Woodhouse-Sakati Syndrome: Clinical and Molecular Study on a Qatari Family with C2orf37 Gene Mutation

Sara Al-Khawaga, Basma Haris, Reem Hasnah, Saras Saraswathi, Amira Saeed, Sanaa Sharari, Idris Mohammad, Khalid Hussain

[1]Department of Pediatric Medicine, Division of Endocrinology, Sidra Medicine, Doha, Qatar.
E-mail: khussain@sidra.org

Sidra Medicine
Member of Qatar Foundation

INTRODUCTION

Woodhouse-Sakati syndrome (WSS) is rare autosomal recessive condition characterized by progressive extrapyramidal signs, mental retardation, hypogonadism, alopecia, and diabetes mellitus. The age at disease onset, manifestation and severity of specific symptoms differs significantly among individuals with this syndrome and even among affected members of the same family. The gene C2orf37, which is responsible for WSS, located on chromosome 2q22.3-q35.

OBJECTIVE(S)

To describe the clinical and genetic characteristics of Woodhouse-Sakati Syndrome diagnosed in three siblings fom the state of Qatar.

CASE REPORT

The phenotype of the three siblings included hypogonadism, alopecia, diabetes mellitus, and different degrees of mental retardation ranging from mild to severe. Whole Exome Sequencing (WES) analysis was performed in the patients and their parents.

METHODS

The patient's genomic DNA was used. Next-generation sequencing using an Illumina system was used to capture the exonic region and flanking splice junctions of the genome. Xome Analyzer was used to analyze the sequence variants all potentially pathogenic variants were confirmed using Capillary sequencing. Sequence and copy number alterations were reported according to the Human Genome Variation Society (HGVS) and International System for human Cytogenetic Nomenclature (ISCN) guideline, respectively. Sanger sequencing was used to confirm the mutation in the patient, both parents, and sibling.

RESULTS

Homozygous mutation c.436delC in exon 4 in the DCAF17 gene was identified in the three siblings. Both parents were heterozygous for the mutations. C2orf37 codes for DCAF17 (DDB1 and CUL4 associated factor 17) a transmembrane protein that localizes to the nuclear envelop of unknown function but that may be associated with the ubiquitin system. C2orf17 codes for a protein of 520 aa. The c. 436DelC mutation causes a frame shift and a predicted truncated protein of 147 aa.

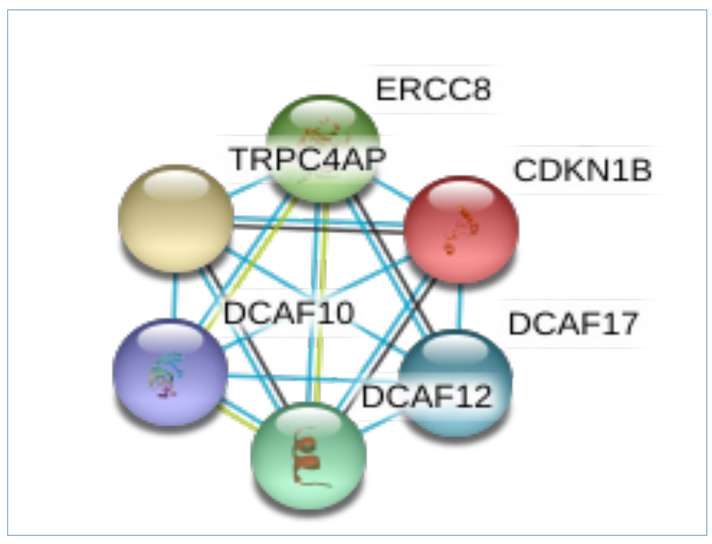

Figure 1. STRING network interaction of DCAF17 gene. Homozygous mutation in the C2ORF37 gene (DCAF17) on chromosome 2q31. This gene encodes a nuclear transmembrane protein that associates with cullin 4A/damaged DNA binding protein 1 ubiquitin ligase complex.

