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**No disclosures**

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**Background**

Wolfram Syndrome (WS) is a rare autosomal recessive genetic disorder. We present two sisters from non-consanguineous parents, who presented to our pediatric endocrinology clinic due to severe polyuria-polydipsia with inappropriately treated DM (HbA1c 8.2% and 10.1%) and untreated DI.

**Methods**

DNA was tested with PCR amplification and sequencing analysis (Sanger sequencing) of the entire coding region and all exon-intron splice junctions of the WFS1 gene (chromosome 4): reference sequence: NM\_006005.3, with the A of the ATG start codon at position 1.

**Results**

A novel homozygous point missense c.2069G>A mutation in amino acid position 690 (p.C690Y) replacing Cysteine with Tyrosine in exon 8 was found in both sisters, the parents being heterozygous. The mutation is damaging with a score of 1.000 (Polyphen-2).

**Cases**

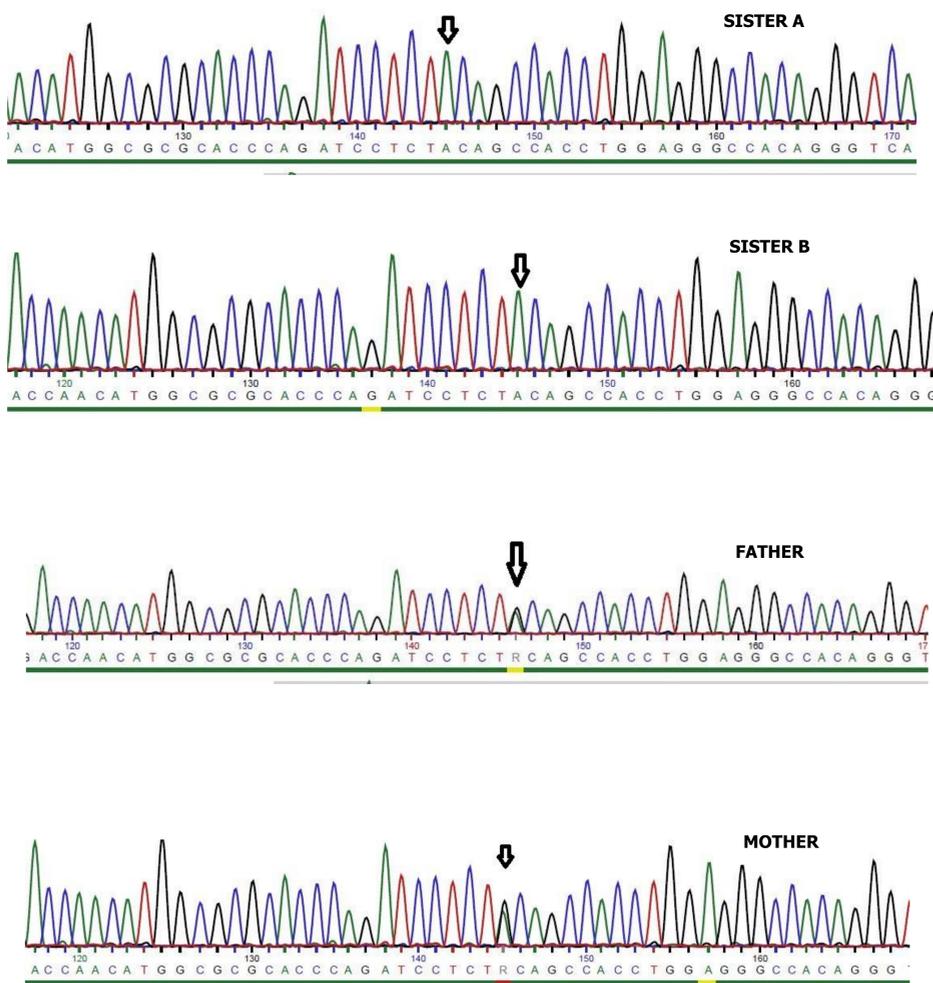
**Sister-A**, a few weeks ago had a sudden death of brain stem atrophy. She was 19 yrs old. At presentation at our outpatient clinic had a BMI<-2SDS, totally blind since 13 yrs, with primary amenorrhea and bladder incontinence;

- normal cranial nerve examination
- oculomotion with roving eye movements
- normal muscle strength and deep tendon reflexes 2/4
- no extrapyramidal or ataxia signs
- visual acuity "No Light Perception" in both eyes
- pupillary light reflex completely absent with meditated pupils
- normal anterior segment
- intraocular pressure 12mmHg bilaterally
- complete optic nerve atrophy in dilated fundus examination
- tympanogram type A
- TOAEs and aABRs "pass" bilateral in Otologic and Audiologic testing
- appropriate for age mental status with signs of severe depression.

**Sister-B**, prepubertal 7yrs old

- normal neurological examination
- visual acuity 6/15 (0.40 LogMAR) and 6/19 (0.50 LogMAR) with +1.00 diopters sphere corrective lens in both eyes
- symmetrically reduced pupillary light reflex with not relative afferent pupillary reflex
- normal anterior segment
- intraocular pressure 12mmHg and 11mmHg
- moderate optic nerve atrophy
- tympanogram type C
- right side "pass" and left "fail" of TOAEs, aABRs "pass" bilateral.

- Both had normal electrolytes, severe neurogenic bladder and Grade III hydronephrosis.
- They presented salt-wasting due to ANP elevation when treatment for DI was started, successfully treated with fludrocortisone along with frequent bladder catheterizations.
- Within six months, patient's A BMI normalized, and she had menstrual onset.
- Persistence of hydronephrosis in patient B revealed a grade III bilateral vesicoureteral reflux that was treated with endoscopic injection of Deflux.



Father and mother heterozygotes for c.2069G>A mutation of WFS1 gene.  
Sisters homozygotes for c.2069G>A mutation of WFS1 gene.

**Conclusion**

We present a novel detrimental homozygous WFS1 gene mutation in two sisters from non-consanguineous parents of Greek descent, both originated 5-6 generations before from Trapezund, an ancient Greek colony located in the Greek –until 1922- Pontos, presently in the state of Turkey, indicating a founder mutation effect