

# A female patient with Xp21 gene deletion syndrome

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Xp21 contiguous gene deletion syndrome is associated with complex glycerol kinase deficiency, congenital adrenal hypoplasia, Duchenne muscular dystrophy, and intellectual disability. Xp21 gene deletion syndrome is X-linked recessive, so most symptomatic patients are male, and only a few female symptomatic patients have been reported. We report the first female Korean case of an Xp21 deletion. NGS data were analyzed for copy number variation, and the Xp21 deletion (chr X: 29301056-31838200) was confirmed using real-time PCR.

**Key words:** Xp21 contiguous gene deletion syndrome, Duchenne muscular dystrophy, Creatine kinase.

## Introduction

Xp21 contiguous gene deletion syndrome is associated with complex glycerol kinase deficiency, congenital adrenal hypoplasia, Duchenne muscular dystrophy (DMD), and intellectual disability [1]. The Xp21 chromosome includes the *GK*, *NROB1*, *DMD*, and *IL1PAPL1* genes. Among these, *GK* gene deletion leads to glycerol kinase deficiency, causing metabolic acidosis, recurrent hypoglycemia, and osteoporosis. *NROB1* gene rearrangements cause congenital adrenal hypoplasia, which is associated with the fatal symptom experienced by patients with Xp21 gene deletion syndrome.

*DMD* gene deletion leads to DMD and Becker muscular dystrophy (BMD). The DMD phenotype is more severe than that of BMD, with earlier onset of symptoms. The absence of dystrophin protein causes neuromuscular symptoms and elevated serum creatine kinase (CK) levels. Patients with DMD are non-ambulatory at 9–10 years of age, while other symptoms start to appear around 12 years of age [2]. *IL1PAPL1* gene deletion is associated


with intellectual disability [1].

Xp21 gene deletion syndrome is X-linked recessive; therefore, most symptomatic patients are male, and only a few symptomatic female patients have been reported. We report the first case of a female Korean patient with Xp21 contiguous gene deletion.

## Case

A 2-year-old female was referred to our hospital for evaluation of the genetic cause of a 4-fold increase in CK levels. She was born at 40 weeks of gestation without any perinatal events. She had one healthy older brother and did not have any family history of neuromuscular disorders. She had chickenpox at five months of age; laboratory findings at that time incidentally revealed elevated CK levels for the first time. Initial electrolyte analysis and acid-base balance were normal. Analysis of urine and plasma organic acid, including glyceric acid, was done, and there were no significant abnormalities. Newborn screening test, including 17- $\alpha$ -hydroxy progesterone and adrenocorti-

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Conflict of interest: The authors declare that they do not have any conflicts of interest.

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cotrophic hormone/cortisol, was normal. Echocardiography and electrocardiography findings were normal, and cardiomegaly was not detected on chest radiography. Her height, weight, and

head circumference were in the 50th percentile, which is within the normal range for her age. She could control her neck at three months of age, sit without support at seven months, walk

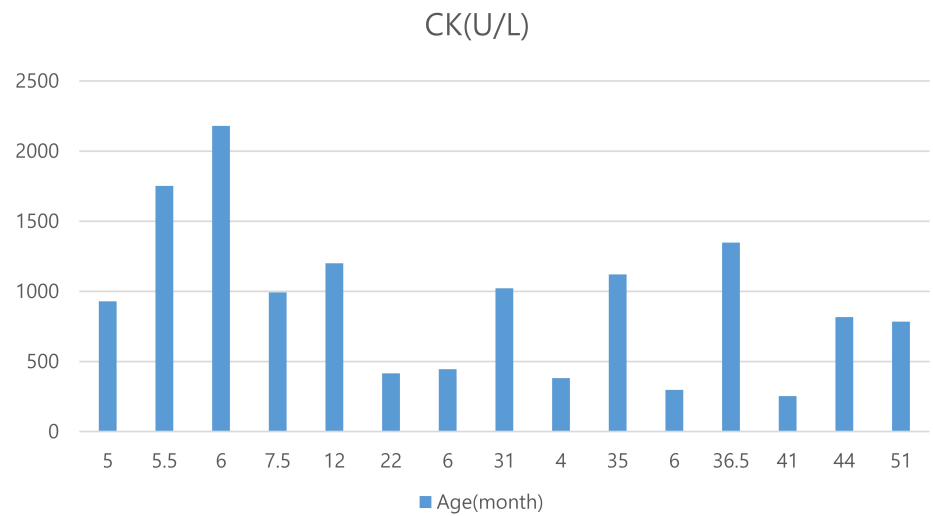


Fig. 1. Creatin kinase level by age. CK, creatin kinase. Normal range, 21-215 U/L.

