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CASE REPORT

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# Imagawa-Matsumoto Syndrome: The First Case From Turkey

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## ABSTRACT

Imagawa-Matsumoto syndrome (IMMAS; MIM #618786) is an autosomal dominant syndrome characterized by overgrowth, dysmorphic features, musculoskeletal abnormalities, developmental delay, and intellectual disability. The first case was reported in 2017 and has subsequently been diagnosed in only another 12 patients. We also present the first IMMAS patient from Turkey. A 19-year-old female was admitted to the neurology outpatient clinic due to a behavioral disorder and intellectual disability. Her physical examination revealed macrocephaly and dysmorphic features like a round face, broad forehead, hypertelorism, and variable skeletal anomalies such as flat feet, clinodactyly, and macrocephaly. Cranial magnetic resonance imaging (MRI) showed agenesis of the corpus callosum and polymicrogyria. Chromosomal analysis results were consistent with a normal constitutional female karyotype and microarray analysis showed a de novo 1.5-MB size deletion on the long arm of chromosome 17; band q11.2 encompassing the Polycomb Repressive Complex 2 Subunit (SUZ12 gene, MIM *606245). This report will contribute to the limited information in the literature.

**Keywords:** Behavioral disorder, Imagawa-Matsumoto syndrome, intellectual disability, macrocephaly, SUZ12

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## INTRODUCTION

Imagawa-Matsumoto syndrome (IMMAS; MIM #618786) is characterized by overgrowth, development delay, intellectual disability, and dysmorphic features. Imagawa et al. were the first to report such a case with mutation in the *SUZ12* (Polycomb Repressive Complex 2 Subunit; MIM *606245) gene –an 11-year-old female (with a dizygotic twin) born to non-consanguineous Japanese parents, that had postnatal overgrowth, intellectual disability, such dysmorphic features as hypertelorism, downward-slanting palpebral fissures, and a prominent forehead, musculoskeletal and structural brain anomalies, in 2017 (1). These findings were initially interpreted as Weaver syndrome (WS; MIM #277590), which is characterized by prenatal or postnatal overgrowth, accelerated osseous maturation, cranial dysmorphism, intellectual impairment, and limb anomalies; however, the patient did not fulfil all the criteria for WS due to the absence of retrognathia, and hoarse and/or low-pitched crying. As such, the patient was diagnosed as 'Weaver-like' syndrome. Subsequently, in 2018, two new patients from unrelated families were described with postnatal overgrowth and development delay, and novel *SUZ12* mutations as Weaver-like syndrome by the same group, the clinical characteristics of these patients were very similar to the first reported patient (2). In 2019, Cyrus et al. reported another 10 patients with an overgrowth phenotype, physical abnormalities, delayed developmental stages, and rare heterozygous *SUZ12* variants (3). Considering these ten patients in addition to the previous three patients, the clinical framework of pathogenic *SUZ12* variants has settled, which mostly causes overgrowth, distinctive facial features, limb anomalies, and intellectual disability. It later began to be called 'Imagawa-Matsumoto syndrome'.

### Highlights

- **Imagawa-Matsumoto syndrome (IMMAS) was first described by Imagawa et al. in 2017.**
- **Imagawa-Matsumoto syndrome has been described in only 13 patients to date.**
- **The first IMMAS case from Turkey is reported.**

Imagawa-Matsumoto syndrome is caused by a heterozygous mutation in the *SUZ12* gene on chromosome 17q11. The transmission pattern of IMMAS is defined as autosomal dominant inheritance because the first described patient's father had a mosaic mutation and mild signs of the syndrome; however, subsequent reports have also shown that *SUZ12* variants can appear *de novo* (3). Autosomal dominant inheritance is a genetic condition passed from parent to child and usually affects every generation. Based on clinical genetic data, it is well known that *de novo* cases of autosomal dominant conditions are not rare due to the 'new mutation' concept, as seen in the presented case. Many severe early-onset dominantly inherited genetic disorders occur because of a spontaneous *de novo* mutation that occurs either during the formation of the gamete or post-zygotically (4). Mistakes during DNA replication, mismatch repair (MMR) pathway defects, and exogenous or endogenous mutagens can lead to *de novo* mutations (4). Furthermore, new mutations continue to occur in somatic and germ cells throughout life, from birth to death. According to traditional inheritance principles, a novel mutation

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is predicted to be passed down to future generations, but its persistence is dependent on the fitness of the carriers (5). *De novo* mutations explain as to why these reproductively fatal disorders continue to occur in the population (4). Consequently, the pathogenic SUZ12 variant that causes IMMAS can occur *de novo* and be inherited.

