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CASE REPORT

Polyendocrinopathy, deafness and albinism, a new combination syndrome

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ABSTRACT

Background: Waardenburg syndrome is a rare genetic disorder with distinct characteristics. Since their discovery, some types of WS have been reported only once. Type 2F, the subject of this article, has only eleven reported cases worldwide.

Case Presentation: In this article, we report a 15-year-old female patient with type 2F who exhibited bilateral sensorineural hearing loss. It is the first reported case of WS type 2F with albinism since birth, type 1 diabetes mellitus (DM), absent internal female reproductive organs, and short stature.

Conclusion: In the current case, it might be classified as a new type of WS with this distinguished and unique presentation. Consanguineous marriages might reveal hidden diseased genes. This condition requires a multidisciplinary team management.

Keywords: Waardenburg syndrome, type 2F, albinism, deafness, type 1 DM, short stature, absent female genital organs, hypergonadotropic hypogonadism, *KITLG* gene.

Introduction

Waardenburg syndrome (WS) is a group of inherited disorders that can cause hearing loss and changes in the pigmentation of the skin, hair, and eyes [1]. In 1916, Dutch ophthalmologist Jan van der Hoeve first reported on two twin girls who were deaf and had dystopia canthorum [2]. In this condition, the inner corners of the eyes are set farther apart than normal. In 1951, Petrus Johannes Waardenburg, another Dutch ophthalmologist and geneticist, formally defined and documented the syndrome as Type I [3]. It is worth noting that WS Type 2 (OMIM 193510) was first established in 1971 [3], while Type 2B (OMIM 600193) was in 1994 [4]. Type 2C (OMIM 606662) was set up in 2001 [5] and Type 2D (OMIM 60215) in 2002 [6]. However, since their inception, Types 2B, C, and D have not been reported [4-6]. WS type 2D with the SNAI2 deletion gene was reclassified in 2022 as a variant of unknown significance [7]. Only 23 cases of Type 2E (OMIM 611584) have been recorded between 1996 and 2016 [8-11]. Finally, type 2F (OMIM 619947) was first reported in 2017 [12]. There have only been 11 reported cases worldwide of WS type 2F [12,13]. It is essential to note that type 3 was initially described as an upper limb deformity by Klein and Opitz [14]. The comorbidity between Hirschsprung's disease and type 4 was first named in 1981 after being noticed in various studies during the 1970s [3] (Table 1). We report, here, a 15-year-old Saudi girl who is known to have bilateral deafness, skin pigmentation defect, type 1 diabetes mellitus (DM), with a history of delayed puberty, and short stature. She was classified as WS type 2 as she does not have dystopia canthoroum (Figure 1A) with no associated limb deformities or intestinal involvement.

Case Presentation

A Saudi girl, 15 years old, born full term, weighed 3.0 kg, had albinism at birth, passed the neonatal hearing test,

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Table 1. *Waardenburg syndrome types, genes affected, and the date it was discovered.*

WS Type	Year of discovery	Gene
Type 1	1951	*PAX3*
Type 2	1971	*MITF*
Type 2B	1994	*WS2B*
Type 2C	2001	*WS2C*
Type 2D	2002	*SNAI2*
Type 2E	1996	*SOX10*
Type 2F	2017	*KITLG*
Type 3	1947	*PAX3*
Type 4	1981	*EDNRB*

and received mixed feeding until she became 1 year old. The mother became aware of her baby's deafness when the child was around 6 months old; when the baby was sleeping peacefully despite loud construction work in the neighborhood, the mother sought medical advice at a private clinic and was referred to ear, nose, and throat service, where a hearing test was conducted. However, the child failed the test, which was conducted when she was 18 months of age (Figure 2). The delay between the discovery and reaching the tertiary care center service was due to missing the appointment once and the hierarchy referral system.

At around the age of 4 years, she was referred for cochlear implantation in her left ear. She underwent speech therapy sessions after the procedure. A right cochlear implant was

