

Akt3 Partial Deletion in a Child with Microcephaly and Autism: A Case Report and Literature Review

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Abstract

V-akt murine thymoma viral oncogene homolog 3 (protein kinase B, gamma) (*AKT3*) is a component of the phosphoinositide-3-kinase (PI3K)-AKT-mechanistic target of rapamycin (MTOR) signaling pathway. Gain of function mutations of *AKT3*, which lead to activation of PI3K-AKT-MTOR pathway, have been identified in patients with macrocephaly and autism spectrum disorder (ASD), whereas deletions of *AKT3* gene have been reported in patients with microcephaly. To our knowledge, only one patient with *AKT3* deletion was reported to present with microcephaly and autistic behavior (DECIPHER Patient 317423). We present another patient with a heterozygous deletion of *AKT3* with microcephaly and a clinical diagnosis of ASD. These cases support the idea that while *AKT3* gain and loss of function mutations are associated with macro- and micro-cephaly, respectively, patients with both changes can develop autism.

Keywords: *AKT*; Chromosome 1q44; Microdeletion, Chromosome microarray; Microcephaly; Autism

Patient History and Chromosome Microarray Result

The patient is a 9-year-old female who was diagnosed with autism spectrum disorder (ASD) [1]. She presents with behavioral problems including poor social interaction, hyperactivity, anxiety, and strict adherence to routine. Her other symptoms include microcephaly (MIC) but no intellectual disabilities (ID). She is nondysmorphic and has above average intelligence. She was adopted by a couple when she was 6 months old. Therefore, there is limited information about her parents or other family members. However, there is reported family history of psychiatric illnesses of her biological relatives (**Figure 1**). Her three biological siblings were all diagnosed with ASD and attention-deficit/hyperactivity disorder (ADHD). Her biological mother has been diagnosed with obsessive compulsive disorder, bipolar disorder and schizophrenia. Her mother's parents have also been diagnosed with unspecified psychiatric illnesses and/or intellectual disabilities. The patient's paternal history of psychiatric illness is unknown. In 2016 clinical visits, her parents described her ASD symptoms as mild. To identify potential genetic cause of her ASD diagnosis, blood samples were collected for chromosomal microarray (CMA) and fragile X syndrome testing. Her result for fragile X syndrome was negative.

Chromosomal microarray was performed using peripheral blood and examined with Cytoscan HD microarray (Affymetrix, Santa Clara, CA, USA). This array consists of 2,696,550 oligonucleotide probes, including 1,953,246 distinctive non-polymorphic oligonucleotide probes, and 743,304 single nucleotide polymorphism (SNP) probes. Genomic DNA (gDNA) was extracted and purified from whole blood sample using Gentra Puregene Blood Kit (Qiagen Inc., Valencia, CA, USA). Procedures for DNA digestion, adapter ligation, polymerase chain reaction (PCR), amplicon DNA fragmentation, labeling and hybridization of the arrays were performed according to manufacturer's instructions

(Affymetrix, Santa Clara, CA, USA). Results were investigated using the Chromosome Analysis Suite (ChAS) made by Affymetrix (Santa Clara, CA, USA). The settings for smallest copy number variation (CNV) regions in ChAS were 25 Kb and 25 markers for losses, and 50 Kb and 50 markers for gains. CMA identified a 239 Kb deletion in 1q44 (**Figure 2**). This deletion included the 5' part of *v-akt* murine thymoma viral oncogene homolog 3 (protein kinase B, gamma) (*AKT3*).

From March 2013 to March 2018, 1,200 germline CMA results were generated in the Molecular Diagnostics Laboratory at the University of Texas Medical Branch (UTMB) in Galveston, Texas, and our patient was the only case carrying 1q44 microdeletion affecting *AKT3* gene. We performed chart review of this patient using UTMB's electronic medical record. The study was approved by UTMB institutional review board (IRB).

To facilitate the assignment of the clinical significance of this deletion, we performed a literature review and database search for individuals carrying a pure *AKT3* deletion involving at least one exon of this gene and identified 14 patients (**Table 1**). Of these 14 patients, 12 displayed microcephaly, and two patients (our patient and DECIPHER Patient 317423) presented with autistic behavior.

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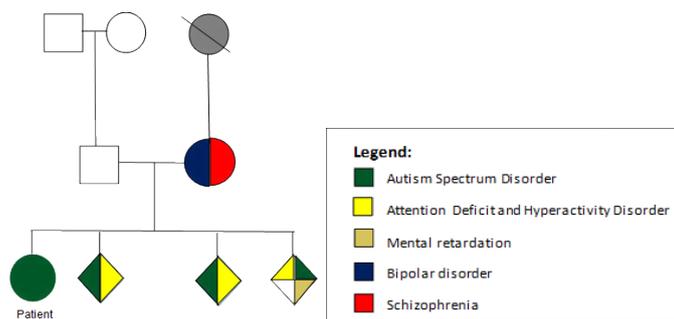


Figure 1: Pedigree of the patient's pertinent biological family members with psychiatric history.

