. *American Journal of Medical Genetics Part A, 188A:*116–129. https://doi.org/10.1002/ajmg.a.62501