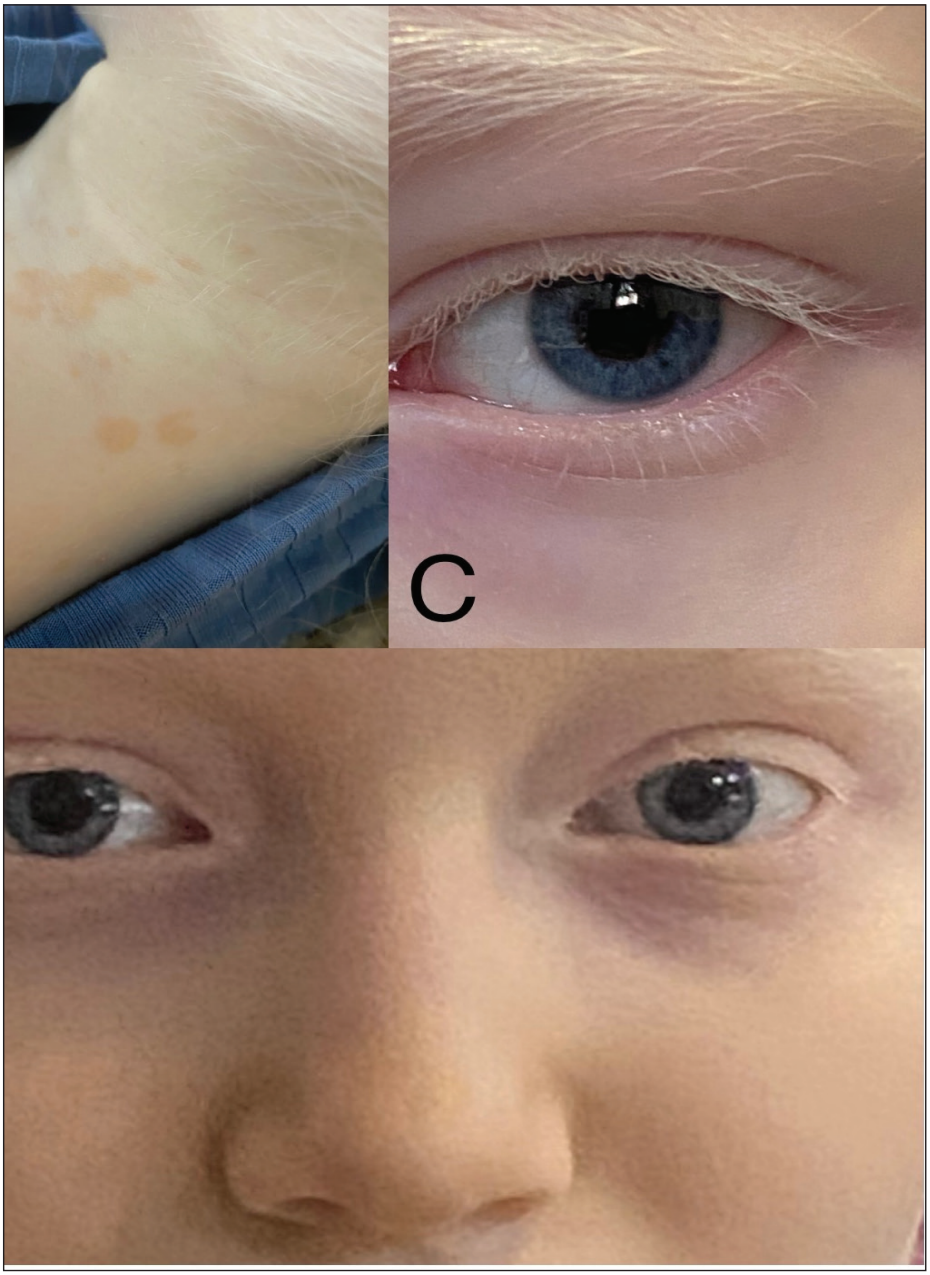

Figure 1. A*. The patient with no dystopia canthorum,* ***B.*** *Multiple small cafe aulit spots over the neck, and* ***C.*** *Gross picture showing the left eye, with loss of the pigment in hair, skin, and iris and coloboma.*