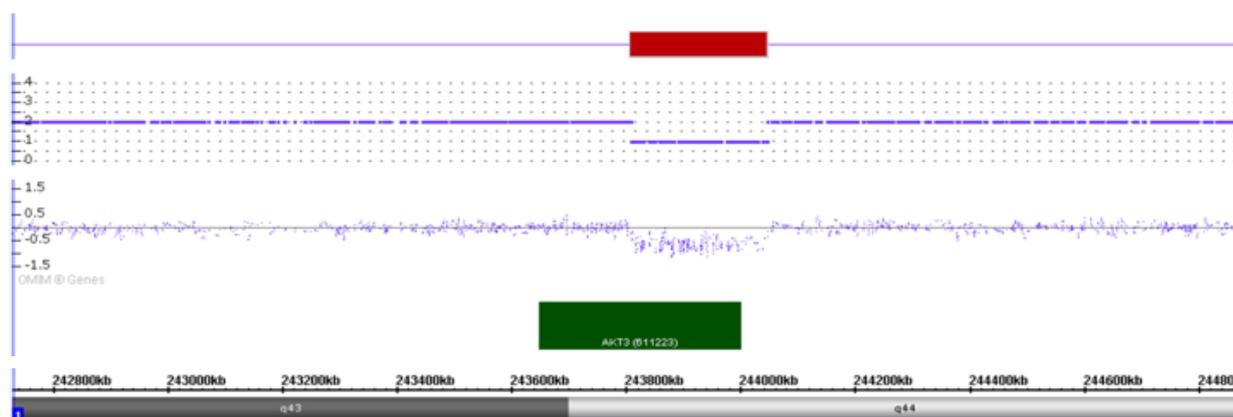


Figure 2: Chromosomal microarray detected a 239 Kb loss in 1q44; ARR[GRCh37] 1q44(chr1:243,810,929-244,050,033)x1. The heterozygous deletion includes 5' untranslated region (5' UTR) and exons 1-3 of *AKT3* gene (RefSeq NM_181690).

Table 1: *AKT3* deletions and associated clinical presentations.

Case No.	Reference	Gender	Deleted Region	Deletion Size (Kb)	Inheritance	Clinical Symptoms
1	Our Patient	F	ARR[GRCh37] 1q44(c hr1:243,810,929-244,050,033)x1	239	Unknown	MIC, ASD
2	Gai et al. [2], Proband	M	ARR[GRCh37] 1q44(c hr1:243,724,990-243,786,019)x1	396	Paternal	MIC, DD , hypotonia, feeding difficulties, minor dysmorphism
3	Ballif et al. [3], Patient 10	M	ARR[GRCh36] 1q44(chr1:241,867,534-242,000,584)x1	133	Maternal	MIC, displacement of posterior pituitary with Rathke cleft cyst
4	Ballif et al. [3], Patient 11	F	ARR[GRCh36] 1q44(chr1:241,897,641-242,110,212)x1	213	Unknown	MIC, borderline left ventriculomegaly; small white matter lesion on brain MRI
5	Nagamani et al. [4], Patient 5	F	ARR[GRCh36] 1q44(chr1:241,833,595-241,925,842)x1	92	Unknown	MIC, global DD dysmorphism, genitourinary abnormalities, ventriculo-septal defect
6	DECIPHER Patient 277653	F	ARR[GRCh37] 1q44(chr1:243,786,018-243,949,960)x1	164	Unknown	MIC, cognitive Impairment
7	DECIPHER Patient 317423	M	ARR[GRCh37] 1q44(chr1:243,734,763-243,827,143)x1	92	Unknown	MIC, autistic behavior, global DD
8	DECIPHER Patient 263408	F	ARR[GRCh37] 1q44(chr1:243,736,246-244,072,145)x1	336	From normal parent	Exaggerated cupid's bow, intellectual disability, nasal speech, obesity
9	DECIPHER Patient 277653	F	ARR[GRCh37] 1q44(chr1:243,786,018-243,949,960)x1	164	Maternal	MIC, cognitive impairment
10	ClinVar SCV000173734	Unknown	ARR[GRCh37] 1q44(chr1:243,949,931-244,033,798)x1	84	Unknown	DD and/or other significant developmental or morphol tensin homolog (PTEN) harmartoma tumor syndromeogical phenotypes
11	ClinVar RCV000512256	Unknown	ARR[GRCh37] 1q44(chr1:243,746,779-243,904,486)x1	158	Maternal	MIC, intrauterine growth retardation; metatarsus adductus, syndactyly
12	ClinVar RCV000510196	M	ARR[GRCh37] 1q44(c hr1:243,681,404-244,004,149)x1	323	Maternal	MIC, muscular hypotonia, premature birth
13	ClinVar RCV000511838	Unknown	ARR[GRCh37] 1q44(c hr1:243,706,704-243,827,143)x1	120	Unknown	MIC, global DD
14	ClinVar RCV000510823	Unknown	ARR[GRCh37] 1q44(c hr1:243,766,497-243,882,990)x1	117	Unknown	MIC, feeding difficulties, hypoglycemia, malnutrition