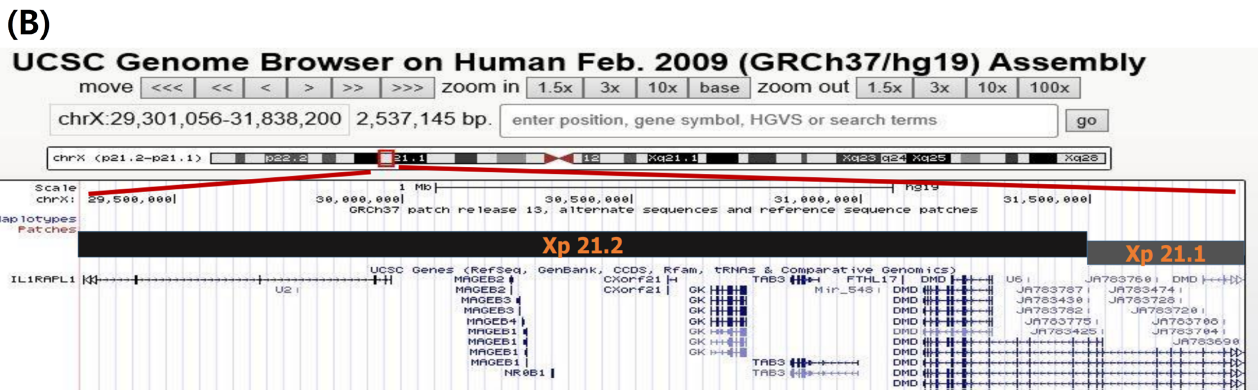
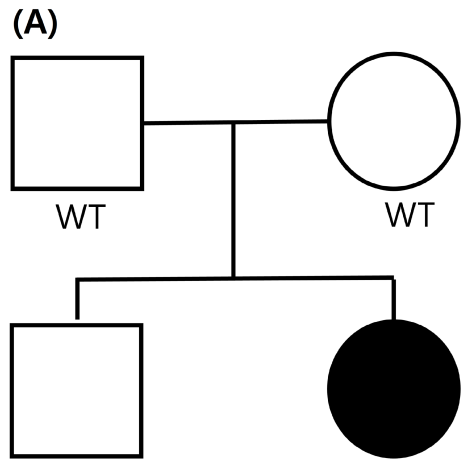


Fig. 2. (A) Pedigree of the patient with Xp21 gene deletion syndrome. (B) Gene copy number variation analysis of the patient with Xp21 gene deletion syndrome.

at one year, and her other developmental milestones were attained normally. She had mild intellectual disability; therefore, she could not speak two-word phrases until the age of two. CK levels were assessed every 3 months and remained consistently elevated in the range of 600 to 1,300 (normal range: 30–135) (Fig. 1). She was referred to the neurology department to evaluate the cause of CK elevation. We performed next-generation sequencing to identify the causative mutations for neuromuscular diseases, but no significant single nucleotide variant was detected. Xp21 deletion (chromosome X: 29301056–31838200) was identified and confirmed using real-time PCR. This deletion encompassed RefSeq genes, as found in the UCSC Genome Browser (<http://genome.ucsc.edu/>) (NCBI Build37, hg19), comprising *DMD*, *GK*, *NROB1*, and *IL1PAPL1*. Trio analysis for proband and her asymptomatic parents was performed. Xp21 deletion was not detected in her parents, indicating that the deletion was *de novo* (Fig. 2). Real-time PCR confirmed that her parents have a normal copy of those genes on the X chromosome. Currently, at five years of age, her CK levels remain elevated, but she does not have any motor deficiencies.

## Discussion

Xp21 gene deletion syndrome is associated with glycerol

kinase deficiency, congenital adrenal hypoplasia, DMD, and intellectual disability. Clinical symptoms vary depending on the size of the deletion. Most female patients who are heterozygous for Xp21 deletion are asymptomatic owing to the remnant X chromosome, whereas male patients with Xp21 gene deletion manifest with fatal symptoms such as electrolyte imbalance and hypotension. We report the case of the first symptomatic Korean female with Xp21 contiguous gene deletion syndrome. She had elevated CK levels and mental retardation.