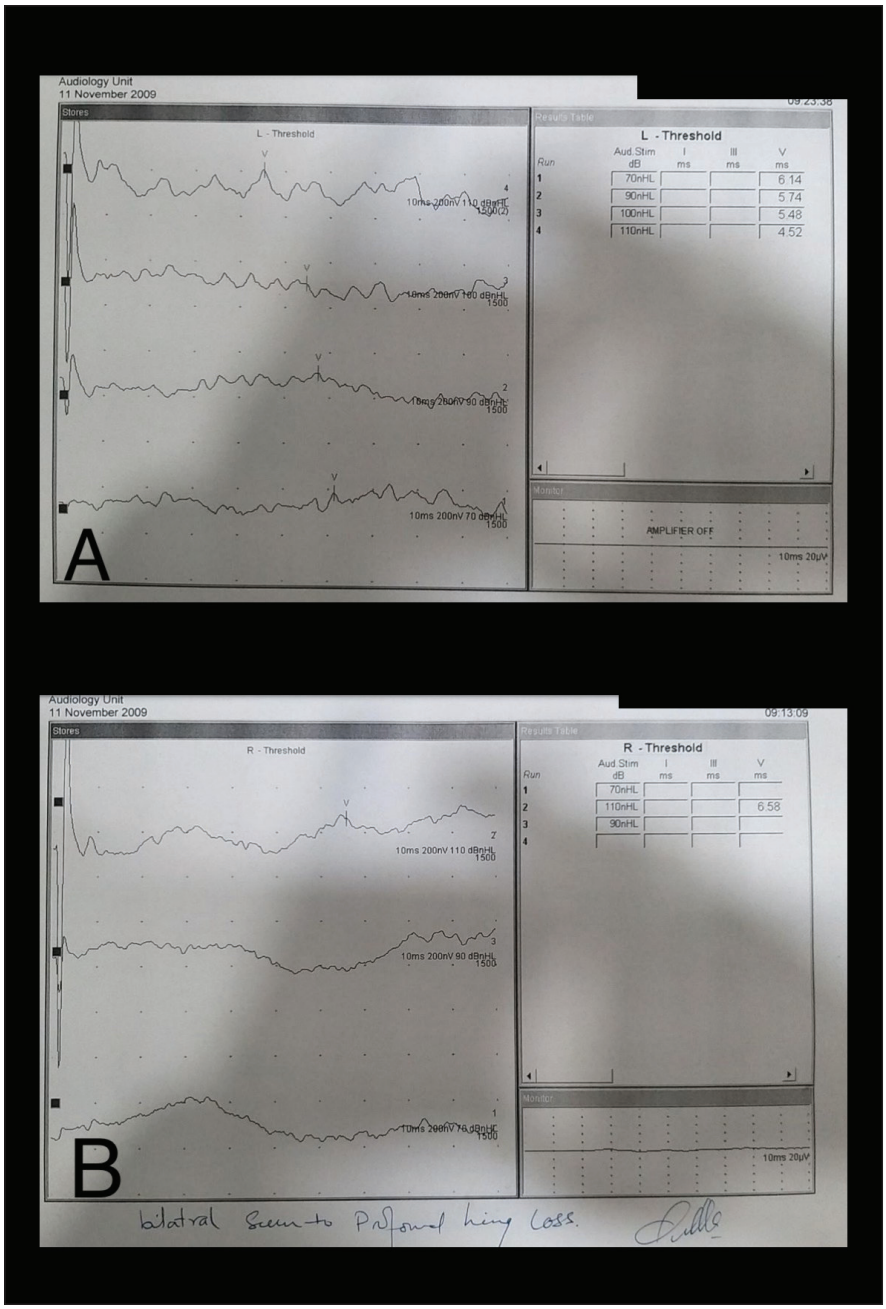

Figure 2. A. *Left ear auditory brain stem response test,* ***B.*** *Right ear auditory brain stem response test: both showing severe sensorineural hearing loss.*

placed 2 years later when she was around 6. By the time she turned seven, her speech and articulation had significantly improved, and she started attending school shortly thereafter. Furthermore, she was diagnosed with type 1 diabetes at the age of five and was admitted to the pediatric intensive care unit with mild diabetic ketoacidosis. She follows a multiple daily injections regimen, currently on Degludec and Aspart, with a total daily dose of 1 unit/kg/day and her average hemoglobin A1c is 8%.

At the age of 10, sporadic skin hyperpigmentation began appearing in various places on the forehead, neck, and back. Nearly still were identified as café au lait spots (Figure 1). At the age of 14 years, the mother noticed an absence of secondary sexual characteristics. There were no signs of developing celiac disease, thyroid abnormalities, or any other autoimmune disorders.

She was developmentally appropriate for her age with no delays, except for language in her early childhood, and is currently performing well in school, she is an A student, in the first grade of secondary school. She is sharing her family diet.

Her family background shows that she is the second surviving child of a fourth degree cousins' marriage. The mother is 34 years old and healthy, while the father is 42 years old with vitiligo. Having three healthy brothers, one of her brothers passed away from sudden infant death syndrome at the age of 2 months. Mother experienced

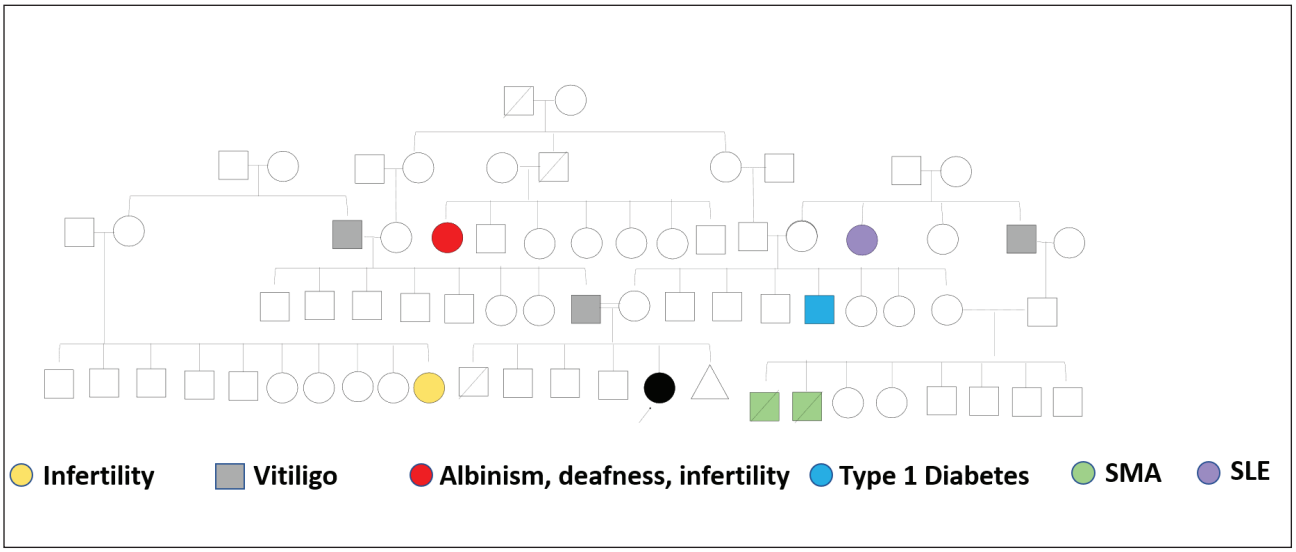

Figure 3. *Patient's family pedigree.*

one miscarriage in the first trimester (about eight weeks gestation) of unknown sex.

