DOI: 10.4274/jcrpe.galenos.2025.2025-5-2

Case Report

A Case of CHARGE Syndrome with a Novel Intronic Variant in the *CHD7* Gene

Kaya E et al. Novel CHD7 Intronic Variant in CHARGE

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What is already known on this topic?
CHARGE syndrome is an autosomal dominant disorder. The characteristic findings of the syndrome include coloboma (C), heart anomalies (H), choanal atresia (A), growth and developmental delay (R), genitourinary system anomalies (G), and ear anomalies and/or hearing loss (E). The CHD7 gene is currently the only confirmed pathogenic gene associated with CHARGE syndrome and is known to be widely expressed in both embryonic and adult tissues. Although numerous pathogenic variants have been identified, intronic variations in CHD7 remain exceedingly rare.

What this study adds?
This study reports a novel heterozygous intronic variant (c.5050+2T>C) in intron 22 of the CHD7 gene in a patient with classical features of CHARGE syndrome. The identification of this rare variant highlights the clinical relevance of intronic mutations and contributes to the growing body of genetic data associated with the syndrome.

ABSTRACT
CHARGE syndrome is an autosomal dominant disorder caused by variations in the *CHD7* gene. The characteristic findings of the syndrome include coloboma (C), heart anomalies (H), choanal atresia (A), growth and developmental delay (R), genitourinary system anomalies (G), and ear anomalies and/or hearing loss (E). A 7.7-years-old male patient was initially referred after a partial empty sella appearance was noted on brain imaging during evaluation for developmental delay at 10 months of age. He had undergone surgery for choanal atresia and congenital heart disease. The patient exhibited severe postnatal growth retardation, hypertelorism, epicanthal folds, cleft palate, a thin upper lip, bilateral ear anomalies, preaxial polydactyly, and bilateral undescended testes. He had motor and mental developmental delay. Ophthalmologic examination showed retinal atrophy and coloboma. Genetic analysis identified a novel heterozygous c.5050+2T>C variant in intron 22 of the *CHD7* gene, confirming the diagnosis of CHARGE syndrome. Furthermore, the patient had undergone bilateral orchiopexy at two years of age, and growth hormone therapy was initiated after a diagnosis of complete growth hormone deficiency at 19 months of age. A novel heterozygous variant in the *CHD7* gene was identified in a patient, who presented with classical signs of CHARGE sydrome. Early recognition and diagnosis is important to enable initiation of timely treatment of potential complications associated with the disorder.
Keywords: Case report, CHARGE, intronic variant, growth hormone, syndrome

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11.05.2025
29.08.2025

Epub: 05.09.2025

Introduction
CHARGE syndrome, also known as Hall-Hittner syndrome, is a rare congenital developmental disorder. It was first described in 1979 (1). Subsequent reports have shown that the syndrome is characterized by coloboma, heart disease, choanal atresia, growth retardation, genital hypoplasia, ear anomalies, and/or deafness, leading to the name "CHARGE syndrome," derived from the abbreviation of these clinical findings (2,3). In 2004, a case of CHARGE syndrome associated with a variant in the chromodomain-helicase-DNA-binding protein 7 (*CHD7*) gene was reported (4). In recent years, variants in other genes, such as *SEMA3E* (*Semaphorin 3E*), *SEMA3A*, *EP300* (*Histone acetyltransferase p300*), *KMT2D* (*Lysine Methyltransferase 2D*), *KDM6A* (*Lysine Demethylase 6A*), and *PUF60* (*Poly(U) Binding Splicing Factor 60*), have also been identified in patients with CHARGE syndrome (5,6). However, variants in the *CHD7* gene remain the most common cause of CHARGE syndrome. Most cases result from sporadic *de novo* mutations, but the disease may rarely be inherited in an autosomal dominant manner (7).
Here, we present a case of CHARGE syndrome with a novel, heterozygous variant detected in the *CHD7* gene.

