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Case Report

A 13-year-old girl with 18p deletion syndrome presenting Turner syndrome-like clinical features of short stature, short webbed neck, low posterior hair line, puffy eyelids and increased carrying angle of the elbows

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ABSTRACT

Objective: We report a 13-year-old girl with 18p deletion syndrome presenting Turner syndrome-like clinical features.

Case report: A 13-year-old girl was referred for genetic counseling of Turner syndrome-like clinical features of short stature, short webbed neck, low posterior hair line, puffy eyelids and increased carrying angle of the elbows. The girl also had mild intellectual disability, psychomotor developmental delay, speech disorder, high-arched palate, hypertelorism and mid-face hypoplasia. Cytogenetic analysis of the girl revealed a karyotype of 46,XX,del(18) (p11.2). The parental karyotypes were normal. Array comparative genomic hybridization analysis on the DNA extracted from the peripheral blood revealed a 13.93-Mb deletion of 18p11.32-p11.21 or arr 18p11.32p11.21 (148,993–14,081,858) × 1.0 [GRCh37 (hg19)] encompassing 52 Online Mendelian Inheritance in Man (OMIM) genes including *USP14*, *TYMS*, *SMCHD1*, *TGIF1*, *LAMA1*, *TWSG1*, *GNAL* and *PTPN2*. Polymorphic DNA marker analysis revealed a maternal origin of the deletion.

Conclusion: Females with Turner syndrome-like clinical features in association with intellectual disability, facial dysmorphism and psychomotor developmental delay should be suspected of having chromosome deletion syndromes.

Introduction

Chromosome 18p deletion syndrome [Online Mendelian Inheritance in Man (OMIM) 146390] is a contiguous gene deletion syndrome characterized by mental retardation, short stature, growth retardation, craniofacial dysmorphisms of depressed nasal bridge, round face, short protruding philtrum, palpebral ptosis, strabismus, large dysplastic ears, wide mouth and dental abnormalities, short webbed neck, cognitive impairment, speech delay,

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hearing loss, holoprosencephaly (10% of the cases), pectus excavatum, kyphoscoliosis, pituitary hormone deficiencies, seizures, dystonia, autoimmune disorders, congenital heart defects of ventricular hypertrophy, patent ductus arteriosus tetralogy of Fallot (~10% of the patients), cryptorchidism, IgA, IgG, or IgM deficiency, optic nerve hypoplasia, congenital cataracts, sacral agenesis, myelomeningocele and keratosis pilaris [1–6].

Here, we report a 13-year-old girl with 18p deletion syndrome presenting Turner syndrome-like clinical features of short stature, short webbed neck, low posterior hair line, puffy eyelids and increased carrying angle of the elbows.

Case report

A 13-year-old female was referred for genetic counseling of Turner syndrome-like phenotype of short stature, short webbed neck, low posterior hair line, puffy eyelids and increased carrying angle of the elbows. The girl was the second child of a 33-year-old father and a 27-year-old mother at her birth at 37 weeks of gestation with a birth weight of 2850 g. At referral, she had a body weight of 45 Kg (50th–75th centile) and body height of 149 cm (25th–50th centile). She had additional manifestations of mild intellectual disability, psychomotor developmental delay, speech disorder, high-arched palate, hypertelorism, large ears and midface hypoplasia. The intelligence quotient (IQ) test at age 8 years revealed the result of mild intellectual disability with a full IQ of 56. She had regular menstrual cycle. Her menarche occurred at age 11 years. She had normal female external genitalia. Cytogenetic analysis of the patient's peripheral blood revealed a karyotype of 46,XX,del(18)(p11.2) (Fig. 1). The parental karyotypes were normal. Array comparative genomic hybridization (aCGH) analysis on the DNA extracted from the peripheral blood using CytoChip ISCA Oligonucleotide Array (Illumina, San Diego, CA, USA) revealed a 13.93-Mb 18p11.32-p11.21 deletion or arr 18p11.32p11.21 (148,993–14,081,858) × 1.0 [GRCh37 (hg19)] encompassing 52 OMIM genes including *USP14*, *TYMS*, *SMCHD1*, *TGIF1*, *LAMA1*, *TWSG1*, *GNAL* and *PTPN2* (Fig. 2). Polymorphic DNA marker analysis on the DNAs extracted from the bloods of the patient and her parents revealed a maternal origin of the deletion (Fig. 3).