There is also a family history of albinism, deafness, infertility, and absence of vaginal opening. Specifically, a grandfather's first cousin has experienced these issues. Family history: Type 1 DM in the maternal uncle; vitiligo in the father and paternal grandfather. Infertility: a cousin of the father (the daughter of the father's ant); her mother's aunt has systemic lupus erythematosus; two maternal cousins died at the age of 1 year with spinal muscular atrophy (Figure 3).

Her general physical examination revealed a young girl with albinism, white hair, and blue iris (Figure 1) and tachycardia of 133 beats/minute. For growth parameters, according to the Center of Diseases Control and Prevention, Girls Growth Chart her height was 142 cm, below the 3rd centile, while her weight was on the 35th centile, her head circumference on the 65th centile, and her BMI of 20.28 kg/m^2 (Figure 4). Ophthalmologic examination showed coloboma bilaterally. Retinal examination shows a hypopigmented retina bilaterally (Figure 5). Cutaneous examination revealed a few café au lait spots over the neck and back, with irregular borders, on an albinism skin background. The largest, measuring about 3 by 4 cm, smallest measuring 0.5 by 0.5 cm, ranging between 10 and 12 spots in each place, well-circumscribed, light brown in color. No neck webbing and normal nipple distance. She is Tanner 1 for thelarche and Tanner 2 for pubarche. External genital examination showed normal labia majora and minora, small, atrophied opening of the vagina with a normal urethral opening.

Her laboratory investigations included high luteinizing hormone (LH) and Follicular stimulating hormone (FSH) with low estradiol, which is suggestive of hypergonadotropic hypogonadism. Her growth hormone GH stimulation test peak was 4.6 ng/ml, suggestive of GH deficiency and low Vitamin D level. Negative DM, thyroid, celiac, liver, gastric parietal cells, and skin antibodies. normal hemoglobin electrophoresis and Glucose 6 PhosphoDehydrogenase enzyme activity. Normal complete blood count, renal, liver, bone, and coagulation profiles. For lipid profile, she has a high level of high density lipoprotein (HDL) cholesterol, others are within normal limits, normal thyroid function test and Vitamin B 12 level, and no microalbuminuria (Table 2).

Her transabdominal pelvic ultrasonography showed a non-visualized uterus and agenesis in both ovaries. However, a magnetic resonance imaging (MRI) of the pelvis could not be performed due to the incompatibility of the MRI machine with the patient's cochlear implant. So computerized tomography (CT) scan was done and confirmed a non-visualized uterus with the absence of both ovaries (Figure 6).

Chromosomal analysis showed a normal female karyotype of 46 XX, with no structural abnormalities found in the examined sample band level. Interphase fluorescence *in situ* hybridization was performed, revealing that 99% of the cells have 2 X signals, while 1% of cells have one signal for the X chromosome. There is no evidence of the SRY gene. Whole exome sequencing (WES) was carried out in Centogene, revealing a homozygous variant of uncertain significance (Class III) in the *KITLG* gene. The genetic diagnosis of autosomal recessive (AR) WS Type 2F is possible. A segregation study of the parents was done and confirmed the same mutation presence. After parents' results, it was reclassified as likely pathogenic, class II. Her bone age was delayed, corresponding to 13 years, while her chronological age is 15 years and 4 months (Figure 7). Her chest X-ray and Echo were normal. Her electrocardiography (ECG) showed only sinus tachycardia (Figure 8). She is started on Cholecalciferol 5,000 IU/week and hormonal estrogen tab therapy was initiated. No known allergy.

Discussion

It is estimated that one in 40,000-42,000 people have WS [3,15]. A review of 417 reported patients in 2015 revealed that Type 1 accounted for 47%, Type 2 accounted for 33% (of whom Type 2 A was the most common, around 85% of them), Type 3 accounted for less than 2%, and