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To facilitate the assignment of the clinical significance of this deletion, we performed a literature review and database search for individuals carrying a pure *AKT3* deletion involving at least one exon of this gene and identified 14 patients (Table 1). Of these 14 patients, 12 displayed microcephaly, and two patients (our patient and DECIPHER Patient 317423) presented with autistic behavior.

Discussion

In this report, we present a case with a clinical diagnosis of ASD and microcephaly and heterozygous deletion of the 5' part of *AKT3* gene. *AKT3* deletion is frequently involved in 1q43q44 deletion syndrome (OMIM 612337). Microdeletions of 1q43q44 have been associated with a variety of developmental abnormalities of brain, including microcephaly (MIC), agenesis of the corpus callosum (ACC), and seizures (SZR) [2-4]. Genotype-phenotype correlation studies of 1q43q44 microdeletions have associated heterozygous deletions of *AKT3* with MIC phenotypes [2-4] supporting haploinsufficiency of this gene in the development of MIC [2,3]. To date, there have been at least 14 patients with pure *AKT3* deletions, and 12 of the patients have microcephaly (Table 1). Interestingly, our patient and patient #7 (DECIPHER Patient 317423) presented with autistic behaviors.

Autism spectrum disorder (ASD) causes social and behavioral abnormalities in about one in every 68 children in the United States [5]. ASDs occur either sporadically or as familial cases and have been categorized into 2 groups: syndromic ASD and nonsyndromic/idiopathic ASD [6,7]. Examples of ASD related syndromes include fragile X syndrome, RASopathies, Rett's syndrome, tuberous sclerosis complex, and phosphatase and tensin homolog (PTEN) hamartoma-tumor syndrome. On the other hand, nonsyndromic ASDs don't have identifiable symptom association [6,7]. The pathophysiology of ASD is not fully understood and believed to associate with variety of genetic mutations and/or environmental contributions. Proposed causes include brain malformations, dysregulation of cell signaling pathways and gene alterations. Genome wide segmental aneuploidy profiling has revealed numerous submicroscopic copy number variations (CNVs), either inherited or emerged de novo in 7% to 27% of ASD patients [6,8].

AKT3 is a component of the phosphoinositide-3-kinase (PI3K)-AKT-mechanistic target of rapamycin (MTOR) pathway. PI3K-AKT-MTOR signaling cascade contributes to multiple intracellular and extracellular signals and cellular processes including cell proliferation, growth, survival, and nutrient uptake. Dysregulation of this pathway has been attributed to several neurodevelopmental diseases, such as megalencephaly, microcephaly, autism spectrum disorders, intellectual disability, schizophrenia, and epilepsy. Dysregulation of this pathway has been indicated in the development of ASD [7]. ASD has been associated with both upregulation [9,10] and downregulation [11,12] of PI3K-AKT-

MTOR pathway, which is consistent with pleiotropic activity of the pathway and multiple factors that contribute to the development of ASD. Although sample from our patient was not available to examine PI3K-AKT-MTOR pathway activity, the microcephaly presentation is consistent with a downregulation of the pathway.

Because of the important regulatory role of *AKT3* in the PI3K-AKT-MTOR pathway, changes in *AKT3* have the potential to induce pathological changes to the brain. Deletion of *AKT3* may lead to ASD but this genotype to phenotype correlation has rarely described. *AKT3* deletion has been associated with other neurological and psychiatric problems in patients, including global developmental delay, ID, and cognitive impairment (Table 1). This is the second reported case, to our knowledge, of a diagnosed ASD patient with microcephaly presenting with a partial *AKT3* deletion. More cases of pure *AKT3* deletion with detailed clinical information will need to be analyzed to improve our understanding of the phenotypes of a pure *AKT3* deletion. To our knowledge no confirmed de novo deletions of *AKT3* have been reported. Patients were reported to inherit the deletions from normal or affected parents (Table 1) supporting incomplete penetrance of the deletions.

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