Case Report
A 7,7 years old male patient was initially referred to our clinic after a brain magnetic resonance imaging (MRI) scan, performed at the pediatric neurology department at ten months of age because of inability to hold his head up revealed a partial empty sella appearance. The patient was born at term with a weight of 2970g (-0.59SDS). He had previously undergone surgery for choanal atresia, atrial septal defect (ASD), and aortic coarctation. His parents were non-consanguineous, and his siblings were healthy. His paternal uncle had died in infancy due to congenital heart disease.
At initial presentation, his body weight was 5 kg (-4.86 SDS), height was 62 cm (-4.23 SDS), head circumference was 42.5 cm (-2.69 SDS), and BMI was 13.01kg/m2 (-3.3 SDS). Parental target height was 174.2 cm (-0.33 SD). Physical examination revealed hypertelorism, epicanthal folds, cleft palate, and a thin upper lip. He had bilaterally low-set, posteriorly rotated ears, with the left auricle being smaller and exhibiting a structural anomaly. Preaxial polydactyly was present in the right hand (Figures 1,2). The thyroid gland was non-palpable, penile length was 3.5 cm, bilateral testes were not palpable, and there was no pubic or axillary hair. Both his motor and mental development were delayed compared to his peers. Ophthalmologic examination revealed retinal atrophy and coloboma.
Laboratory findings included fT4: 1.15 ng/mL (0.94-1.44), TSH: 2.72 mIU/mL (0.33-8.6), FSH: 0.72 mIU/mL (1.5-33.4), LH: 0.02 mIU/mL (1.24-58.6), total testosterone: 3.75 ng/dL (2-7), prolactin: 7.8 ng/mL (2.1-17.7), IGF-1: <15 ng/mL (49-327), and IGFBP-3: 1.43 µg/mL.
The brain MRI report stated: "All ventricles are dilated, a partially empty sella is present, secondary to a suprasellar herniation, bilateral optic discs appear compressed, and strabismus is observed in the orbits."

A heterozygous sporadic novel *CHD7* variant, c.5050+2T>C (NM_017780.4) was detected in intron 22 of the *CHD7* gene by next-generation sequencing (NGS), performed using a Kallmann Syndrome Panel due to suspected CHARGE syndrome when he was 15.5 months old**.** This is a commercially available panel (Mikrogen Genetic Disorders Diagnosis Center: Çankaya Neighborhood, Cinnah Street, No:47/1, Çankaya/Ankara). The variant was confirmed by Sanger sequencing (Figure 3 A) . The Franklin Genoox database and the American College of Medical Genetics (ACMG) guidelines suggest this variant was *"likely pathogenic."* Segregation analysis was performed in the parents, and Sanger sequencing of the same gene region revealed that the variant identified in the case was not present in either parent (Figure 3 B,C).

At 11 months of age [weight: 5.2 kg (-4.5 SD); length: 63 cm (-4.06 SD)] malnutrition treatment was initiated and continued until 19 months of age. At 19 months, the patient's weight was 8.1 kg (-3.0 SD) and length was 72.5 cm (-3.1 SD), indicating a height gain of 9.5 cm over 8.3 months. The growth velocity SDS was calculated as +0.59 SD. Despite eight months of nutritional therapy, growth retardation persisted. At 19 months of age, L-DOPA and Clonidine growth hormone (GH) stimulation tests confirmed complete GH deficiency with an L-DOPA test GH peak response of 2.26 ng/mL and a clonidine test peak GH response of 4.2ng/mL. Subcutaneous somatropin therapy was initiated at a dose of 25 mcg/kg/day, with dosage adjustments based on follow-up. The patient underwent bilateral orchiopexy at two years and three months of age. He was also monitored for hypogonadism. During the first year of somatropin treatment, the patient showed a height gain of 13.2 cm/year. Over a total somatropin treatment period of 4 years and 4 months, the average annual height gain was 9.4 cm, with a total improvement of +1.51 SD in height SDS (-3,1 SD to -1,59 SD).

Due to issues with the supply of somatropin, treatment was switched at 7 years and 1 month of age to subcutaneous somatrogon at a dose of 0.66 mg/kg/week. Under somatrogon treatment, the patient grew 3.8 cm over 8 months, with only +0.03 SD increase in height SDS.

At the patient's most recent follow-up at 7 years and 9 months chronological age, height was 117.4 cm (-1.56 SD), body weight was 20.1 kg (-1.16 SD), and BMI was 14.58 (-0.96 SD). On physical examination, the thyroid was non-palpable, and pubertal development was consistent with Tanner stage 1. While on somatrogon treatment, IGF-1 was measured at 92.9 ng/mL (normal range 57-311 ng/mL).