## CASE

A 19-year-old female presented to our neurology outpatient clinic with a history of intellectual disability and behavioral disorder since childhood. The patient has non-consanguineous Turkish parents and was born via spontaneous vaginal delivery after an uneventful full-term pregnancy. She had a low birth weight (<2500 g, <3 percentile) and was hospitalized in the newborn intensive care unit for 2 months due to neonatal pneumonia. The parents reported a history of mild motor developmental delay; the patient was able to sit at age 12 months and walk at age 2 years. Notably, her development of speech and language skills was delayed; her first word was pronounced at the age of 3. At the age of 6, the parents first applied to Child and Adolescent Psychiatry due to atypical behaviors, including social interactions and communication skills deficiency, but they did not follow up afterward. At age 7 years the patient started school with her peers but could only continue for 2 years due to behavioral problems. Subsequently, she transferred to a special education school, which she has attended since. Nonetheless, her behavioral problems progressed to anger and physical aggression in the following years.

Upon physical examination, the first remarkable feature was a dysmorphic phenotype, including a prominent forehead, round face, broad nasal ridge, and macrocephaly. The patient's head circumference was 58 cm (+2 SD), while her weight and height were within the normal range. Musculoskeletal system assessment showed flat feet, large hands, camptodactyly, and clinodactyly. Her neurological examination was normal, except for cognitive impairment. Cardiovascular and respiratory inspections are normal, but a detailed assessment could not be performed because the patient did not accept them. In the genitourinary system examination, it was learned that she had irregular menstrual periods. She applied to the gynecologist with this symptom; subsequent suprapubic pelvic and urinary ultrasonography (USG) performed by a gynecologist revealed an ectopically located left kidney in the pelvis, which also had a rotation anomaly.

Routine blood tests were within normal limits. Cranial magnetic resonance imaging (MRI) showed agenesis of the corpus callosum and polymicrogyria (Figure 1; MRI imaging of the patient's structural brain abnormalities), which was followed by chromosomal analysis as the patient showed an intellectual disability, developmental delay, structural brain anomalies, and dysmorphic features. Chromosomal analysis results were consistent with a normal constitutional female karyotype. Chromosomal micro-array was the next step of the genetic testing algorithm and showed a copy number loss (1 copy) of 1.5 MB (195 markers) size deletion on the long arm of chromosome 17; band q11.2 encompassing the *SUZ12* gene (Figure 2). The deletion was reported *de novo* because the change in the index could not be detected in the parents. Our patient had on deletion of 1.5 MB size in the *SUZ12* gene region which is rare and was previously reported in only one other patient. Written informed consent was obtained from the patient.