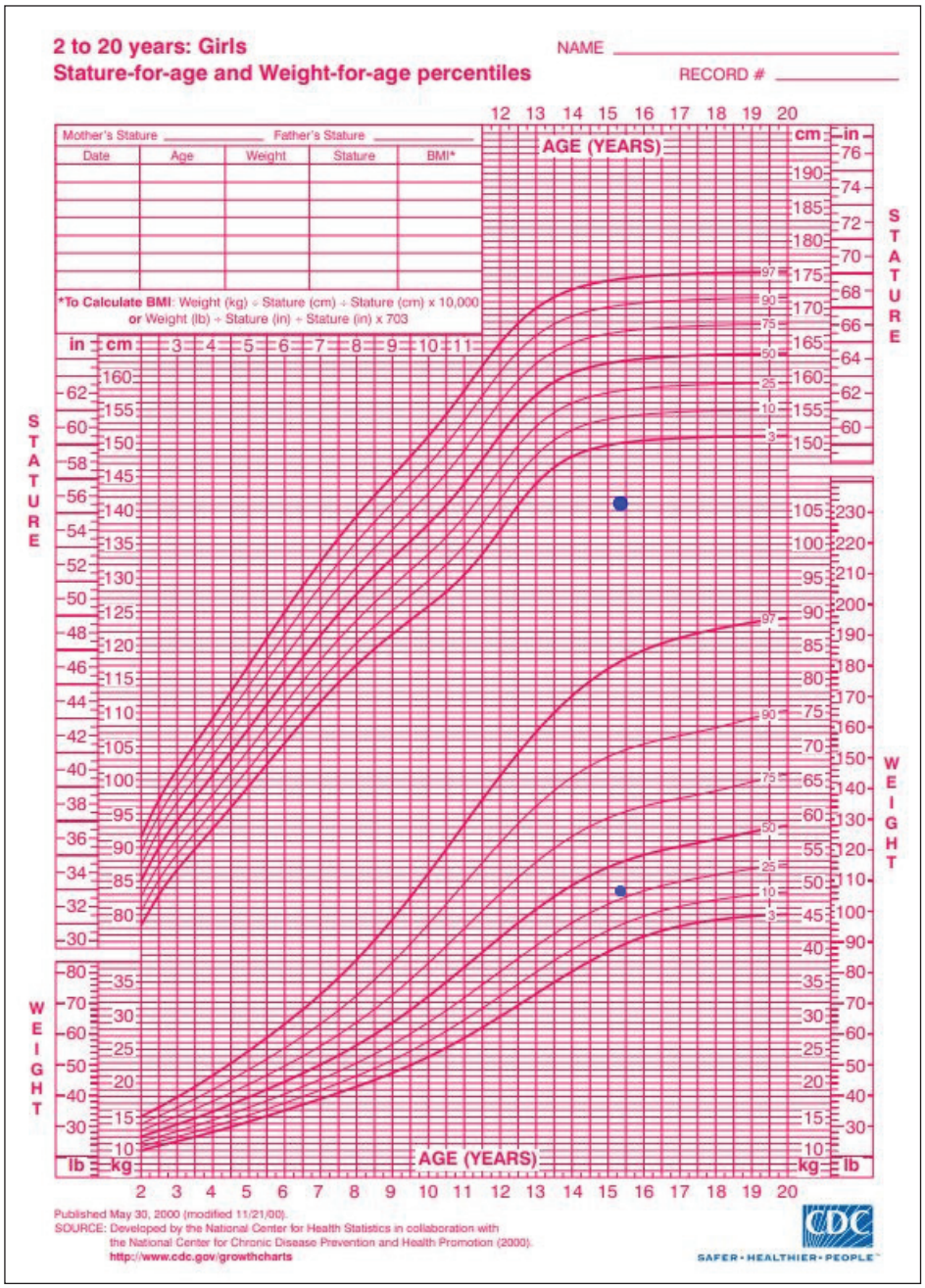

Figure 4. *Girls growth chart, showing her height < 3rd centile.*

Type 4 accounted for 19%12. WS represents 1%-3% to 2%-5% of the global population of people born deaf [11,15]. In school-age deaf students, it is found in about 1 in 30 cases [11]. Except for types 2 D and 2 F, which follow an AR inheritance pattern, it typically follows an autosomal dominant (AD) inheritance pattern. However, Types 3, 4A, and 4B could be either AD or AR. There have been a few reported cases with De Novo mutations [3,10,12,16,17] Cases of the WS have been documented globally in various regions, including North America (the United States and Canada), Europe (Romania, Italy, Holland, UK, France, and Germany), Asia (China, India, Japan, South Korea, Iran, and Turkey), Africa (Libya) and South America (Brazil). Most reported cases came from ophthalmologists, audiologists, dermatologists, or geneticists. For further details, please refer to references [11,15,18-23,13,12]. Although there have been few documented cases of WS2 in Saudi Arabia, Mullaney et al. [24] did report a 4-month-old Saudi girl with this condition. In 2019, Albarry et al. [25] reported 11 patients from one family with MITF gene mutation WS2. In 2021, AlGonaid et al. [26] reported on a 4-month-old infant with WS and neurofibromatosis type 1. The infant had an isolated right superior vena cava draining to the left atrium [24-27].