Discussion

CHARGE syndrome is estimated to affect 1 in 10.000–15.000 newborns (4). Due to its heterogeneous clinical presentation, the diagnosis may often be missed or delayed (2). Despite presenting with all the major anomalies associated with CHARGE syndrome, our patient was only diagnosed genetically after he was 15.5 months old.

The most common ophthalmological finding in the syndrome is chorioretinal coloboma, and it is observed in 75–90% of cases (bilateral involvement in 70–80%) (8). Our patient exhibited bilateral choroidal coloboma accompanied by nystagmus.

Regarding ear anomalies, external ear malformations are observed in 95–100% of cases. The ears are typically cup-shaped, with lobular hypoplasia, and are often low-set and anteriorly rotated. In our case, the patient had bilaterally low-set, posteriorly rotated ears, with the left auricle being small and exhibiting structural anomalies. Inner ear abnormalities occur in 90% of cases and include features such as absence of semicircular canals and reduced cochlear turns (Mondini dysplasia) (3). In our patient, temporal bone CT revealed the absence of both lateral and posterior semicircular canals bilaterally. Early detection of hearing loss is important, as 60–90% of patients may experience some degree of deafness (8). Our patient was diagnosed with mild conductive hearing loss in the left ear and severe conductive hearing loss in the right ear, leading to the placement of bilateral hearing aids.

Intellectual disability is observed in 70% of patients with CHARGE syndrome, while central nervous system (CNS) abnormalities are reported in 55–85% of cases (9). Our patient exhibited mild to moderate intellectual disability. Brain MRI revealed dilation of all ventricles and a partial empty sella appearance. Other CNS anomalies seen in CHARGE syndrome include anosmia with olfactory bulb hypoplasia, facial palsy (50–90%), and involvement of the VIII, IX, X, and XI cranial nerves (10).

Genitourinary anomalies are observed in 50–70% of CHARGE syndrome patients. The most common findings in males are micropenis and cryptorchidism, while females may present with labial hypoplasia (9). Renal abnormalities are less common (10–40%) and may include ectopic kidneys, horseshoe kidney, and ureteral anomalies. Our patient did not exhibit any renal anomalies but underwent surgery for bilateral undescended testes.

Limb anomalies such as syndactyly, clinodactyly, camptodactyly, and polydactyly have been reported in CHARGE syndrome (11,12,13). In our case, preaxial polydactyly was present in the right hand.

Growth retardation is one of the distinguishing features of CHARGE syndrome. Although most children have a normal length at birth (14), postnatal linear growth failure is observed in up to 90% of cases, particularly within the first three years of life (15). As a result, average adult height typically remains at or below the 3rd percentile. In CHARGE syndrome, growth failure is generally attributed to feeding difficulties or renal, gastrointestinal, or cardiovascular anomalies. However, GH deficiency has also been diagnosed in some patients with CHARGE syndrome (16,17). In our case with confirmed GH deficiency, a height gain of 1.51 SD was achieved over a period of four years and four months with somatropin treatment. After switching to somatrogon therapy, an additional increase of 0.03 SD in height SDS was observed over eight months. There are reported cases of patients with CHARGE syndrome reaching their target final height with somatropin treatment (17). Ongoing studies are investigating the therapeutic indications of somatrogon in syndromic conditions. Long-acting GH therapy has been reported in cases with Turner syndrome, SGA, and idiopathic short stature. In these cases, it has been demonstrated that long-acting GH and daily GH therapy have similar efficacy (18,19,20). To the best of our knowledge, somatrogon use in CHARGE syndrome has not been previously reported. Our case offers only a limited contribution to the literature, as the duration of somatrogon treatment has been relatively short.

CHD7 haploinsufficiency accounts for 60–80% of CHARGE syndrome cases (21). In patients with CHARGE-like features and no identifiable CHD7 variant, extended genetic analysis has revealed pathogenic variants in other genes, including KMT2D, KDM6A, EP300, and PUF60. These variants are associated with overlapping phenotypic features such as coloboma, choanal atresia, and auricular malformations (22). SEMA3A contributes to the pathogenesis of Kallmann syndrome, which is characterized by hypogonadotropic hypogonadism and anosmia—both of which are also commonly observed in CHARGE syndrome (23). In a case carrying a de novo missense variant in SEMA3E, coloboma, choanal atresia, ear malformation, deafness, tetralogy of Fallot, developmental delay, and growth retardation were identified (24).