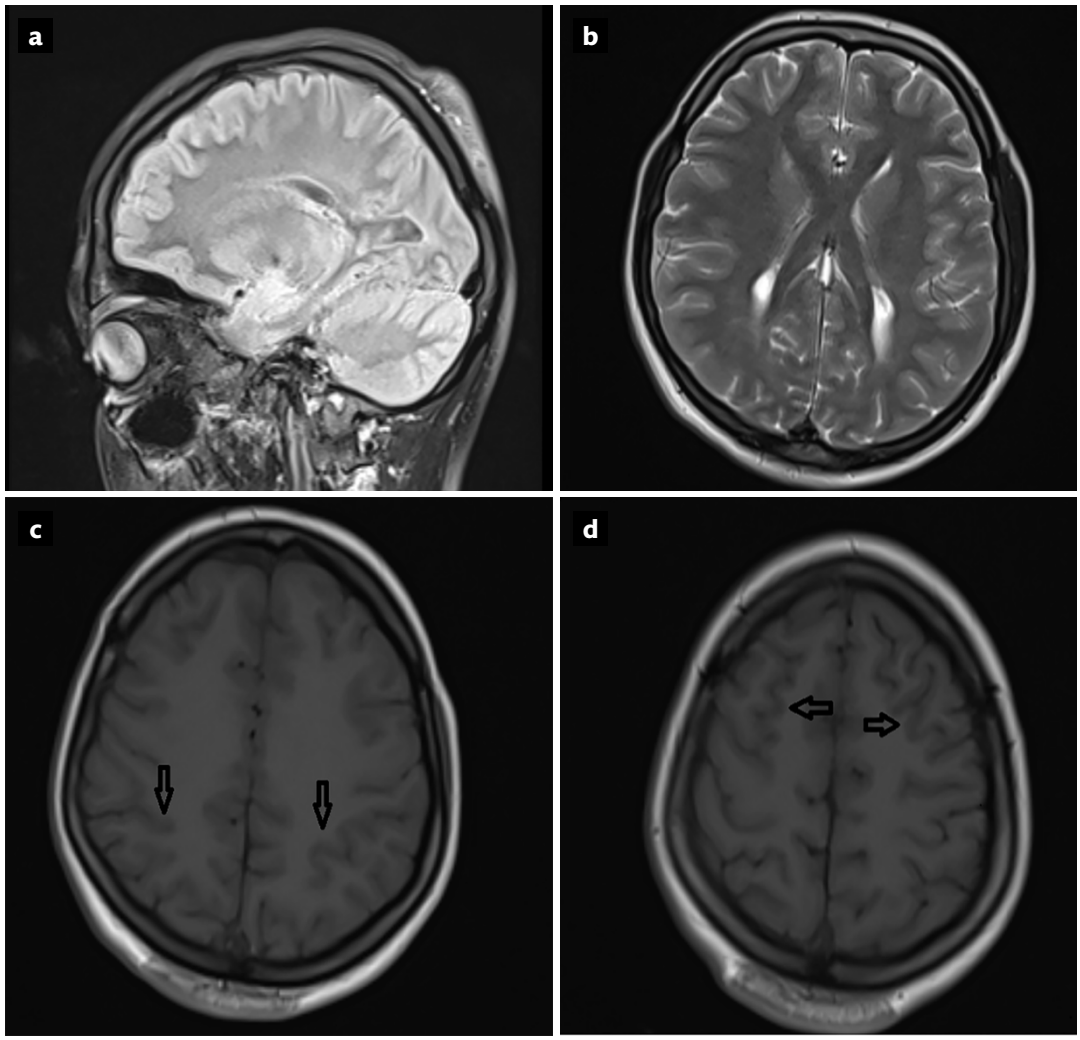


**Figure 1.** MRI imaging of the patient's structural brain abnormalities.

**a–d.** MRI imaging demonstrated at sagittal **(a)** and axial **(b)** fluid attenuation inversion recovery (FLAIR) sequence agenesis of the corpus callosum and axial **(c, d)** T1-weighted (T1W) sequence bilaterally frontotemporoparietal polymicrogyria.

