

## Novel *NR2F1* variant identified by whole-exome sequencing in a patient with Bosch–Boonstra–Schaaf optic atrophy syndrome

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Bosch–Boonstra–Schaaf optic atrophy syndrome (BBSOAS) is an extremely rare autosomal dominant disorder characterized by intellectual disability, developmental delay, seizures, hypotonia, hearing loss, and optic nerve atrophy. This syndrome is caused by loss-of-function variants in the nuclear receptor subfamily 2 group F member 1 (*NR2F1*) gene. To date, approximately 80 patients have been reported with BBSOAS. Here, we describe a 3-year-old infant with delayed development, intellectual disability, strabismus, nystagmus, and optic atrophy with well-characterized features associated with BBSOAS. Whole-exome sequencing revealed a novel heterozygous missense mutation (NM\_005654.6:c.437G>A, p.Cys146Tyr) in the *NR2F1* gene. This missense variant is predicted to be deleterious by the protein prediction tools (SIFT, PolyPhen-2, and

MutationTaster). To the best of our knowledge, this is the first patient with BBSOAS reported from Turkey.

**Key words:** Bosch–Boonstra–Schaaf Optic Atrophy Syndrome, developmental delay, *NR2F1*, optic atrophy, whole-exome sequencing

Bosch–Boonstra–Schaaf optic atrophy syndrome (BBSOAS; OMIM 615722) is an ultra-rare autosomal dominant disorder characterized by intellectual disability, neurodevelopmental delay, hypotonia, seizures, autism, nystagmus, strabismus, and optic nerve atrophy.<sup>[1]</sup> The patients have nonspecific dysmorphic features including protruding ears, small or high nasal bridge, epicanthus, upslanting palpebral fissures, and retrognathia. Pathogenic mutations in the nuclear receptor subfamily 2 group F member 1 (*NR2F1*) gene cause this disorder.<sup>[2,3]</sup> According to a latest literature search, about 80 cases have been reported previously.<sup>[4]</sup> Here, we report the case of a 3-year-old infant boy with BBSOAS presenting with delayed development, intellectual disability, strabismus, nystagmus, and bilateral optic nerve atrophy. Whole-exome sequencing revealed a *de novo* novel heterozygous missense mutation (c.437G>A; p.Cys146Tyr) in exon 1 of the *NR2F1* gene. We herein present the first Turkish patient with BBSOAS.

A 3-year-old boy was referred to our clinic for evaluation of developmental delay, intellectual disability, and hypotonia. He is the third born child of healthy consanguineous parents. The grandfathers were brothers. There was nothing remarkable in the family history. He was born by normal vaginal delivery at 39 weeks, after an uneventful pregnancy. The birth weight was 2.430 g (25<sup>th</sup>–50<sup>th</sup>), the birth length was 47 cm (25<sup>th</sup>–50<sup>th</sup>), and

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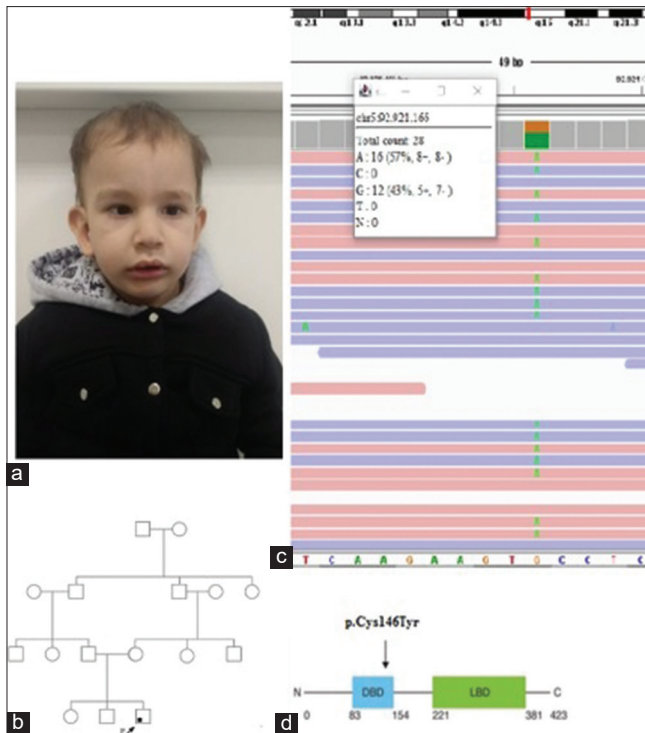
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**Figure 1:** (a) Proband's facial features. (b) The family's pedigree goes back to the third generation. The proband is indicated by an arrow. (c) The results of the whole-exome sequencing revealed a novel missense mutation in the *NR2F1* gene. (d) Protein structure of the *NR2F1* gene

