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Novel Insights from Clinical Practice

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Blended Phenotypes of Sexual Development Disorder and Coenzyme Q10 Deficiency, Together with a Sibling with Homozygous Variants in the *AHI1* Gene

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Established Facts

- Phenotypes resulting from variants in exons 5–7 of the *COQ4* gene starting at an early age lead to neonatal death, and patients have a more severe clinical course. On the contrary, variants in exons 1–4 manifest later and patients have a milder clinical course.
- Consanguineous marriages frequently give rise to rare, blended phenotypes and the occurrence of multiple homozygous variants.

Novel Insights

- It is noteworthy that although the c.437T>G variant in the *COQ4* gene is located in exon 5, it causes milder clinical symptoms, unlike the cases reported in the literature.
- To the best of our knowledge, our patient represents the first reported case with a very rare blended phenotype of sexual development anomaly and primary CoQ10 deficiency.

Keywords
SRY · Sex development disorder · Hypotonia · Coenzyme Q10 · *COQ4*

Abstract
Introduction: In consanguineous marriages, different homozygous variants in a single gene may occur in the same family. This may lead to blended phenotypes. This study

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presents a family in which different rare mechanisms come together as a result of consanguineous marriage. Primary coenzyme Q10 deficiency is a very rare disease that occurs due to homozygous or compound heterozygous variants in the *COQ4* gene. ***Case Presentation:*** A 2-year-old proband with a blended phenotype with sex development disorder and coenzyme Q (CoQ) 10 deficiency has psychomotor retardation, dysmorphic findings, hypotonia, micropenis, and bilateral cryptorchidism. The patient's cytogenetic analysis results were compatible with *SRY*-positive 46,XX sex reversal disease. In the subsequent whole-exome analysis, a c.437T>G (Phe146Cys) missense homozygous probable pathogenic variant was detected in the 5th exon of the *COQ4* gene (NM_016035) that explains other clinical findings. The brother of the index was previously deceased due to hydrocephalus and had a nonsense homozygous variant c.1051C>T p.(Arg351*) in the 7th exon of the *AHI1* gene (NM_001134830). ***Discussion:*** Alterations in exons 5–7 of the COQ4 gene manifest early in life, resulting in neonatal fatality and a more pronounced clinical trajectory. Conversely, mutations occurring in exons 1–4 emerge later and exhibit a less severe clinical progression. Interestingly, the c.437T>G variant within exon 5 of the COQ4 gene induces comparatively milder clinical symptoms, deviating from the documented cases in the literature. To our knowledge, there is no other reported case in the literature with a blended phenotype of a sexual development anomaly and primary CoQ10 deficiency.

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Introduction

A collection of congenital diseases known as disorders of sex development (DSD) are linked to the aberrant development of the internal and external genitalia. De la Chapelle first reported 46,XX testicular DSD in 1964 [1]. About 80% of the patients diagnosed with 46,XX testicular DSD are positive for sex-determining region Y (*SRY*). The most significant gene linked to 46,XX testicular DSD is *SRY*, which codes for the SRY protein [2]. The *SRY* gene on the Y chromosome has a pivotal role in the encoding of testis-determining factor [3]. It has been suggested that nonallelic homologous recombination between the inverted pseudogene of protein kinase Y (*PRKY*) and the gene encoding protein kinase X (*PRKX*) may lead to this phenomenon [4]. The clinical findings in the *SRY*-positive 46,XX sex reversal (OMIM: #400045) include primary hypogonadism, small-soft testes, azoospermia, gynecomastia, seminiferous tubules without germ cells, and infertility [5].

