

A novel de novo mutation involving the MLL2 gene in a Kabuki syndrome patient presenting with seizures

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Kabuki syndrome is a rare multiple congenital anomaly disorder. Although mental retardation is one of the main features, various neurological symptoms such as hypotonia and seizures can occur. Here we report on a 18-year-old Turkish male patient who was diagnosed previously as Kabuki syndrome. Molecular genetic analysis showed a novel de novo heterozygous mutation (c.12964C>T [p.Gln4322*]) in the MLL2 gene, that leads to the synthesis of a truncated protein. The aim of the present report is to increase the awareness of Kabuki Syndrome among adult neurologists and to present a previously unreported non-sense mutation in the MLL2 gene.

Key words: Kabuki syndrome, epilepsy, EEG, MLL2, novel genetic mutation.

Kabuki syndrome (KS; OMIM 147920) is a mental retardation–malformation syndrome characterized by a peculiar face that is characterized by eversion of the lower lateral lids, arched eye brows with sparse or one-third dispersed lateral, depressed nasal tip and prominent ears; skeletal anomalies including brachydactyly and spinal deformity; dermatoglyphic abnormalities including: increased digital ulnar loop, presence of fingertip pads; mild to moderate mental retardation; and postnatal growth deficiency. This syndrome was first described in 1981 by Niikawa et al.¹ and Kuroki et al.². The prevalence of KS in the Japanese population has been estimated as 1/32.000³, and more than 400 cases have been described in the literature. Although it has been first described in the Japanese population, there have been numerous reports from other ethnic groups⁴, including patients of Turkish descent⁵⁻⁸. It generally occurs because of a “*de novo*” mutation, involving either the myeloid/lymphoid or mixed-lineage leukemia 2 (MLL2) gene⁹ or less frequently the lysine (K)-specific demethylase 6A (KDM6A) gene^{10, 11}. Here we report on a Turkish KS patient with epilepsy carrying a novel heterozygous mutation in the MLL2 gene.

Case Report

A male patient was referred to the pediatric neurology clinic because of a complex partial seizure characterized by unresponsiveness, at the age of 9. His past medical history included growth retardation, cryptorchidism, and hydronephrosis due to ureteropelvic stenosis. His parents were second-degree cousins; otherwise his family story was unremarkable. Physical examination revealed head circumference: 58 cm (+2SD), body height: 173 cm (25-50th centile) and body weight: 99 kg (90-97th centile). He had long palpebral fissures, bilateral ptosis, depressed nasal tip, prominent ears, high-arched palate, bilateral fetal finger pads and short fifth finger (Fig. 1). Dysarthria and mild mental retardation (full-scale IQ score was 56) were noted in his neurological examination. His clinical findings led to the diagnosis of KS. Sequence analysis of MLL2 identified the heterozygous mutation c.12964C>T in exon 39. This mutation leads to a premature stop of MLL2 protein synthesis (p.Gln4322*). Both parents do not carry the mutation identified in their son.

The patient was put on carbamazepine, 600 mg/day and during the follow-up, he reported two similar seizures per year. His electroencephalogram (EEG) depicted

paroxysmal sharp waves over the left parieto-occipital region (Fig. 2), however cranial magnetic resonance imaging (MRI) did not show any pathology. At the age of 18 years, he was admitted to the adult neurology department because of a secondary generalized tonic-clonic seizure despite treatment. Levetiracetam 2000 mg/day was added to his current medication and presently he is experiencing one complex partial seizure a year.

