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Case Report

18p Deletion Syndrome Associated with Type 1 Diabetes and Hashimoto's Thyroiditis: A Case Report on Autoimmune Disorders and Genetic Factors

Oktay MA et al. 18p Deletion Syndrome with Autoimmune Endocrinopathy

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What is already known on this topic?

- 18p deletion syndrome is a rare chromosomal disorder characterized by highly variable phenotypic features, including intellectual disability, craniofacial dysmorphism, and systemic involvement.
- Although some autoimmune diseases, particularly autoimmune thyroiditis, have been reported in patients with 18p deletions, the mechanisms linking the chromosomal deletion to immune dysregulation are poorly understood.
- Only a few cases in the literature have described a co-occurrence of 18p deletion syndrome with type 1 diabetes mellitus (T1DM).

What this study adds?

- This case report presents a rare co-occurrence of early-onset T1DM and Hashimoto's thyroiditis in a child with 18p deletion syndrome.
- The study identifies the deletion of multiple immunoregulatory genes (e.g., *PTPN2*, *PTPRM*, *LPIN2*, *USP14*, *ADCYAP1*) and discusses their possible contribution to autoimmune disease pathogenesis in the context of chromosomal deletion.
- The findings emphasize the importance of long-term endocrine and immunological surveillance in individuals with 18p deletion syndrome, especially in dysmorphic features and systemic involvement.

Abstract
18p deletion syndrome is a rare chromosomal disorder that can present with a wide range of phenotypic features and is occasionally associated with autoimmune diseases. We report the case of a 3-year and 8-month-old girl who presented with polydipsia and polyuria and was subsequently diagnosed with type 1 diabetes mellitus (T1DM) based on clinical and laboratory findings. The patient exhibited dysmorphic facial features and developmental delay, leading to genetic testing, which revealed a 13.7 Mb deletion on the short arm of chromosome 18 (18p11.32p11.21). Over the following years, she developed additional features, including Hashimoto's thyroiditis, epilepsy, subaortic stenosis requiring surgical resection, IgA deficiency, bilateral sensorineural hearing loss, and myopia. Genetic analysis also identified the deletion of several potentially disease-modifying genes, including *PTPN2, PTPRM, LPIN2, USP14*, and *ADCYAP1*. This case highlights the potential role of genes within the 18p region in the pathogenesis of autoimmune endocrinopathies. It supports further investigation into the immunogenetic mechanisms in 18p deletion syndrome.
Keywords: 18p deletion syndrome, Type 1 diabetes mellitus, Hashimoto's thyroiditis, Autoimmunity

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Introduction

18p deletion syndrome (monosomy 18p), first described by Jean de Grouchy in 1963, is a rare chromosomal anomaly resulting from the partial or complete loss of genetic material on the short arm of chromosome 18 (1). The syndrome has an estimated incidence of approximately 1 in 50,000 live births. It presents with a variable phenotypic spectrum, including mild to moderate intellectual disability, short stature, marked speech delay, and craniofacial dysmorphism (2–4). While most cases result from de novo terminal deletions, some may arise from familial translocations or ring chromosome structures (5). The diversity of breakpoint regions contributes to the wide clinical variability observed, leading to differences in growth, cognitive function, and involvement of multiple systems, particularly craniofacial and skeletal development (4).

18p deletion syndrome is also a rare chromosomal disorder associated with several autoimmune diseases (4). Individuals with this syndrome may be predisposed to autoimmune thyroid diseases, rheumatoid arthritis, celiac disease, and alopecia (4,6). However, the genetic mechanisms underlying autoimmunity and the complex pathophysiology of 18p deletion syndrome remain poorly understood (6).

In this report, we present the case of a patient with 18p deletion who was diagnosed with early-onset type 1 diabetes mellitus (T1DM), Hashimoto's thyroiditis, and selective IgA deficiency.

Case Presentation

A 3-year and 8-month-old girl was admitted to our center with complaints of excessive water intake (polydipsia) and frequent urination (polyuria). On physical examination, dysmorphic features were noted, including a round face, broad nasal bridge, long philtrum, anteverted ears, hypertelorism, and a short neck. Cardiovascular evaluation revealed a grade 3/6 systolic murmur. Neurodevelopmental assessment indicated mild intellectual disability.