Heterozygous single-nucleotide variants predominantly affect protein function, with 44% nonsense, 34% frameshift, 11% splice site, and 8% missense mutations. Whole exon deletions or microdeletions in the 8q12.1 region, including the *CHD7* gene, account for less than 5% of cases (9,25)(Figure 4). Genetic analysis of our patient revealed a novel splice-site variant in the 22nd intron of the *CHD7* gene (c.5050+2T>C). In Turkey, Giray Bozkaya et al. identified three novel variations in the *CHD7* gene in two Turkish patients with CHARGE syndrome (one double point variation and one insertion) (26). In addition, Rossi et al. reported two unrelated cases with the same *CHD7* intron 27 variant, where both patients, similar to ours, exhibited absence of semicircular canals (27).

CHARGE syndrome exhibits a broad and heterogeneous clinical spectrum. Clinically, typical, partial, and atypical forms are classified based on major and minor diagnostic criteria. Although several studies have addressed this issue, a clear genotype–phenotype correlation has not yet been established (28,29). Truncating, nonsense, and frameshift loss-of-function variants have been more frequently associated with the CHARGE phenotype, whereas relatively hypomorphic missense alterations have been reported more commonly in isolated hypogonadotropic hypogonadism. However, this trend is not absolute (29, 30,31).In conclusion, a novel heterozygous intronic c.5050+2T>C variant in the *CHD7* gene was identified in our patient, who presented in infancy with choanal atresia, cardiac anomalies, coloboma, severe postnatal growth retardation, bilateral cryptorchidism, ear anomalies, and polydactyly. A total height gain of +1.54 SD was achieved with

treatment using somatropin and subsequently somatrogon, contributing to the current literature. Early diagnosis of CHARGE syndrome is important as it allows for the timely treatment and monitoring of potential complications related to the condition, as occurred in our patient. Moreover, providing appropriate genetic counseling for parents of affected children is also of importance.

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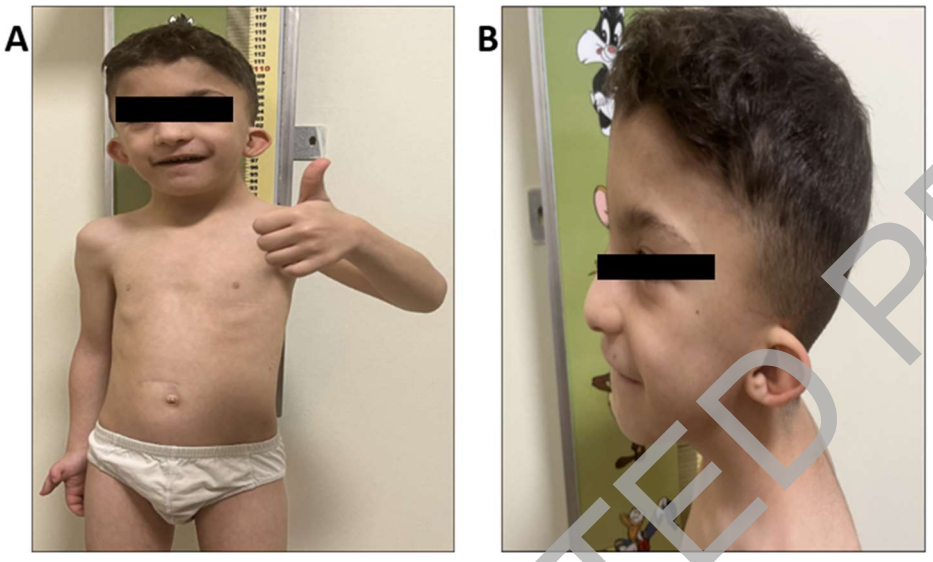

Figure 1. The patient's anterior (A) and lateral views including the head and neck region(B)