Patients with glycerol kinase deficiency can be symptomatic with metabolic acidosis, vomiting, or lethargy [3]. Symptoms of glycerol kinase deficiency often occur between the ages of 2 and 7 years [4]. The deletion, in this case, encompasses the *GK* gene; therefore, assessing glycerol levels in plasma and urine may be helpful. A low-fat diet is recommended because it can reduce glycerol production [5].

Additionally, we reviewed the clinical features of previously reported symptomatic female patients with Xp21 contiguous gene deletion (Table 1) [1,6–8]. Female carriers had mild-to-moderate intellectual deficiency. CK levels were elevated in four out of the ten patients reported, and CK levels were not reported for four patients. Heide et al. [1] reported that one patient presented with muscular pain during exercise, and two patients presented with global hypotonia, a neuromuscular symptom.

**Table 1.** Clinical features of female carriers with Xp21 deletion, overlapping with the present cases

Reference	Chromosome region	Deletion size	Mb position [hg19]	Age last evaluation	Intellectual deficiency	Neuro-muscular symptoms	Epilepsy	El-evated creatin kinase
This study	Xp21.2-p21.1	2.5 Mb	29.301,056-31,838,200	4 yr	+ (mild)	—	—	+
Heide et al., 2015 [1]								
Patient 1	Xp21.3-p21.1	6.1 Mb	25,878,399-31,987,991	9 yr	+ (moderate)	—	—	—
Patient 2	Xp21.3-p21.1	2.5 Mb	29,008,175-31,496,701	20 yr	+ (moderate)	+ (muscular pain)	+	+
Fries et al., 1993 [6]								
Family 1	Xp21	NR	NR	Adult	+ (mild)	—	—	—
Family 1	Xp21	NR	NR	4 yr	+ (mild)	NR	NR	+
Family 2	Xp21	NR	NR	Adult	+ (mild)	NR	NR	NR
Family 2	Xp21	NR	NR	Adult	+ (mild)	NR	NR	NR
Family 2	Xp21	NR	NR	Adult	+ (mild)	NR	NR	NR
Family 2	Xp21	NR	NR	Adult	+ (NR)	NR	NR	NR
Shaikh et al., 2008 [7]								
Patient 1	Xp21.2	NR	NR	7 yr	+ (NR)	+ (global hypotonia)	—	+
Falsaperla et al., 2003 [8]								
Patient 1	Xp23.1-p21.1	NR	NR	2 yr	+ (moderate)	+ (global hypotonia)	—	+

+, present; –, not present; NR, not reported.

Most male patients with Xp21 deletion syndrome present with electrolyte imbalance, caused by adrenal insufficiency, as the first manifestation, and it is the most fatal symptom [9]. However, Xp21 deletion syndrome rarely manifests as electrolyte imbalance in female carriers. Only one of the female patients presented with electrolyte imbalance or glucocorticoid deficiency. The main symptoms of female carriers are intellectual disability and progressive myopathy.

Clinical manifestations of female patients are due to X chromosome inactivation. Symptoms vary depending on the size of the deletion and degree of inactivation. A limitation of our study is that we did not analyze the X chromosome inactivation pattern in our patient, which can differ between tissues (i.e., brain, muscle, and peripheral blood) [1].

This case report suggests that Xp21 gene deletion syndrome should be considered in both male and female patients with elevated serum CK levels and mild mental retardation. This study was limited in that we did not perform a detailed cognitive function test since her intellectual disability was very mild and there was no problem in peer conversation. We will closely monitor development of her cognitive function in the outpatient clinic. The progress of female carriers of Xp21 gene deletion is not well known. There have been only 10 female carriers of the disease reported so far, and the longest follow-up period of these female carriers was 20 years. Long-term follow-up of our patient's neuromuscular symptoms, cardiac involvement, and intelligence will contribute to the diagnosis and treatment of this disease.

## Authors' Contributions

Conception and design: HL, YML. Acquisition of data: HL, JK. Analysis and interpretation of data: HL, YML. Drafting the article: JK, HL. Critical revision of the article: HL, JHN, YML. Final approval of the version to be published: all authors.

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