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Laboratory investigations revealed a blood glucose level of 339 mg/dL, insulin 11.43 mU/L, C-peptide 1.26 ng/mL, HbA1c 9.4%, and ketone level 1.2 mmol/L. Among autoimmune diabetes markers, anti-glutamic acid decarboxylase (anti-GAD) antibodies were elevated at 835.68 IU/mL (reference: 0–10), and anti-insulin antibodies were positive at 21.9% (reference: 0–8.2), while anti-islet cell antibodies were negative. Thyroid function tests were within normal limits, and thyroid and celiac autoantibodies were negative. Based on these findings, a diagnosis of type 1 diabetes mellitus (T1DM) was established, and insulin therapy was initiated.

Further investigations due to the presence of dysmorphic facial features revealed bilateral sensorineural hearing loss, myopia, and selective IgA deficiency. Subaortic stenosis was detected on echocardiography, and discrete subaortic membrane (DSM) resection was performed. During follow-up, the patient developed epilepsy two years after the initial T1DM diagnosis, and antiepileptic treatment was initiated. Cranial magnetic resonance imaging (MRI) findings were reported as usual. In light of the multisystemic and dysmorphic features, chromosomal microarray analysis (array-CGH) was performed, which identified a 13.7 Mb deletion involving most of the short arm of chromosome 18 (arr[hg19]18p11.32p11.21(148963-13875138)x1) (Figure 1).

Five years after the T1DM diagnosis, the patient presented again with fatigue and cold intolerance. Laboratory tests revealed elevated anti-thyroid peroxidase (anti-TPO) antibodies at 1006 IU/mL (reference: 0–34) and anti-thyroglobulin (anti-TG) antibodies at 200 IU/mL (reference: 0–115), leading to a diagnosis of Hashimoto's thyroiditis. Levothyroxine (LT4) therapy was initiated. The patient has been followed for ten years with comorbid T1DM and Hashimoto's thyroiditis.

Genetic Analysis and Results

Chromosomal microarray analysis was performed using the GenetiSure Cyto CGH Microarray Kit, 8 X 60K (Agilent Technologies, Santa, Clara, USA). The average resolution of the platform was 100 kb. The analysis identified a heterozygous 13.7 Mb deletion in the 18p11.32–p11.21 region (hg19: chr18:148 963–13 875 138). High-resolution (550-band) G-banded karyotyping confirmed the finding as 46,XX,del(18)(p11.2). Parental karyotypes were normal, indicating that the deletion arose de novo. The deleted interval encompasses 69 protein-coding genes, including immune-endocrine regulatory genes *PTPN2, PTPRM, LPIN2, USP14*, and *ADCYAP1*, as well as structural genes such as *LAMA1* (Table 1).

Discussion

18p deletion syndrome is a rare genetic condition encompassing a broad spectrum of clinical manifestations (7). Symptoms can range from mild features to severe brain malformations (7). The clinical presentation is typically associated with the size of the deletion and the loss of critical genes within the affected region (3). Typical findings include short stature, facial dysmorphism, intellectual disability, skeletal deformities (kyphoscoliosis, pectus excavatum), and ophthalmologic abnormalities (strabismus, ptosis, hypermetropia) (8). Additionally, muscle hypotonia, extensive dental caries, and, less frequently, cardiac anomalies and movement disorders may be observed (4, 9). Among the neurological complications, seizures are particularly notable and may occur with or without structural brain abnormalities (10, 11). Autoimmune diseases in individuals with 18p deletion syndrome have been associated with various clinical entities, including Graves' disease (6), Hashimoto's thyroiditis (12), juvenile idiopathic arthritis (13), and celiac disease (4). Furthermore, early-onset autoimmune thyroid diseases, as well as vitiligo, lupus, psoriasis, and alopecia, have been reported (4, 12). In our case, both T1DM and Hashimoto's thyroiditis were identified. According to the literature available, only one other case has been reported showing a co-occurrence of T1DM and 18p deletion (10).