Discussion

The present case had a *de novo* pure isolated deletion of maternal origin. Schaub et al. [7] found that about half of the cases with 18p deletion had breakpoints in the centromeric region, and about half of the deletions, regardless of breakpoint location, occurred on the maternal chromosome. Hasi-Zogaj et al. [5] in a cohort study of individuals with 18p deletion found that 89% had *de novo* isolated deletions, and among 56% *de novo* cases, 25 cases had the deletion occurring on the paternal chromosome, whereas the other 31 cases had the deletion occurring on the maternal chromosome. Women with chromosome 18p deletion syndrome may be fertile, and familial 18p deletion syndrome of direct parent-to-child transmission of the deletion have been reported [5,8–13]. To our knowledge, in all of the reports of familial transmission, the deletion was inherited from the mother. In this regard, genetic counseling of possible familial transmission is important in females with 18p deletion syndrome, especially when they are pregnant, and prenatal diagnosis is mandatory.

The present case manifested Turner syndrome-like clinical features of short stature, short webbed neck, edema of face and increased carrying angle of the elbows. Turner syndrome is characterized by short stature, webbed neck, characteristic facies, short metacarpals, broad chest with widely spaced nipples, hyperconvex fingers and toenails, decreased growth velocity and delayed puberty [14]. Barstow and Rerucha [14] suggested that differential diagnosis of short stature in children should include (1) normal variants of constitutional delay of growth and puberty, familial short stature and idiopathic short stature; (2) chronic diseases of anemia, celiac disease, chronic renal insufficiency and inflammatory bowel disease; (3) endocrine disorders of achondroplasia, acquired growth hormone deficiency, congenital growth hormone

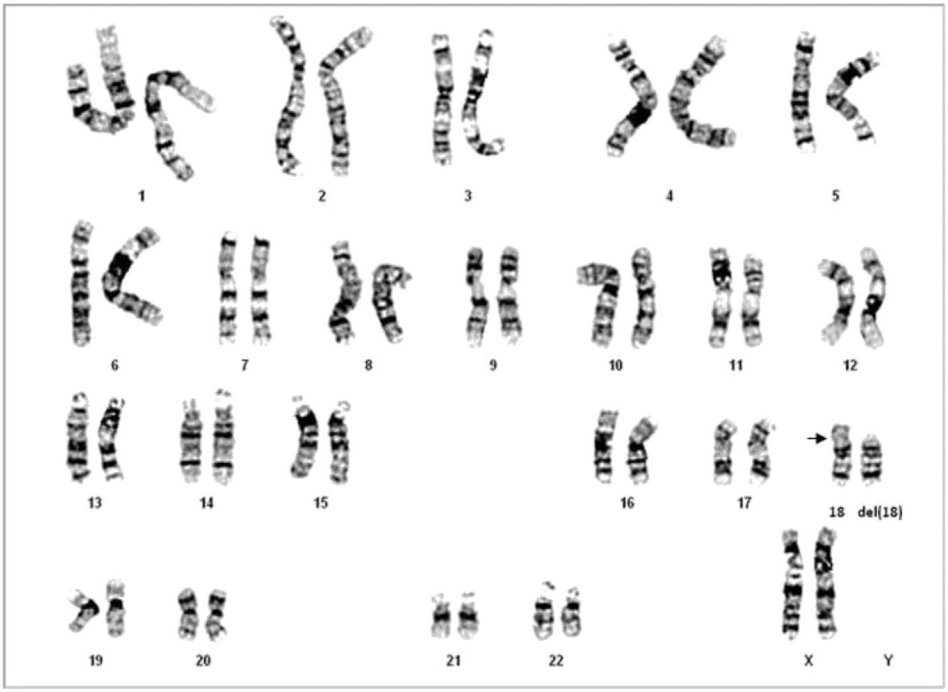

Fig. 1. A karyotype of 46,XX,del(18) (p11.2). The arrow indicates the breakpoint.