WS is a genetic disorder that can cause various physical abnormalities. These can include congenital sensory neural hearing loss (mostly associated with type 2), pigmentation deficiencies, heterochromia, a white forelock of hair, and a dystopia canthorum (telecanthus) (type 1). Other symptoms include abnormalities of the

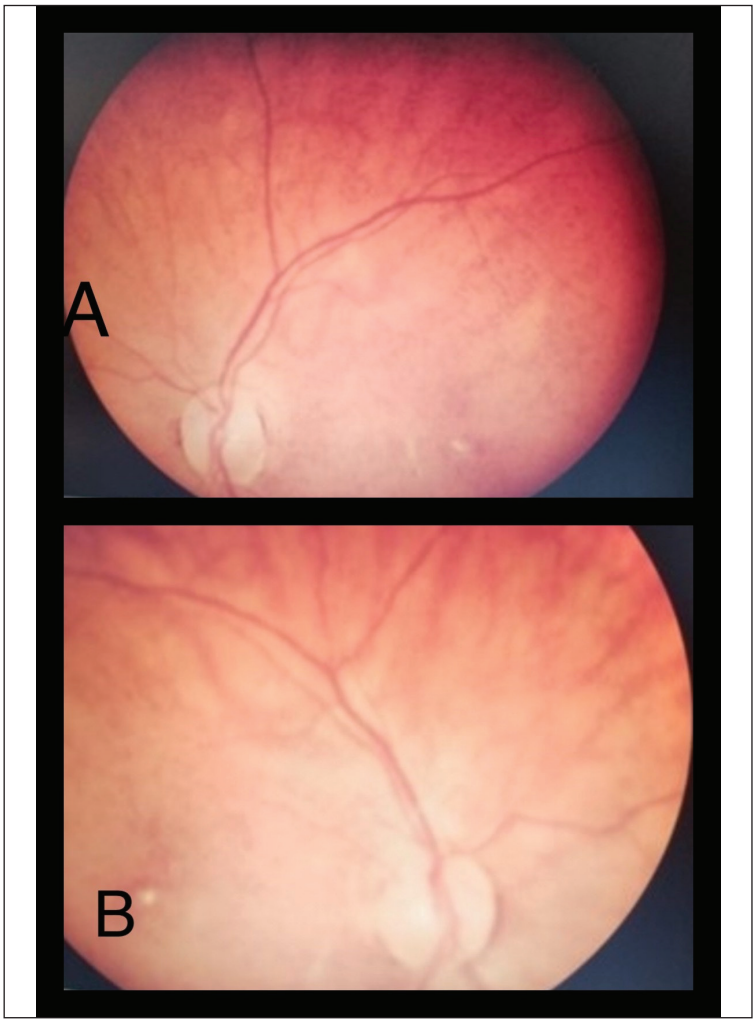

Figure 5. A. *Left hypopigmented retina.* ***B.*** *Right hypopigmented retina.*

Table 2. *Laboratory investigations results.*

Test	Result	Reference range
Hormones		
LH (Luteinizing hormone)	25.70 mIU/ml	0.1 - 13.4
FSH (Follicle stimulating Hormone)	87.4 mIU/ml	0.1 - 12
ESTRADIOL (E2)	5.0 pg/ml	20 - 87
GH stimulation test peak	4.6 ng/ml	10 - 50 ng/ml
Vit D	16.9 ng/ml	20 - 40
C-Peptide	0.06 ng/ml	1.1 - 4.4
DM Abs		
Anti Islet cells Abs	-ve	
Bone Profile		
Alk P	246 IU/l	33 - 115
Ca	2.5 mmol/l	2.2 - 2.65
Mg	0.78 mmol/l	0.73 - 1.06
Ph	1.5 mg/dl	0.81 - 1.45
Alb	41.6 g/l	34 - 50
Lipid profile		
Triglycerides	133 mg/dl	0 - 200
Cholesterol	198 mg/dl	50.27 - 243.6
HDL	80 mg/dl	35 - 60