Coenzyme Q (CoQ), also recognized as ubiquinone, functions as a lipophilic component within the electron transport chain. CoQ facilitates the transfer of electrons derived from flavin adenine dinucleotide (FADH2) and nicotinamide adenine dinucleotide + hydrogen to ubiquinone-cytochrome c reductase, also referred to as electron transport chain complex III. CoQ identified as a 1,4-benzoquinone exhibits a hydrophobic tail comprising 10 isoprenyl units in humans and therefore designated as CoQ10 [6]. Pathogenic variants in genes encoding proteins crucial to the biosynthesis of CoQ10 cause CoQ10 primary deficiency. Biallelic variants of the genes relevant to the synthesis of CoQ10 have been detected in *COQ2*, *COQ4*, *COQ5*, *COQ6*, *COQ7*, *COQ8A/ADCK3*, *COQ8B/ADCK4*, *COQ9*, *PDSS1*, and *PDSS2* [7]. *COQ4* is a nuclear gene located at 9q34.11 and is predominantly expressed on the matrix side of the inner mitochondrial membrane. It plays a pivotal role in the essential stabilization of a multi-heteromeric complex housing various CoQ10 biosynthetic enzymes [8]. The primary CoQ10 deficiency-7 (COQ10D7) results from biallelic pathogenic variants of the *COQ4* gene. COQ10D7 patients have phenotypic variability, including epileptic encephalopathy, regression of psychomotor development, hypertrophic cardiomyopathy, left ventricular hypoplasia, patent ductus arteriosus, ataxia, neonatal hypotonia, and retinopathy [6, 9–14]. Laboratory findings of primary COQ10D7 include hyperlactatemia, high glutaric acid and pyruvate levels, hyperammonemia, and/or hyperalaninemia. Neuroimaging findings include cerebellar hypoplasia, cerebral/cerebellar atrophy, cystic degeneration of the cerebellar hemispheres, stroke-like lesions with occipito-parietal localization, bilateral basal ganglia and thalamic lesions, and delayed myelination [15]. However, there are no specific clinical, laboratory, or neuroimaging findings specific to this disease and there is considerable overlap with findings in other mitochondrial disorders. Since CoQ10 treatment is an option in the management of this condition, early genetic diagnosis is of paramount importance [15, 16].

Given the clinical heterogeneity of *COQ4* deficiency, it is important to investigate larger patient cohorts to determine the prognosis of the disease and establish appropriate treatment strategies. To the best of our knowledge, this study presents the first case of COQ10D7 in a patient with *SRY*-positive 46,XX DSD.

Case Presentation

The 2-year-old patient was born at 39 weeks with an uneventful pregnancy to consanguineous parents who are first-degree cousins of each other. In the patient's

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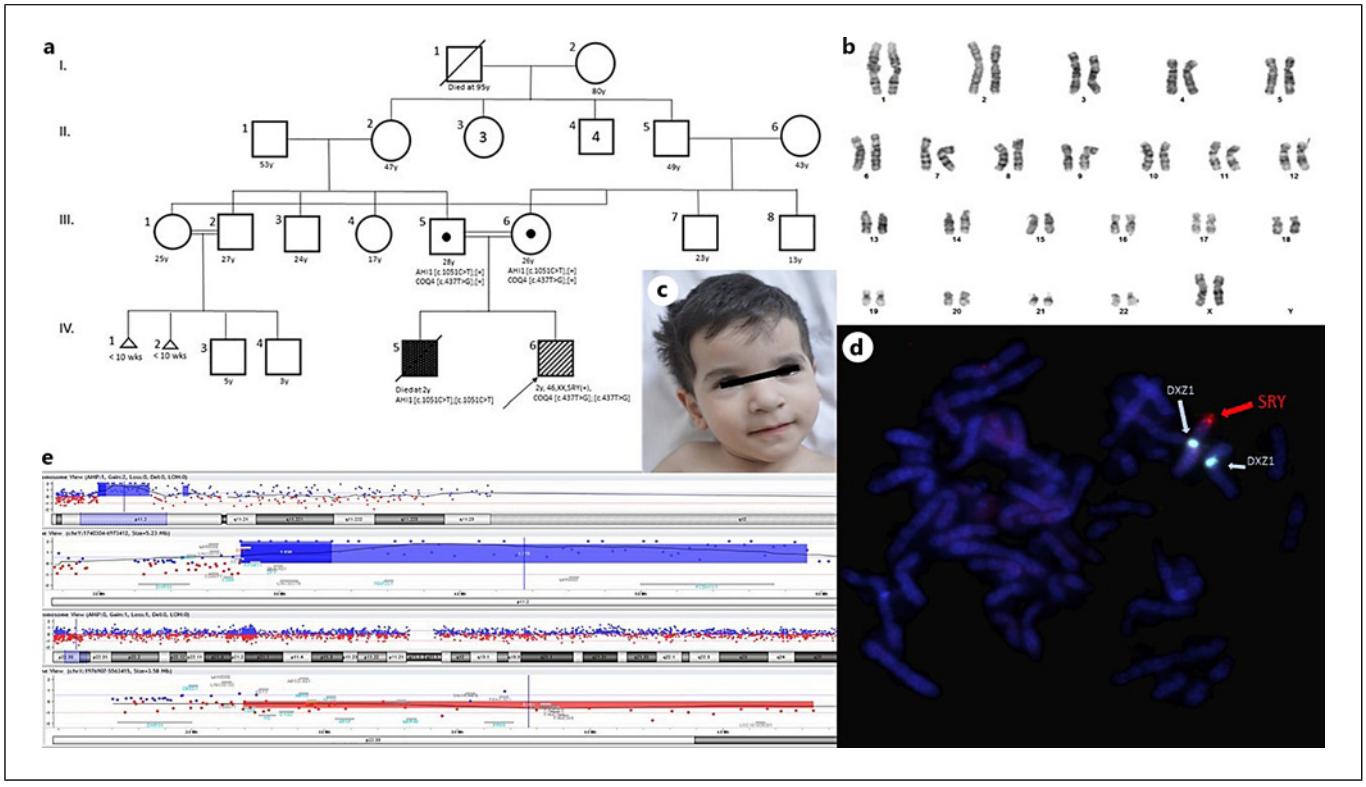