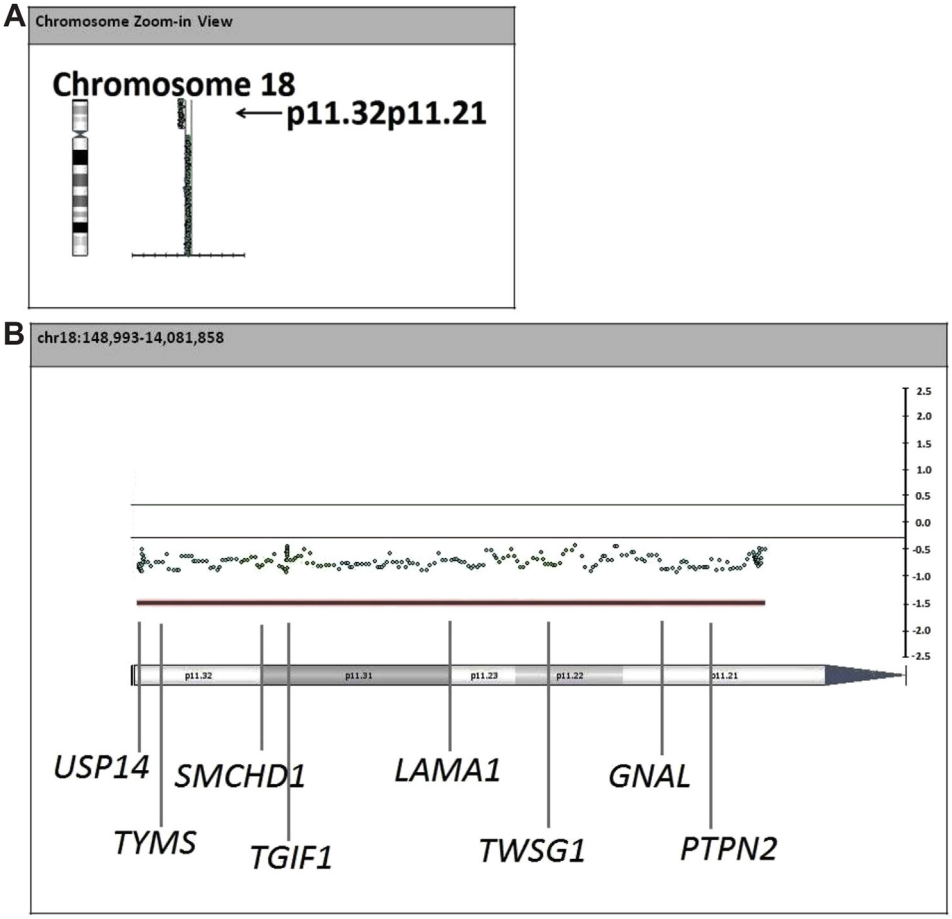

Fig. 2. Array comparative genomic hybridization analysis shows a 13.93-Mb 18p11.32-p11.21 deletion, encompassing the genes of *USP14*, *TYMS*, *SMCHD1*, *TGIF1*, *LAMA1*, *TWSG1*, *GNAL* and *PTPN2*.

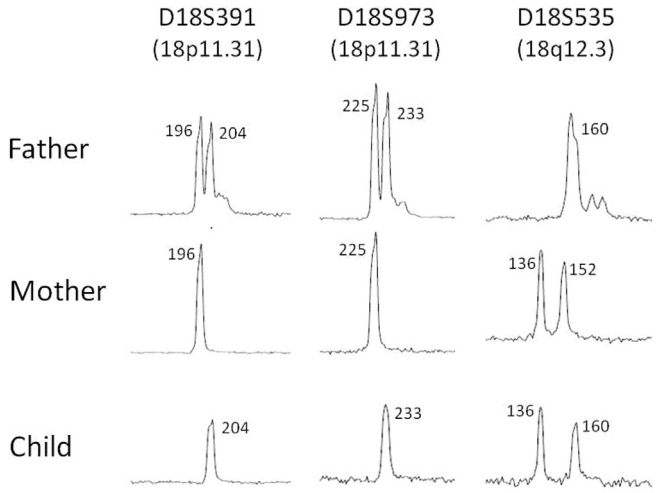

Fig. 3. Polymorphic DNA marker analysis using the informative markers of D18S391 (18p11.31), D18S973 (18p11.31) and D18S535 (18q12.3) shows a maternal origin of the deletion. The 18p deletion occurs on the maternal chromosome.

deficiency, congenital hypothyroidism, intrauterine growth deficiency and primary nutritional deficiency; and (4) genetic conditions of Turner syndrome. Genetic syndromes associated with impaired bone mass and quality include Down syndrome, Turner syndrome, Klinefelter syndrome, Prader–Willi syndrome, Marfan syndrome, Noonan syndrome, Williams syndrome and DiGeorge syndrome [15]. Among these syndromes, Turner syndrome, Noonan syndrome, Williams syndrome and Prader–Willi syndrome are characterized by short stature [15]. We suggest that chromosome 18p deletion should be included in the differential diagnosis of short stature in children.