Discussion

Neurological manifestations in KS are usually characterized by hypotonia, mental retardation and epileptic seizures. Approximately 10-39% of these patients are reported to have seizures^{12,13}, most of which are localization-related and have a favorable outcome^{14, 15}. The onset of seizures can vary between neonatal period and 15 years^{13,14}. Most of the electroencephalographic studies have revealed posteriorly located focal spikes¹⁶, despite recently reported fronto-central predominance in several patients¹⁵. Cranial MRI results can be normal¹⁴ or indicate various findings such as mild cerebral atrophy with enlarged

ventricles¹³, lateral ventricular asymmetry¹⁵, corpus callosum hypoplasia¹⁵, aqueductal stenosis with hydrocephalus^{17,18} and arachnoid cyst¹⁹. Apart from these abnormalities, bilateral occipital polymicrogyria¹⁸, periventricular nodular heterotopia⁶, bilateral perisylvian polymicrogyria²⁰, diffuse pachygyria¹⁵, and unilateral hippocampal atrophy¹⁶ can undoubtedly be correlated with seizures. Like the majority of previous cases described in the literature, our patient also had a normal MRI, posteriorly located unilateral epileptiform discharges and very rare seizures with one or two anticonvulsant drugs. Although the mechanisms of seizures in KS are not clear, it has been hypothesized previously that both EEG abnormalities and seizures depend on diffuse brain hyperexcitability rather than abnormalities of cerebral structure¹⁵.

Kabuki syndrome was a clinical diagnosis until 2010, when Ng and colleagues²¹ identified *MLL2* mutations for the first time, as the causative factor of the syndrome. Since then there have been several reports of patient series describing *MLL2* mutations in 52-76% of the cases^{9-11, 22-24}. *MLL2* is a 36.3 kb gene located on chromosome 12q13.12²¹, and encodes a protein of 5537 amino acids which is located in a multiprotein complex. The synthesized protein is a histone H3 lysine 4 (H3K4)-specific methyltransferase that belongs to the SET1 family of human SET-domain protein methyltransferase superfamily²⁵. H3K4 methylation is a transcriptional activation mechanism that regulates the transcription of a set of genes involved in embryogenesis and development²⁶. The *MLL2* gene is comprised of 54 exons and its mutations lead to loss of protein function and therefore repressed transcription of a variety of developmental genes, thus causing multiple organ involvement and characteristic phenotype of the syndrome. Mutations can be observed throughout the gene, however, a great majority of them are located in exons 39 and 48^{9, 23}. Most mutations of the gene are nonsense, leading to formation of a truncated protein. Other mutations such as frameshift, missense and splice site, together with small duplications have also been described^{22, 23}. Exon 39 contains several regions that encode long polyglutamine tracts suggesting the presence of a mutational hot spot, which could explain the high rate of

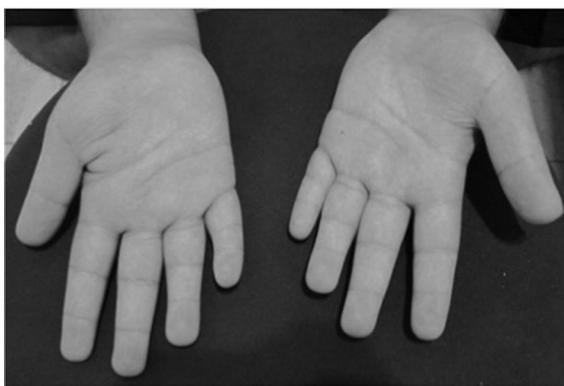


Fig. 1. The patient's fifth fingers are short bilaterally.



Fig. 2. EEG recording reveals paroxysmal sharp waves over the left parieto-occipital region.

mutations in this exon. About 300 mutations have been demonstrated in MLL2 gene so far¹¹. The mutation identified in the present patient which leads to a truncated protein and thus most likely to haploinsufficiency of MLL2 has not yet been described in the literature. Therefore the present patient adds another novel mutation to the previous 45 mutations detected in exon 39²⁴.

In conclusion, Kabuki syndrome is one of the most common causes of developmental delay, which is characterized by peculiar facial features, multiple organ involvement, mental retardation and seizures in some patients. It is not clear why cranial imaging findings can be so heterogeneous in KS. Further studies are needed to unravel the mechanisms of epileptogenesis, especially in patients with normal or nonspecific imaging results. As physicians' awareness of the syndrome increases, more patients are likely to be diagnosed.

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