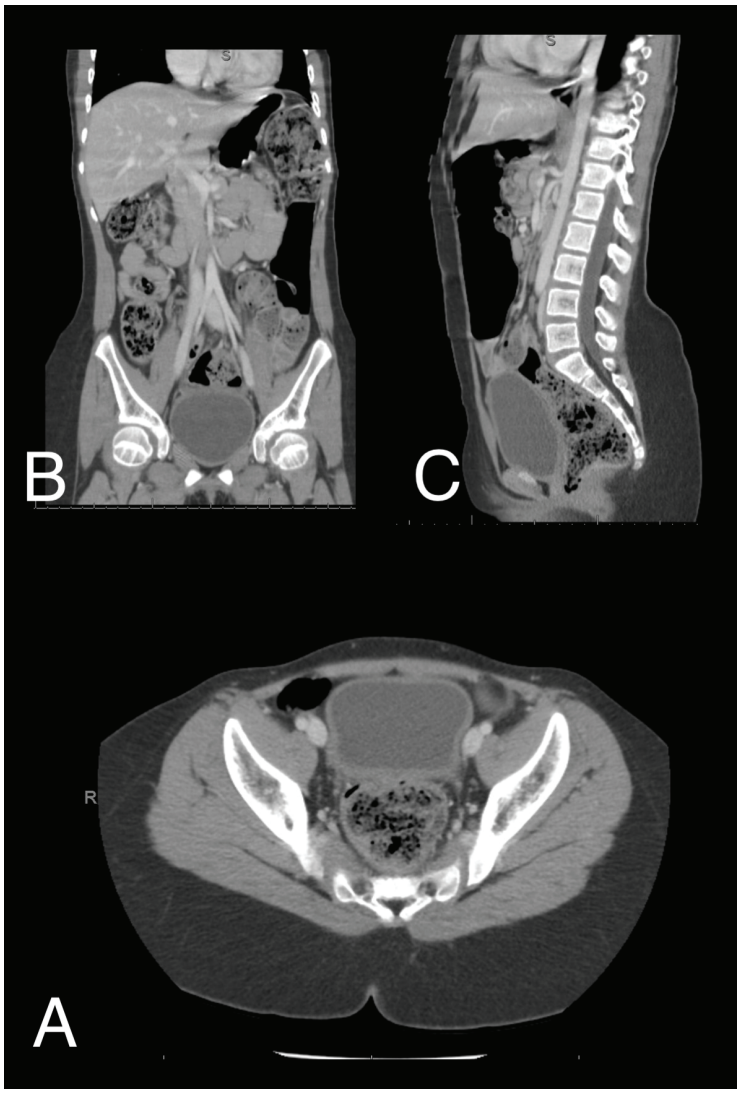

Figure 6. A. *Cross Sectional,* ***B.*** *Coronal, and* ***C.*** *Sagittal Sections, CT scan of the abdomen, showing absence of ovaries and uterus.*

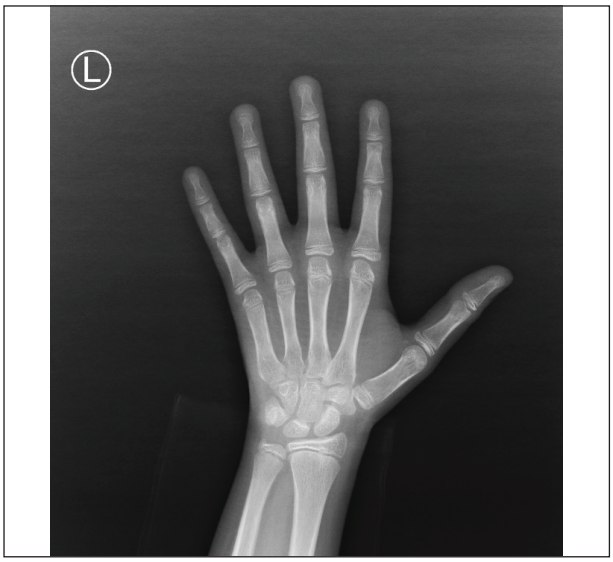

Figure 7. *Left wrist and hand X-ray, showing open epiphyseal plates, starting ossification of sesamoid bone, corresponding to bone age of 13 years. While chronological age of the patient at the time of the study corresponds to 15 years and 4 months.*

upper limbs, such as fused fingers or contractures and difficulty completely straightening joints (type 3), as well as Hirschsprung's disease or cleft lip (rare), and constipation (type 4). Central nervous system involvement like developmental delays, hypotonia, and ataxia in types 2E and 4C. Although they share the same gene mutation defect, what is peculiar to Type 2E is that it can also cause hypogonadotropic hypogonadism with anosmia "Kallman's Syndrome" and underdevelopment of the front of the eyes leading to blindness [3,8,9,15,16,28,29]. Specific characteristics have been observed in patients with Type 2 (coloboma), microphthalmia, osteopetrosis, macrocephaly, albinism, and deafness [3]. These may include nystagmus during early childhood, hypertonus, cerebral hypomyelination, or abnormalities in the white matter. Such individuals may also exhibit autistic behaviors and may have underdeveloped or absent inner ear structures, including the cochlea and vestibular system. Additionally, they may experience anosmia due to a missing olfactory bulb in the brain [15].