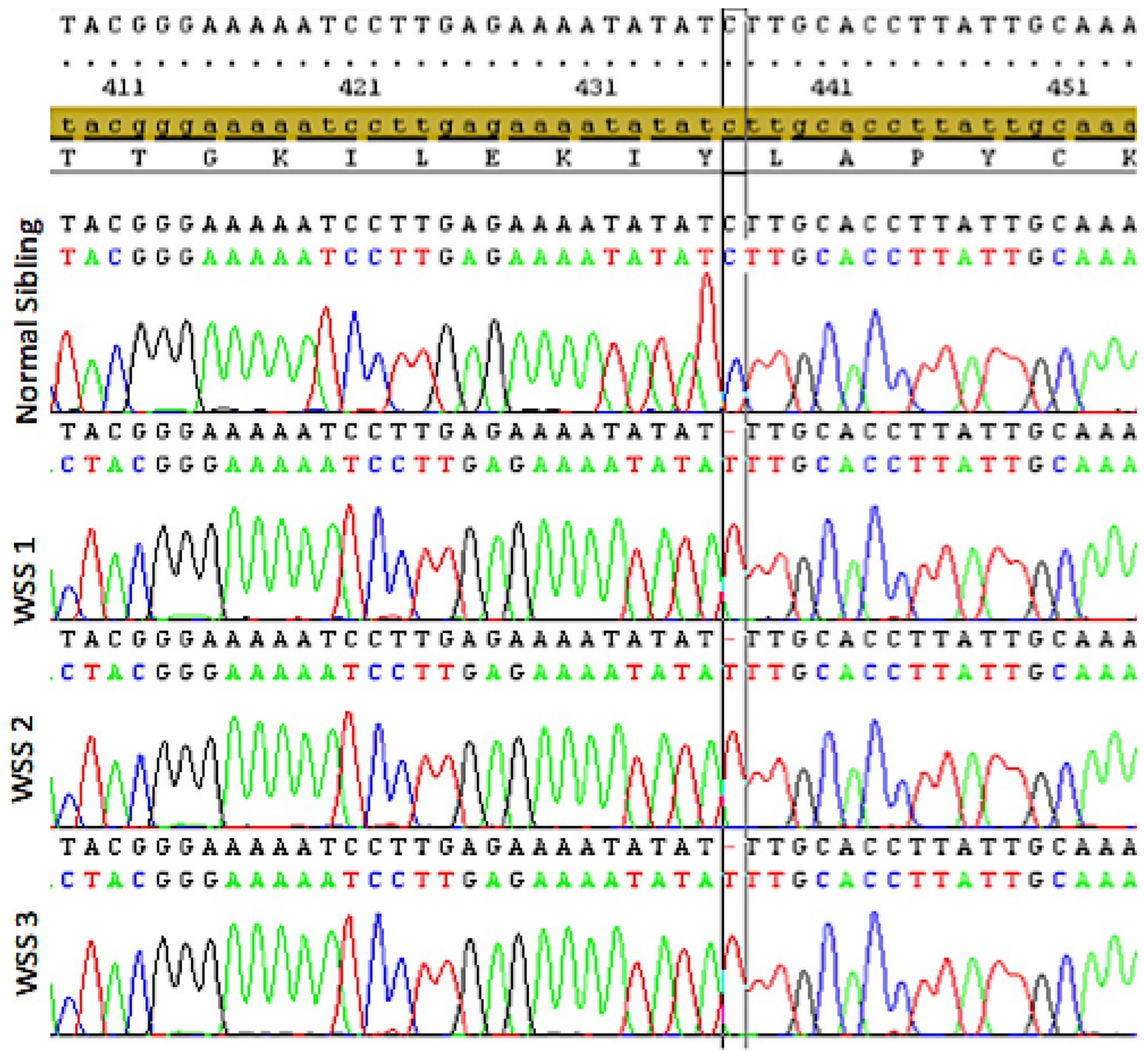

Figure 2. Sanger sequencing of the three affected siblings with WSS.

CONCLUSION

- Mutations in DCAF17 account for the features of Woodhouse-Sakati syndrome.
- The exact mechanisms behind hormonal abnormalities and the other signs and symptoms remain unclear. Understanding the molecular basis of WSS will provide novel insights into the role of the C2orf37 gene in normal physiology.
- In relation to the endocrine manifestations, understanding the role of C2orf37 gene in diabetes mellitus, hypogonadism and hypothyroidism will provide unique insights into the function of the pancreas, gonads and the thyroid gland.
- The translational implications of this are that we might be able to develop novel therapies for this disorder if we know how mutations in C2orf37 gene lead to the multiple endocrine manifestations.

REFERNCES

1. Woodhouse, N.J. and N.A. Sakati, *A syndrome of hypogonadism, alopecia, diabetes mellitus, mental retardation, deafness, and ECG abnormalities.* J Med Genet, 1983. **20**(3): p. 216-9.
2. Alazami, A.M., et al., *Mutations in C2orf37, encoding a nucleolar protein, cause hypogonadism, alopecia, diabetes mellitus, mental retardation, and extrapyramidal syndrome.* Am J Hum Genet, 2008. **83**(6): p. 684-91.
3. Almeqdadi, M., et al., *Phenotypic Variability of c.436delC DCAF17 Gene Mutation in Woodhouse-Sakati Syndrome.* Am J Case Rep, 2018. **19**: p. 347-353.