

# Kleefstra Syndrome: Review of the Literature

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Kleefstra syndrome is caused by chromosome 9q34.3 deletion or heterozygous mutations in the Euchromatin Histone Methyl Transferase 1 (*EHMT1*) gene. The prevalence is estimated 1:25,000 to 1:35,000. Intellectual disability, distinctive facial features, hypotonia in childhood can be accompanied. The spectrum of Kleefstra syndrome includes behavioral/psychiatric problems, hearing and visual impairments, seizures, congenital heart defects, genitourinary defects, and obesity. Therefore, it is necessary to understand the pathophysiology and various manifestation of Kleefstra syndrome and discussing with a multidisciplinary team will help diagnose and treat Kleefstra syndrome patients.

**Key words:** Kleefstra syndrome, 9q subtelomeric deletion syndrome, Euchromatin histone methyltransferase 1, EHMT1

## REVIEW ARTICLE

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## INTRODUCTION

Kleefstra syndrome (OMIM #610253) was previously named 9q subtelomeric deletion syndrome. A case with 9q34.3 deletion was first reported by Schimmenti et al. in 1994 [1]. Kleefstra et al. [2-4] identified that Euchromatin histone methyltransferase 1 (*EHMT1*) gene is the causative gene in Kleefstra syndrome (KS). Most cases are caused by *de novo* mutations. The prevalence is estimated at 1:25,000 to 1:35,000 individuals based on incidence estimates of *de novo* variants in neurodevelopmental disorders [5]. It is probably underestimated as many individuals are not diagnosed. KS is caused by a subtelomeric deletion in the chromosomal region 9q34.3 or an intragenic mutation of the *EHMT1* gene. It can be accompanied by intellectual disability, characteristic facial dysmorphism and childhood hypotonia [6]. Here, I will review the clinical characteristics, diagnosis, management, and genomics of KS patients.

### Clinical characteristics

A wide range of pathologic clinical features involving multiple organs is observed in KS (Table 1). Males and females are affected equally. Distinctive facial dysmorphism is accompanied, characterized by brachycephaly, microcephaly, broad forehead, arched eyebrows, hypertelorism, midface retrusion, anteverted nares, and tented lips. Facial appearance becomes coarser with age [6].

Affected individuals display a moderate to a severe spectrum of intellectual disability. Speech delay is often severe. Behavior/psychiatric problems are also noted. Autism spectrum disorders were observed in 95.7% of affected individuals. Patients are prone to psychosis, obsessive compulsive disorder, and major depressive disorder. Sleep disturbances are present, which may precede psychosis [7]. Seizures are reported in 30% of patients [6].

Childhood hypotonia is seen in many patients, but most patients were able to

**Table 1.** Clinical Features and Management of Kleeftstra Syndrome

System	Clinical features	Management
Head	Brachycephaly Microcephaly	
Face	Broad forehead Arched eyebrows Hypertelorism Midface hypoplasia Anteverted nares Tented lips	
Eyes	Hypermetropia	Standard treatment by Ophthalmologist
Ears	Hearing impairment	Refer to otolaryngologist Hearing aids
Cardiovascular	Congenital heart defect Rhythm disturbance	Refer to cardiologist
Gastrointestinal	Gastroesophageal reflux disease	Refer to gastroenterologist
Genitourinary	Hydronephrosis Vesicoureteral reflux Chronic renal insufficiency Micropenis Cryptorchidism Hypospadias	Refer to nephrologist/ endocrinologist
Neurologic	Seizures	Refer to neurologist Antiepileptic drug
Psychiatric/ behavioral	Speech/motor delay Autism Obsessive compulsive disorder Major depressive disorder Sleep disturbance	Physical rehabilitation therapy Speech-language rehabilitation therapy ABA therapy Antipsychotics Antidepressive agents

walk between the age of two and three years [6]. Hearing and vision impairments such as hypermetropia may appear at a young age. Congenital heart defects, such as atrial septal defect, ventricular septal defect, coarctation of aorta, tetralogy of Fallot, bicuspid aortic valve, and pulmonic stenosis is present in 50% of the patients. Cardiac arrhythmias such as atrial flutter can possibly occur during follow-up. Renal anomalies, such as hydronephrosis, vesicoureteral reflux, and renal cysts are observed in 10-30% of affected individuals. Genital anomalies, such as micropenis, cryptorchidism, and hypospadias are present in 30-40% of male KS patients [6]. Weight at birth is usually within the normal range, but weight gain during childhood causes obesity to be observed in 50% of affected patients [8].

Comparison of the clinical phenotypes observed between the *EHMT1* mutation group and the 9q34.3 deletion group revealed only a few notable differences [6].

### Diagnosis

The diagnosis of KS is made in a proband with a heterozygous deletion in the chromosomal region 9q34.3 or a hetero-

zygous pathogenic variant involving *EHMT1* gene [9].

By chromosomal microarray analysis (CMA) method, deletions of 9q34.3 can be identified. Approximately 50% of pathogenic variants in Kleeftstra syndrome was detected by CMA. Intragenic mutation of *EHMT1* may not be found by the CMA method. 9q34.3 deletion is usually not detected by a routine karyotype analysis.