Fig. 1. a Pedigree of the family with variants in the *COQ4* and *AHI1* genes. The arrow indicates the proband. The genotypes of parents and affected family members are shown, and III-5 (father) and III-6 (mother) are carriers, having heterozygous genotypes for both variants. IV-5 is homozygous for *AHI1* c.1051C>T and was affected by Joubert syndrome 3. The proband (IV-6) is homozygous for *COQ4* c.437C>T and was affected by primary coenzyme Q10 deficiency-7. **b** Result of karyotype analysis: 46,XX. **c** Photographs of the patient showing strabismus, a bulbous nose, and a thin upper lip vermillion. **d** Fluorescence in situ hybridization (FISH) result: two copies of DXZ1 (blue) and one copy of *SRY* (red). **e** Chromosomal microarray results, using female DNA reference. The blue (including the *SRY* gene) and red rectangles that highlight the corresponding segments indicate the increased and decreased copy numbers, respectively.

clinical examination, dysmorphic features, micropenis, cryptorchidism, hypotonia, epilepsy, and growth and developmental delays were observed. The patient could not make eye contact and could not hold his head. The case had dysmorphic features such as strabismus, a bulbous nose, and thin upper lip vermillion (shown in Fig. 1). The patient's height was 80 cm (0.37 P), weight was 8.1 kg (<0.02 P), and head circumference was 45 cm (0.14 P). In the cranial magnetic resonance imaging, the frontotemporal peripheral cerebrospinal fluid distance was greater than expected for his age, and cerebellar atrophy findings were detected. MR spectroscopy showed deep reverse lactate peaks in measurements at the level of the basal ganglia and reduced clarity of the internal structure of the basal ganglia. In the electroencephalogram, the presence of high-amplitude sharp wave activities in the bilateral temporal, temporo-occipital, and parieto-occipital regions, with higher amplitudes especially in the right hemisphere, was detected. Serum lactate levels were elevated and were found to be 2.75 mM (normal [n.v.] 0.4–2.2 mM). Serum creatine kinase levels were normal and were found to be 121 U/L (n.v. 39–308 U/L). In the pelvic ultrasonographic examination, the left gonad was located in the distal part of the inguinal canal and had dimensions of 15 × 8 × 6.5 mm (0.4 cc), while the right gonad was located in the middle of the inguinal canal and had dimensions of 13 × 7 × 5 mm (0.25 cc). Bilateral gonads were observed in testicular appearance with a homogeneous parenchyma.