The *PTPN2* gene, located on chromosome 18p, is one of the key candidates potentially involved in the development of autoimmune diseases. This gene has been associated with autoimmune conditions such as T1DM and rheumatoid arthritis (14, 15). Rheumatoid arthritis cases have been reported in individuals with 18p deletions encompassing the *PTPN2* gene (16, 17). However, one study also reported rheumatoid arthritis in an individual whose deletion did not include *PTPN2*. This suggests that other critical regulatory regions may exist within the deletion interval or that autoimmune disease may arise from the disruption of regulatory elements affecting P*TPN2* (4). Thus, deletion of *PTPN2* is proposed as a potential mechanism contributing to the development of autoimmune diseases such as T1DM and Hashimoto's thyroiditis.

The *PTPRM* gene, located within the deleted region, encodes a receptor-type tyrosine phosphatase that negatively regulates STAT3, a key modulator of immune function (18). Deletion of *PTPRM* may lead to increased STAT3 phosphorylation, precipitating immune dysregulation and, via expansion of Th17 cell populations, heightening susceptibility to autoimmune processes (6,19). This pathway is thought to drive the pathogenesis of immune-mediated disorders such as T1DM and Hashimoto's thyroiditis, conditions characterized by immune system hyperactivity (20).

From a clinical standpoint, we recommend that children with an 18p deletion and confirmed *PTPRM* hemizygosity undergo early screening for autoantibodies (anti-GAD, anti-TPO, anti-TG), fasting/post-prandial glycaemic monitoring, and thyroid-function testing at 6- to 12-month intervals. In addition, symptom-based screening for other organ-specific autoimmune diseases linked to Th17-mediated inflammation such as coeliac disease and juvenile idiopathic arthritis represents a practical and valuable approach.

The *LAMA1* gene, located within the deleted region, encodes a protein critical for basement membrane assembly and is expressed in tissues such as the kidney, testis, and retina. Animal studies have demonstrated that mutations in this gene can lead to retinal vasculopathy and vascular anomalies (21). Poretti-Boltshauser syndrome, associated with *LAMA1* dysfunction, cerebellar anomalies, and retinal dystrophies, has been described (22). Although the neurological and ophthalmologic effects of *LAMA1* may not directly impair pancreatic beta cell function, they exacerbate endothelial injury in the pancreatic microvasculature, leading to β-cell ischemia and dysfunction and ultimately triggering the development of diabetes.

The *USP14* gene encodes a ubiquitin-specific protease that is critical for protein degradation, synaptic regulation, and endoplasmic-reticulum (ER) quality control. In mouse models, *USP14* deficiency causes neurological dysfunction and abnormal synaptic transmission (23), and in humans biallelic mutations are linked to distal arthrogryposis, corpus callosum anomalies, and facial dysmorphism (24). Moreover, during ER stress *USP14* safeguards protein quality; its dysfunction can precipitate β-cell apoptosis and impair insulin secretion (25,26). Together, these observations position *USP14* as a compelling candidate for further investigation in both neurodevelopmental and metabolic phenotypes.

In our case, chromosomal microarray analysis identified a deletion spanning the *ADCYAP1* and *LPIN2* genes. *ADCYAP1* is believed to confer protection against cytokine-induced beta-cell apoptosis, thereby potentially attenuating the pathogenesis of diabetes (27). *LPIN2* deficiency, in addition to disrupting lipid metabolism and energy homeostasis, impairs the regulation of inflammatory responses; this dysfunction heightens pro-inflammatory cytokine expression and promotes excessive immune activation, indirectly contributing to the development of T1DM (28-30).

When a paediatric patient presents with two or more autoimmune endocrinopathies (e.g., T1DM accompanied by autoimmune thyroiditis) particularly in the setting of facial dysmorphism, developmental delay, sensory deficits, or congenital cardiac defects chromosomal abnormalities must be considered in the differential diagnosis.

Conclusion

18p deletion syndrome remains an important study area due to its genetic heterogeneity and phenotypic complexity. This case contributes to a better understanding of the genetic underpinnings of autoimmune conditions such as T1DM and Hashimoto's thyroiditis. Further molecular and genetic studies are needed to elucidate the roles of genes such as *PTPN2, PTPRM, LPIN2, USP14,* and *ADCYAP1* in the pathogenesis of this syndrome.