The present case had intellectual disability, facial dysmorphism, psychomotor developmental delay and haploinsufficiency of *USP14*, *TYMS*, *SMCHD1*, *TGIF1*, *LAMA1*, *TWSG1*, *GNAL* and *PTPN2*.

USP14 (OMIM 607274) encodes ubiquitin-specific protease 14 which is deubiquitinating enzyme that inhibits multiple proteasomal activities and ubiquitin-independent proteolysis [16]. Chen et al. [17] found that USP14 is essential for neuronal function and ubiquitin deficiency causes neurological defects in mice. Marshall et al. [18] found that loss of USP14 causes neuromuscular disease in mice. Walters et al. [19] found that USP14 regulates hippocampal synaptic short-term plasticity and vesicle number. Ortuno et al. [20] found that inactivation of *USP14* is associated with neurodegenerative diseases.

TYMS (OMIM 188350) encodes thymidylate synthetase. Zhu et al. [21] found that thymidylate synthetase polymorphisms increase the risk of conotruncal heart defects. Yi et al. [4] suggested that haploinsufficiency of *TYMS* may contribute to tetralogy of Fallot in the case of 18p deletion with congenital heart defects.

SMCHD1 (OMIM 614982) plays a role in X chromosome inactivation [22]. Lemmers et al. [23] identified heterozygous loss-of-

function mutations in the *SMCHD1* gene in patients with fascioscapulohumeral muscular dystrophy (OMIM 158901). Shaw et al. [24] and Gordon et al. [25] identified heterozygous mutations in the *SMCHD1* gene in patients with isolated arhinia and Bosma arhinia microphthalmia syndrome.

TGIF1 (OMIM 602630) encodes transforming growth factor-β-induced factor. Heterozygous mutation in *TGIF1* causes autosomal dominant holoprosencephaly 4 (HPE4) (OMIM 142946) [26–29]. We previously reported prenatal diagnosis of holoprosencephaly associated with 18p deletion [3,30,31]. Yi et al. [4] additionally reported prenatal diagnosis of 18p deletion in a fetus with holoprosencephaly and congenital heart defects. However, in patients with chromosome 18p deletion syndrome, only 10% will present holoprosencephaly. In a study of 65 patients with 18p deletion, Hasi-Zogaj, et al. [5] found only six patients (6/65 = 11%) had malformations on the holoprosencephaly spectrum.

LAMA1 (OMIM 150320) encodes laminin α-1. Patients with 18p deletion may manifest keratosis pilaris/ulerythema ophryogenes [32,33]. Zouboulis et al. [33] suggested that haploinsufficiency of *LAMA1* may be responsible for the pathogenesis of keratosis pilaris/ulerythema ophryogenes in chromosome 18p deletion syndrome. Homozygous or compound heterozygous mutations in *LAMA1* are associated with autosomal recessive Poretti-Boltshauser syndrome (OMIM 615960), which is characterized by cerebellar anomalies, high myopia, retinal dystrophy, developmental delay and cognitive impairment [34,35].

TWSG1 (OMIM 605049) encodes twisted gastrulation homolog 1 which is a bone morphogenetic protein (BNP) binding protein. Sun et al. [36] found that *TWSG1* is expressed in the adult mouse and human fetal choroid plexus, and *TWSG1*-deficient mice had holoprosencephaly and hydrocephalus, and suggested that *TWSG1* plays a role in the pathogenesis in brain disorders. However, Kauvar et al. [37] found minimal evidence for a direct involvement of *TWSG1* in human holoprosencephaly.

GNAL (OMIM 139312) encodes guanine nucleotide-binding protein, α-activating activity polypeptide, olfactory type. Heterozygous mutation in *GNAL* is associated with autosomal dominant dystonia 25 (OMIM 615073) [38]. Dystonia has been observed in 84% of the patients with chromosome 18p deletion syndrome [5].

PTPN2 (OMIM 176887) encodes protein-tyrosine phosphatase, nonreceptor-type, 2. *PTPN2* is associated with rheumatoid arthritis [39,40]. Wiede et al. [41] found that *PTPN2*-deficiency exacerbates T follicular helper cell and B cell responses, and promotes the development of autoimmunity. Autoimmunity disorders have been observed in 10% of the patients with chromosome 18p deletion syndrome [5].

In conclusion, we suggest that females with Turner syndrome-like clinical features in association with intellectual disability, facial dysmorphism and psychomotor developmental delay should be suspected of having chromosome deletion syndromes.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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