The result of cytogenetic analysis interpreted as 46,XX,ish,der(X)t(X;Y)(p22.3;p11.2)(SRY+). The chromosomal microarray showed a 2.1 Mb of deletion in the Xp22.33p22.32 region and an additional 3.1 Mb segment from the Yp11.2 region. The final karyotype was 46,-XX,ish,der(X)t(X;Y)(p22.3;p11.2)(SRY+),arr[GRCh38]

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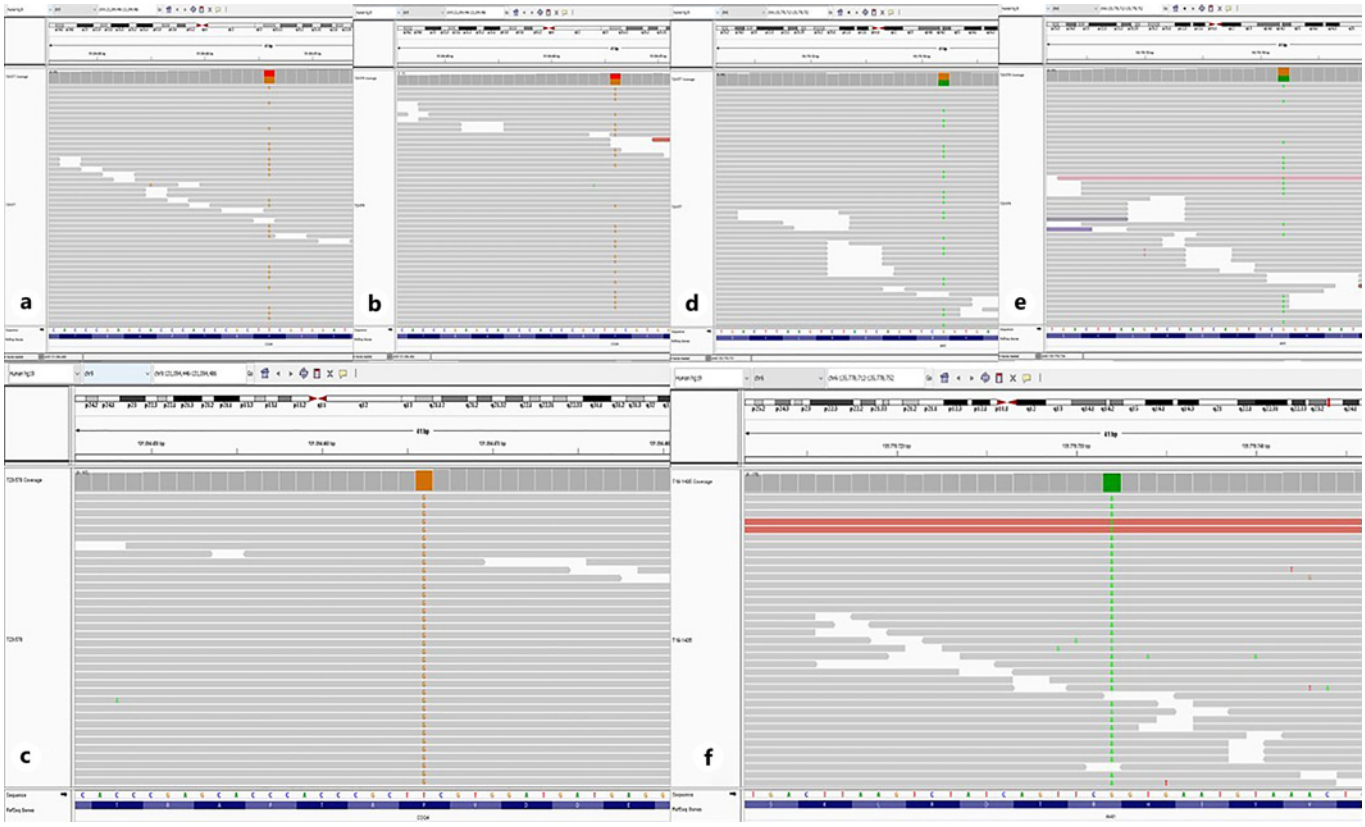