the cranial circumference was 34 cm (25<sup>th</sup>–50<sup>th</sup>). On physical examination, he had a head circumference of 50.6 cm (percentile: 50<sup>th</sup>–75<sup>th</sup>). There were mild facial dysmorphic features, including a long face, a high anterior hairline, a broad forehead, large protruding ears, a short philtrum, and a high palate [Fig. 1]. His seizures started when he was 6 months old. He did not use any drug for seizures. Psychomotor development was delayed; he was able to support his head at about 11 months, sit without support at 14 months, stand up and stand still at 30 months, and was not able to walk unaided yet. He could not speak a single word. He could not stand up and stand still. He had normal deep tendon reflexes and a bilateral negative Babinski sign. Abdominal ultrasonography and echocardiograph were normal. The brain magnetic resonance imaging (MRI) and magnetic resonance spectroscopy were normal. He had normal electroencephalography (EEG). The blood lactate and creatinine kinase levels were unremarkable. His best-corrected visual acuity in both eyes was 20/100 at the time of his initial ophthalmological examination. There were no significant refractive errors discovered. Extraocular motility testing revealed both full duction and latent nystagmus. The results of the slit-lamp examination were normal, and a fundus examination indicated optic atrophy in both eyes as well as generalized loss of the retinal nerve fiber layer. In both eyes, spectral-domain optical coherence tomography revealed weakening of the retinal nerve fiber layer. The clinical findings of the patient are summarized in Table 1.

Karyotype analysis indicated a normal 46, XX karyotype. When the Agilent cytogenomic 5.0.0.38 (GRCH 37/hg 19) analysis program was used, there was no deletion or

**Table 1: The main clinical features of BBSOAS patients and the present case**

BBSOAS main features	Present case
Developmental delay	+
Intellectual disability	+
Visual impairment (optic nerve abnormalities, optic nerve atrophy or pallor, optic nerve hypoplasia, alacrima, nystagmus, significant refractive errors, amblyopia)	+
Hearing impairment	–
Hypotonia	+
Autism spectrum disorder	–
Seizures	+
Dysmorphic facial features	+
Thin corpus callosum and neocortical dysgyria	–

BBSOAS=Boonstra–Schaaf optic atrophy syndrome

duplication in the patient. The next-generation sequencing of the mitochondrial DNA genome was also normal. The Whole exome sequencing (WES) analysis showed a *de novo* novel heterozygous (NM\_005654.6: c.437G>A, p.Cys146Tyr) missense variant in the *NR2F1* gene. Variant analysis of the parents showed that they carried the normal (wild) allele. This variant was not observed in various population genomic databases (1000 Genome Project and Genome Aggregation Database). The c.437G>A variant was predicted to be deleterious by *in silico* prediction programs (SIFT, PolyPhen-2, MutationTaster, and Combined Annotation Dependent Depletion [CADD]). This variant was also considered “pathogenic” according to the guidelines of the American College of Medical Genetics and Genomics (ACMG). Informed consent was obtained from the parents of the proband.