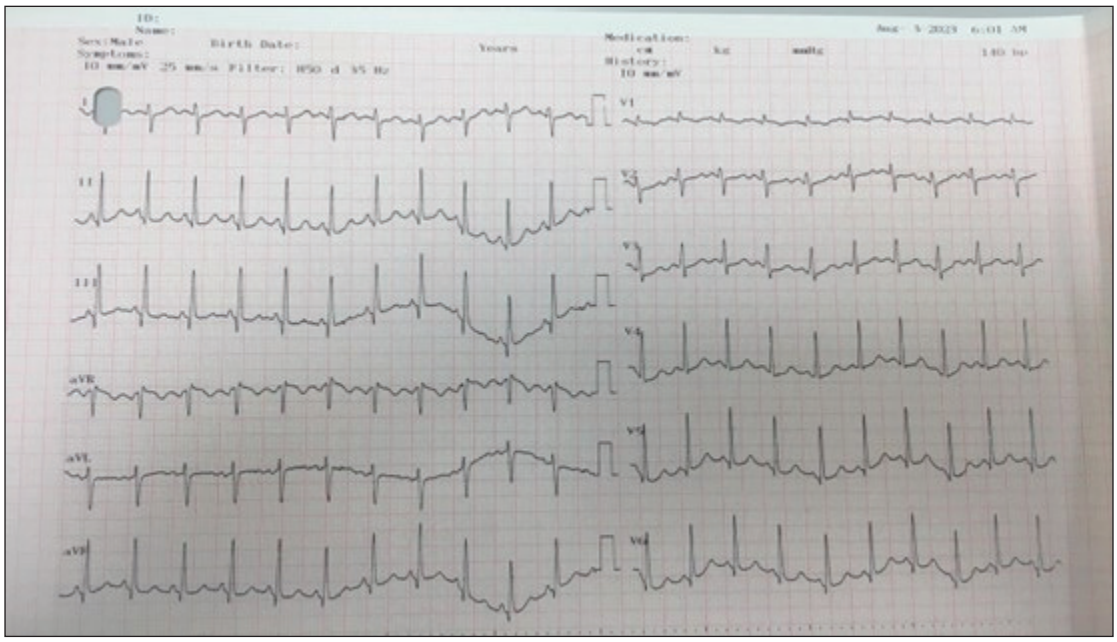

Figure 8. *ECG showing sinus tachycardia.*

WS Type 2 is an inherited disorder through AD genes. Unlike other types of WS, Type 2 is rare and does not involve dystopia canthorum. This condition can cause varying degrees of deafness and pigmentation anomalies in the hair, skin, and eyes [15]. It affects fewer than 1,000 people in the United States, with a prevalence of less than 1 in a million cases. Symptoms of Type 2 usually appear within the first 4 weeks of life, with 47% of cases showing heterochromia iridium and 77% showing sensorineural hearing loss [15]. WS type 2F (WS2F) may present with various symptoms, such as alterations in the skin, hair, and iris pigmentation, as well as sensorineural hearing loss that can occur at birth or during the neonatal period. Variable expressivity has been reported, even among patients with the same mutation. There have been only a few reported cases worldwide of WS type 2 F, with 11 cases only. The *KITLG* gene is the gene that is affected in WS2F and is found on chromosome 12q2113. The *KITLG* gene is vital for various biological processes, including melanogenesis, hematopoiesis, gametogenesis, mast cell formation, migration, and cell survival and proliferation [30]. Examples of differential diagnoses may include WS types 1 and 4, Tietz syndrome, and oculocutaneous albinism [15].

For our patient, autoimmune polyglandular syndrome, disorders of sexual differentiation, and Turner syndrome were kept in mind as well. She presented with multiple medical conditions, including congenital oculocutaneous albinism (pigmentation defect), with no heterochromia iridis nor white forelock as she had complete albinism. She had congenital sensory neural hearing loss, on bilateral cochlear implants. Although she passed the initial newborn hearing test, this could be a false negative result. She lacked dystopia canthorum, with no associated limb deformities or intestinal involvement, which highly suggests the clinical presentation of WS type 2. These suspicions were confirmed by the WES suggesting type 2F. The *KITLG* variant c.806_807del p. (Glu269Valfs*41), as in our case, is a novel mutation, never been reported before. For her distinctive presentation with Type 1 DM, short stature due to growth hormone deficiency, delayed puberty with hypergonadotropic hypogonadism, and absence of mullarian structures, these multiple endocrinopathies were not reported previously in association with WS2F. It might be classified as a new type of WS with this distinguished and unique presentation. In the current case, Polyendocrinopathy, diabetes was managed with insulin, short stature with growth hormone deficiency was managed with somatropin, and she was supplemented with estrogen tab to overcome the delayed appearance of the secondary sexual characteristics.

Conclusion

Our patient has been diagnosed with a rare syndrome that exhibits a range of distinct symptoms. Only 11 cases were reported worldwide from WS type 2F. All the patients have sensorineural hearing loss. This is the only case with albinism since birth, absent internal reproductive organs, type 1 DM, and short stature. It might be classified as a new type of WS with this distinguished and unique presentation. Consanguineous marriages might reveal hidden diseased genes. This condition requires multidisciplinary team management, including pediatricians, pediatric endocrinologists, geneticists, ENT physicians, speech therapists, ophthalmologist, psychologists, and dermatologists, to work in collaboration to provide the best patient care. The patient has been prescribed vitamin D, estrogen tab, and growth hormone to help address her condition. The patient improved after 6 months of treatment regarding height, now she is just below the 3rd centile, Z score improved from -3.5 to -2.25, improved as well regarding secondary sexual characteristics with Tanner two breast. Segregation studies done to parents revealed that they are carriers of the same affected gene. Parents were referred

for preimplantation genetic diagnosis PGD and siblings were for screening as well. We suggest classifying this presentation of WS as WS type 2G.

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Conflict of interest

The authors of this article have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Consent for publication

Informed consent was obtained from the patient and her primary caregiver, and all reasonable efforts were made to maintain patient confidentiality.

Ethical approval

The present study was approved by the Research and Ethics Committee at Maternity and Children Hospital, Al Ahsa, Saudi Arabia, with approval number 090324, dated: 12/03/2024.

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