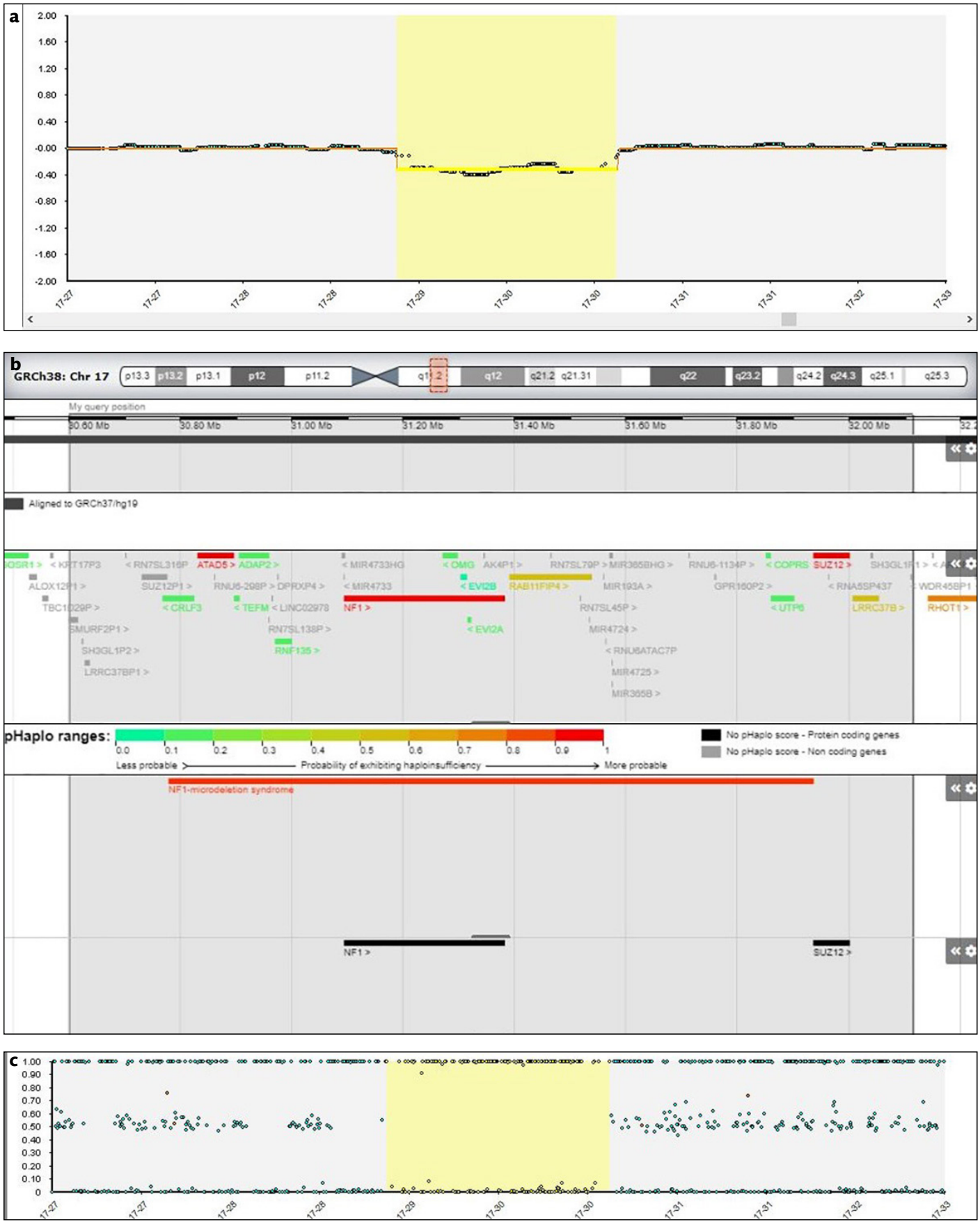


**Figure 2.** Chromosomal microarray analysis of the patient.

**a–c.** The Log R Chart **(a)** showed deletion of the region and the B-allele chart **(b)** revealed the absence of heterozygous allele peak in deleted region. The deletion (gray shaded area) included the "NF1-microdeletion syndrome region" and NF1, SUZ12 genes which is shown by Decipher Genome Browser **(c)** (https://www.deciphergenomics.org/browser).

## DISCUSSION

IMMAS, first described in 2017, is characterized by overgrowth, prominent facial dysmorphism, developmental delay, intellectual disability, and variable skeletal abnormalities. The primary features of this syndrome are overgrowth and dysmorphic phenotype, including a prominent forehead, large ears, round face, broad forehead, hypertelorism, and down slanting palpebral fissures. Additionally, a wide range of musculoskeletal anomalies including pectus excavatum, scapular winging, short clavicle, wide distal ulna, brachydactyly, mild scoliosis, camptodactyly, wide distal femur, coxa valga, flat feet, pronation of the feet, and hypotonia have been reported in IMMAS patients. Another common feature is mild or severe intellectual disability, which is reported to occur in 69% of cases; however, structural brain abnormalities are rare (30%).

Our patient had corpus callosum agenesis and polymicrogyria, as we previously mentioned; therefore, it is important to include neuroimaging in the diagnostic algorithm of this syndrome to detect structural brain abnormalities. Additionally, Cyrus et al. reported cardiac, genitourinary, and respiratory tract issues not observed in earlier cases (3). Respiratory issues were described in three patients, including chronic respiratory tract infections in one (who also had ductus arteriosus and a patent foramen ovale) and asthma in another. Our patient had a history of neonatal pneumonia; however, detailed pulmonary and cardiac examination could not be performed because the patient declined the procedures. Genitourinary abnormalities were observed in 6 patients reported by Cyrus et al., including an anteriorly-placed anus, a chorda penis, cryptorchidism, phimosis, and disjoined epididymitis (3). Interestingly, all the reported patients with genitourinary anomalies were male. Our patient is the first female IMMAS patient with a genitourinary abnormality and renal anomalies, including renal ectopia which also had a rotation anomaly. In this respect, our case adds a new clinical component to the syndromic profile of IMMAS.

Imagawa-Matsumoto syndrome (IMMAS) results from heterozygous mutations in the SUZ12 gene on chromosome 17q11. These heterozygous mutations in IMMAS patients have been reported in a variety of forms, including missense, frameshift, and truncation mutations. Missense variants appear to cause IMMAS more frequently than truncation, frameshift, deletion, or splice site mutations. In our patient, there was a 1.5-MB deletion in the SUZ12 gene region, which is uncommon (previously reported in only 1 other patient (3)). Recent studies have shown that SUZ12 gene mutations are associated with miscellaneous carcinomas, including malignant peripheral nerve sheath tumors, T-cell acute lymphoblastic leukemia, ovarian stromal tumors, lymphomas, and gastric cancer (6–10); however, no carcinoma has developed in any IMMAS patient to date.

There isn't a specific treatment for IMMAS; treatment is only supportive. Appropriate referral to a child and adolescent psychiatrist is essential for behavioral and neurocognitive assessment, and therapy. As intellectual disability is quite common in IMMAS patients, timely evaluation is essential for proper school placement and/or for the provision of adequate in-school support. Routine musculoskeletal examination for limb anomalies and scoliosis, and appropriate referrals to physical therapy and orthopedic surgery are recommended, as needed. Physical therapy and adaptive devices can help optimize the quality of life for patients and their families. Moreover, it may be important to screen patients for cancer at regular intervals, as it has been shown that cancer associated with *SUZ12* variants can occur.

Finally, we present the first IMMAS patient from Turkey who is the 14th documented instance worldwide. As such, the present case report will help improve the syndromic profile of IMMAS and expand the limited IMMAS database.

**Informed Consent:** An informed consent form was obtained from the patient.

**Peer-review:** Externally peer-reviewed.

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