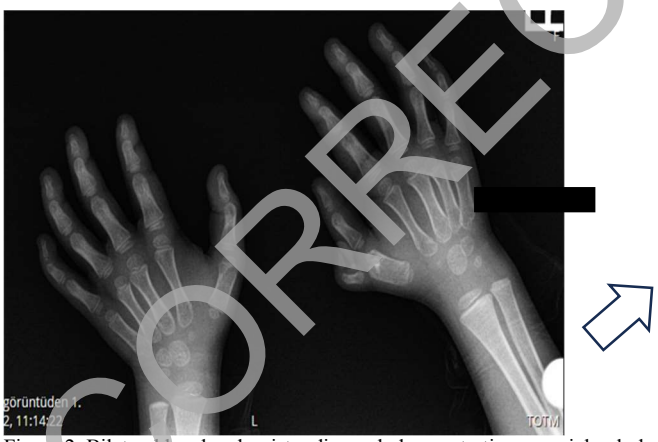

Figure 2. Bilateral hand and wrist radiograph demonstrating preaxial polydactyly of the right hand.

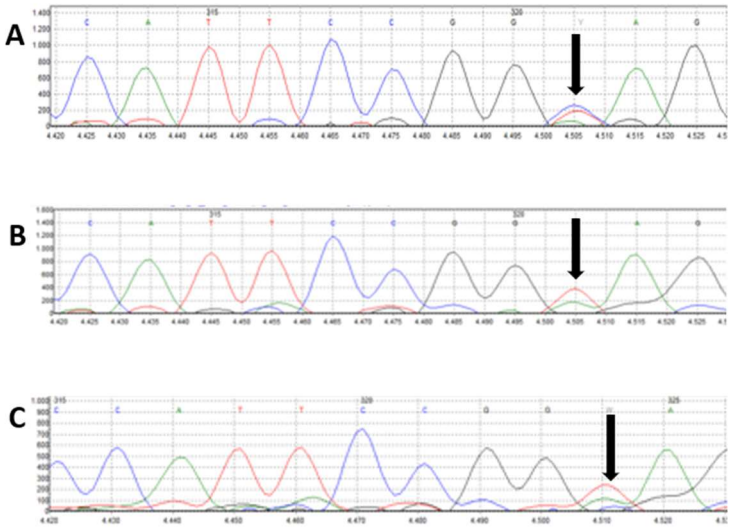

Figure 3: Sanger sequencing electropherogram showing the intron 22 region of the *CHD7* gene in the index (A), mother (B) and father (C).

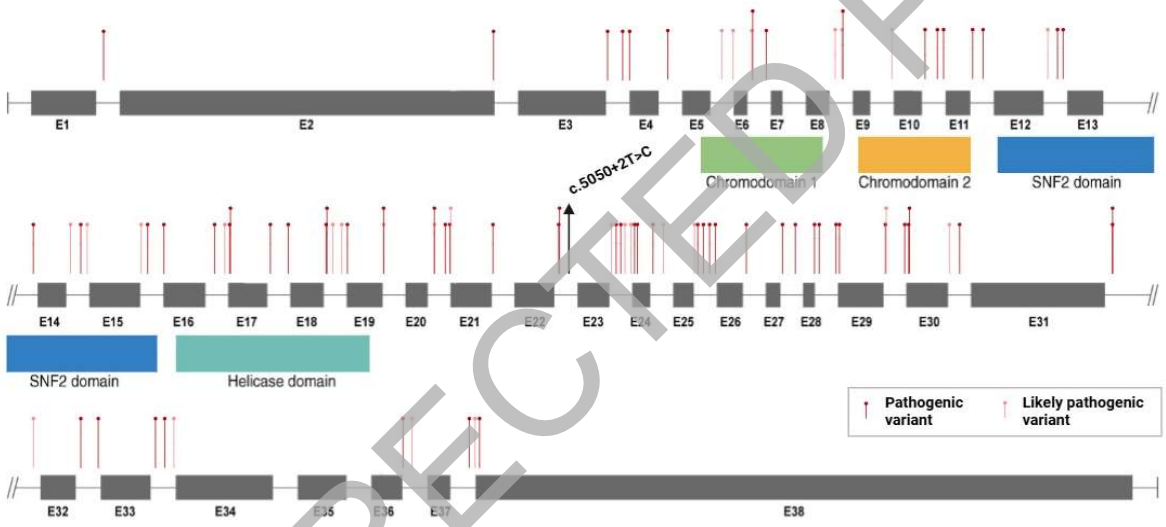

Figure 4. Schematic representation of intronic variant distribution in the CHD7 gene, based on Qin et al. (2020) and ClinVar, created with BioRender.com (25).