## Discussion

To date, approximately 80 patients with BBSOAS have been published in the literature.<sup>[4]</sup> Monoallelic variants in the *NR2F1* gene can cause BBSOAS.<sup>[5]</sup> Functional studies showed that *NR2F1* is involved in neural development and differentiation, as well as in eye and optic nerve development in mouse models.<sup>[6]</sup> The NR2F1 protein has two highly conserved functional domains, such as the DNA-binding domain (DBD) and the ligand-binding domain (LBD).<sup>[5]</sup> Most of the reported *NR2F1* variants are usually localized in these regions and may lead to haploinsufficiency or predominant negative effects.<sup>[7]</sup> The identified variants of *NR2F1* in the BBSOAS patients included 61% missense, 14% nonsense, and 12% frameshift mutations.<sup>[8,9]</sup> Milder clinical features were found in patients with gene mutations in the LBD, and therefore, a possible genotype–phenotype correlation has been proposed for BBSOAS.<sup>[9]</sup> Although the phenotypic spectrum varies in patients affected by BBSOAS, this sometimes complicates the diagnostic evaluation, but ophthalmologic involvement is an important feature of this disease.<sup>[10]</sup> Here, we report a novel missense mutation in the *NR2F1* DBD (c.437G>A; p.Cys146Tyr) identified in an infant boy with developmental delay, intellectual disability, hypotonia, nystagmus, strabismus, and optic nerve atrophy. The missense mutation, c.437G>A, leading to an amino acid substitution of cysteine with tyrosine at codon position 146 (p.Cys146Tyr), was revealed to be within exon 1 of the

*NR2F1* gene. This mutation, which was discovered using whole-exome sequencing in our patient, appears to be a new mutation that has not been previously reported in the literature. The variant was predicted as deleterious by in silico tools such as CADD (score 32), MutationTaster, SIFT, and PROVEAN. Severe phenotypic findings such as developmental delay, intellectual disability, hypotonia, strabismus, and optic nerve atrophy in our patient seem to be compatible with the genotype–phenotype correlation suggested for missense variants affecting DBD. Considering the patient’s phenotypic findings, this genetic diagnosis was compatible with the patient’s symptoms.

Patients with BBSOAS may also manifest seizures, autism, attention deficit hyperactivity disorder, congenital hearing deficits, and hypoplasia of the corpus callosum.<sup>[11]</sup> Our patient did not have a history of hearing loss, and the brain MRI did not reveal any abnormal finding. Various mild dysmorphic findings have been described in BBSOAS patients, but no common feature has yet been identified. The craniofacial features of the proband were nonspecific, and the examination revealed a long face, a broad forehead, large protruding ears, and retrognathia. Ophthalmological abnormalities of patients with BBSOAS include various optic disk abnormalities, such as pale disks, small and large disks, visual field defects, and optic nerve atrophy.<sup>[5,8]</sup> The main causes of optic nerve atrophy include hypoxia, ischemia, trauma, tumors, infection, mitochondrialopathy, and inherited genetic disorders.<sup>[12,13]</sup> Periventricular leukomalacia and hypoxic ischemic encephalopathy are other important causes of optic atrophy in newborns.<sup>[14–16]</sup> Optic atrophies due to genetic causes such as BBSOAS should be investigated in patients without such a medical history and without an identifiable cause of perinatal complication.

In conclusion, BBSOAS is an autosomal dominant, rare genetic disease characterized by developmental delay, intellectual disability, and optic atrophy. It is caused by loss-of-function variants in *NR2F1*.<sup>[2,5]</sup> Here, we identified a novel missense mutation, c.437G>A, in the *NR2F1* gene as a cause of BBSOAS. To the best of our knowledge, this is the first Turkish case report with BBSOAS and *NR2F1* gene mutation.

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#### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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#### Conflicts of interest

There are no conflicts of interest.

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