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Ethics
Informed Consent: An informed consent form was obtained from the patient's parents.
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Authorship Contributions
Surgical and Medical Practices: Mehmet Ali Oktay, Aylin Kılınç Uğurlu, Gülsüm Kayhan, Mahmut Orhun Çamurdan, Aysun Bideci
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Table 1. Protein-coding genes located within the 18p11.32–p11.21 deletion detected in the patient

ADCYAP1*	*AFG3L2*	*AKAIN1*	*ANKRD12*	*ANKRD62*	*APCDD1*	*ARHGAP28*	*C18orf15*
C18orf61	*CBX3P2*	*CEP192*	*CEP76*	*CETN1*	*CHMP1B*	*CHORDC1P4*	*CIDEA*
CLUL1	*COLEC12*	*DLGAP1*	*EMILIN2*	*ENOSF1*	*EPB41L3*	*FAM210A*	*GACAT2*
GAPLINC	*GNAL*	*IMPA2*	*L3MBTL4*	***LAMA1****	*LDLRAD4*	*LOC101927410*	***LPIN2****
LRRC30	*MC5R*	*METTL4*	*MPPE1*	*MTCL1*	*MYL12A*	*MYL12B*	*MYOM1*
NAPG	*NDC80*	*NDUFV2*	*PIEZO2*	*PPP4R1*	*PRELID3A*	*PSMG2*	***PTPN2****
PTPRM*	*RAB12*	*RAB31*	*RALBP1*	*RNMT*	*SEH1L*	*SLC35G4*	*SMCHD1*
SPIRE1	*TGIF1*	*THOC1*	*TMEM200C*	*TUBB6*	*TWSG1*	*TXNDC2*	*TYMS*
TYMSOS	***USP14****	*VAPA*	*YES1*	*ZBTB14*			

*Immune/endocrine–related genes are shown in bold

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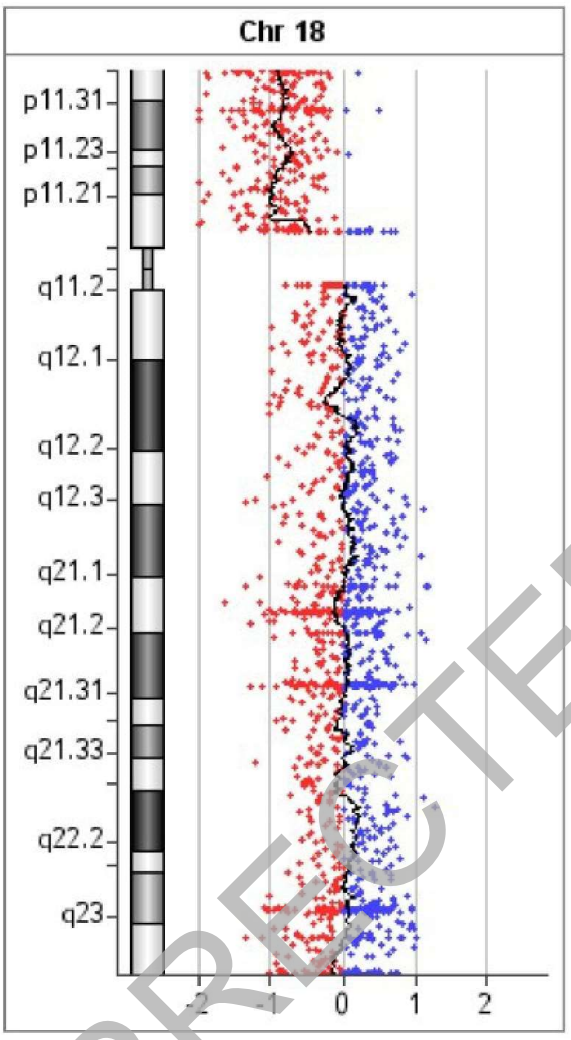

Figure 1. The deleted region located on the short arm of chromosome 18 (18p11.31–p11.21)

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