Fig. 2. a IGV (Integrative Genomics Viewer) image of the heterozygous c.437C>T variant in the mother's *COQ4* gene. **b** IGV image of the heterozygous c.437C>T variant in the father's *COQ4* gene. **c** IGV image of the homozygous c.437C>T variant in the patient's *COQ4* gene. **d** IGV image of the heterozygous c.1051C>T variant in the mother's *AHI1* gene. **e** IGV image of the heterozygous c.1051C>T variant in the father's *AHI1* gene. **f** IGV image of the homozygous c.1051C>T variant in the patient's brother *AHI1* gene.

Xp22.33p22.32(2694209-4846114)x1,Yp11.2(2786926-5926791)x1 (shown in Fig. 1). This alteration was associated with 46,XX Sex Reversal 1 disease (SRXX1, OMIM number: #400045) and explained the patient's cryptorchidism and micropenis findings. Karyotype analyses and chromosomal microarray studies of the parents showed no aberrations.

In the trio exome sequencing that was performed to investigate the patient's hypotonia, 21,589 genes were analyzed. In the proband, a missense homozygous variant c.437T>G, p.(Phe146Cys) was detected in the 5th exon of the *COQ4* gene (NM_016035) (shown in Fig. 2). According to the American College of Medical Genetics (ACMG) guide, this variant was classified as likely pathogenic [17]. This variant was identified as heterozygous in both the mother and the father during the family segregation analysis, indicating carrier status. The gene panel used in the previously deceased sibling did not include the *COQ4* gene. As the sibling was already deceased, segregation analysis for the *COQ4* gene could not be performed.

A 569-gene panel was studied in our clinic with the new generation sequencing method for the family's first child, who died at the age of 2 years due to respiratory distress and dehydration, diagnosed with Joubert syndrome. In the patient's brother, a nonsense homozygous variant c.1051C>T p.(Arg351*) was detected in the 7th exon of the transcript of the *AHI1* gene (NM_001134830) (shown in Fig. 2). According to the ACMG classification, this variant met PVS1, PM2, and PM3 criteria and was classified as a pathogenic variant [17]. This variant was identified as heterozygous in both the mother and the father during the family segregation analysis, indicating carrier status. However, this variant was not detected in the index case. Homozygous pathogenic variants in the *AHI1* gene cause Joubert syndrome 3 (OMIM number: #608629). The patient's brother had hypotonia, motor developmental

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delay, and epilepsy. His height was 81.5 cm (8 P), his weight was 9 kg (<3 P), and his head circumference was 46 cm (<3 P). In the cranial magnetic resonance imaging, molar tooth signs, cerebellar vermis hypoplasia, and Dandy-Walker malformation findings were detected. These findings were significant for Joubert syndrome. He died at the age of 2 years. The mother and father were carriers for two different variants detected in their children (shown in Fig. 1).

Materials and Methods

Karyotyping analysis was performed at the level of 400 bands by G-banding technique from lymphocyte cultures obtained by applying standard cytogenetic protocols from peripheral blood samples taken from the proband [18]. Fluorescence in situ hybridization was performed for proband using the CEPX(DXZ1), CEPY(DXY1), and the SRY probe (Aquarius® Microdeletion Syndrome probes, Cytocell Ltd., Cambridge, UK).

The DNA sample obtained from peripheral blood was studied using the Agilent GenetiSure Cyto 8 × 60K CGH (Agilent Technologies, Inc., Santa Clara, CA, USA). Microarray system, scanned on the Agilent SureScan Microarray Scanner (Agilent Technologies, Inc., Santa Clara, CA, USA), and the results were analyzed via the Agilent CytoGenomics version 5.2.1.4 (Agilent Technologies, Inc., Santa Clara, CA, USA).