Sequence analysis of *EHMT1* allows the detection of 50% of pathogenic variants. Sequencing analysis of *EHMT1* allows the detection of intragenic deletions/insertions, missense, nonsense, and splice site variants of *EHMT1*. Single-exon deletion and duplication testing using qPCR, multiplex ligation-dependent probe amplification, gene-targeted microarray may detect an additional 5% of affected individuals with normal CMA result. An intellectual disability multigene panel including *EHMT1* can be also helpful. Method in multigene panel includes sequence analysis, deletion/duplication analysis, and other non-sequencing-based tests. Rarely, balanced chromosomal rearrangements that disrupt *EHMT1* can be detected by karyotype analysis [9].

### Genes and molecular pathogenicity

In the region of chromosome 9q34.3, *COL5A1*, *OLFM1*, *CAMSAP1*, *LHX3*, *SEC16A*, *NOTCH1*, *GRIN1*, *CACNA1B*, and *EHMT1* are genes that can cause diseases in the cases of loss of function. A female patient with intellectual disabilities with clinical features similar to 9q subtelomeric deletion syndrome had *de novo* balanced translocation in t(X;9)(p11.23;q34.3). The only gene disrupted in this patient was *EHMT1* [2]. Kleeftstra et al. [3] performed mutation analysis of the *EHMT1* gene in patients with clinical features of 9q subtelomeric deletion syndrome and revealed that haploinsufficiency of *EHMT1* is causative for 9q subtelomeric deletion syndrome. Studies [2-4] identified *EHMT1* as the gene responsible for the core phenotype of KS.

Ogawa et al. [10] identified euchromatin histone methyltransferase-1 as component of E2F6 complex, which had transcription repression activity through methylation. Epigenetic regulation can modulate biological functions and these changes may play an important role in various human diseases [11]. Histone tails undergo various post-translational modifications including acetylation, phosphorylation and methylation. Studies revealed that histone methylation modulates chromatin structure and function [12]. Methylation of histone occurs at lysine residues (H3K4/K9/K27/K36/K79 and H4K20). Histone lysine methyltransferases controls the methylations of ly-

sine residues. *EHMT1* methylates H3K9 in euchromatin, and this results in chromatin remodeling and epigenetic transcriptional repression [11].

Dysregulation of chromatin structure adversely affects gene transcription and protein expression. This can cause genetic disorders including developmental delay [9].

### Management of Kleefstra syndrome

Management is primarily supportive. Ongoing routine care by a multidisciplinary team including the nephrologist, cardiologist, neurologist, endocrinologist, urologist, psychiatrist and rehabilitation medicine specialist is needed (Table 1). Physical and speech-language rehabilitation therapy is needed to maximize mobility and speech ability, respectively. The general guideline for the treatment of autism is to reduce stimuli, but low dosages of antipsychotics to reduce hypersensitivity may be helpful for severe cases [7]. Applied behavior analysis (ABA) performed by a board-certified behavior analyst is used in the treatment of autism spectrum disorder [9]. To treat psychosis, reducing stress and treatment with normal to high doses of atypical antipsychotics is used. Depressive mood disorder can be controlled by antidepressant agents. As for the sleep disturbance, well-controlled therapies have not yet been reported [7], but Vermeulen et al. [13] reported that prompt treatment with high doses of antipsychotics to restore sleep is important to prevent further regression of psychosis. Seizures should be controlled with anti-epileptic drugs by an experienced neurologist [9].

Auditory amplification is needed in patients with hearing impairments. Assessing for refractive errors and optimal management should be provided by an ophthalmologist. Congenital heart defects and rhythm disturbance should be referred to cardiologist for standard treatment. Renal anomalies should be referred to an urologist and/or nephrologist [9]. A systematic endocrine work up should be performed in cases of combined genital abnormalities. Intramuscular testosterone injection treatment for micropenis was effective in a pre-pubertal patient [14]. Multidisciplinary team management with a nutrition team can help manage childhood obesity.

### Family Counseling

Most reported cases are caused by *de novo* mutations. However, a genetic approach to the patient's parents and siblings is also required because Kleefstra syndrome is inherited in an autosomal dominant inheritance manner. A 9q34.3 deletion that results from a complex chromosomal rearrangement has

been described in studies [15,16]. de Boer et al. [17] reported a somatic mosaicism in the proband's parents. Rump et al. [18] reported a patient diagnosed as KS with a novel mutation in *EHMT1*, and his mother had tissue-specific mosaicism. Prenatal testing and diagnosis are recommended before pregnancy in the proband or in balanced carriers. Molecular genetic testing through chromosomal microarray analysis performed in a pregnancy may detect 9q34.3 deletion [19].

## CONCLUSION

This review focused on the clinical and genetic characteristics of patients with KS. Earlier diagnosis and better understanding of KS will allow physicians to provide appropriate treatment to patients. Once the diagnosis has been made, multidisciplinary team management is helpful.

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## CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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