The isolation of DNA from peripheral blood samples was conducted utilizing the MagNAPure LC DNA isolation kit (Roche Diagnostic GmbH, Mannheim, Germany) and the MagNAPure LC 2.0 device (Roche Diagnostic Ltd., Rotkreuz, Switzerland), following the manufacturer's recommendations. Quantification of DNA concentration and library enrichment procedures were executed using a Qubit® 3.0 Fluorometer (Invitrogen, Life Technologies Holdings Pte Ltd., Malaysia).

The assessment of library size distribution was conducted employing the Agilent 2100 Bioanalyzer (Agilent Technologies, Waldbronn, Germany). The library preparation and exome enrichment processes were conducted using the Whole-Exome Solution kit from SOPHiA GENETICS (Saint Sulpice, Switzerland). Subsequent DNA sequencing was performed on the Illumina Next-Seq 500 instrument (Illumina, Inc., San Diego, CA, USA). The bioinformatic analysis was created by Sophia DDM version 5.10.43, developed by SOPHiA GENETICS (Saint Sulpice, Switzerland).

Discussion

The homozygous pathogenic variant in the *COQ4* gene is related to primary CoQ10 deficiency 7 (OMIM number: #616276). Defects of CoQ10, which is a lipid component of the mitochondrial respiratory chain, may lead to hypotonia, decreased CoQ levels in muscle tissue, regression in psychomotor development, seizures, and increased serum lactate levels. It is generally lethal in the first years of life [11, 19]. In this respect, it is thought that the clinical findings of the proband will contribute to the literature with their milder course.

The gene variants in the *COQ4* gene are classified into two groups according to their clinical presentation. Variants in exons 1–4 provoke a later onset of disease, show a clinically milder course, and are responsive to CoQ10 treatment. Variants in exons 5–7 show an earlier onset of symptoms, have a more severe clinical course, lead to neonatal death, and are unresponsive to CoQ10 treatment [19]. Although the variant of the proband is in exon 5, its difference from the patient group in exons 5–7 is noteworthy because of its milder clinical manifestations. Another patient has been reported with mild clinical findings, as in our case, although he was in the exons 5–7 group. This patient also had the same variant as our proband [20]. The mild clinical presentation of these 2 patients suggests that this variant has a different clinical course than other variants in the exons 5–7.

The estimated incidence of 46,XX testicular DSD in newborn males is approximately 1 in 20,000 [21]. The number of patients reported in the literature with primary CoQ10 deficiency involving pathogenic variants in the *COQ4* gene is less than 50 [15, 22].

Consanguineous marriages may lead blended phenotypes due to the emergence of different homozygous variants in the same family [23]. This report adds to the body of literature by describing a family in which three different disorders occur simultaneously.

Genetic counseling plays a key role in consanguineous families. Families should be informed about the possibility of genetic diseases occurring in subsequent pregnancies and about preimplantation genetic testing to have healthy children.

To our knowledge, there is no other case in the literature reporting sex development disorder and primary COQ10 deficiency. This family, which included children with different genetic diseases as a result of consanguineous marriage, had a blended phenotype in which two extremely rare mechanisms coexisted.

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Statement of Ethics

This study was performed in accordance with the Declaration of Helsinki principles. Ethical approval was not required for this study in accordance with local/national guidelines. Written informed consent was obtained from the patients' parents for the publication of this case report and accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare. All coauthors have seen and agree with the contents of the manuscript and there is no financial interest to report. We certify that the submission is original work and is not under review at any other publication.

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Author Contributions

Rumeysa Atasay took the lead in writing the manuscript. Rumeysa Atasay and Leyla Nur Yılmaz examined the patient, designed, and planned the tests to be performed. They performed karyotype, fluorescence in situ hybridization, microarray, and new generation sequencing analysis and wrote the paper. Ayten Gulec, Mehmet Canpolat, and Huseyin Per performed a neurological examination and assessment of the patient. Fatih Kardas performed and assessed the patient for metabolic diseases. Bilge Ozsait Selcuk and Birsen Karaman assisted with the microarray analysis. Aslihan Kiraz and Munis Dundar provided critical feedback and helped to research, analyze, and shape the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this manuscript. Further inquiries can be directed to the corresponding author.

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