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Case Report

Two Pathogenic Variants in Two Ultra Rare Syndromes; Smith- Kingsmore Syndrome and Rubinstein Taybi Syndrome Type2

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Abstract

Smith-Kingsmore Syndrome is a very rare autosomal dominant intellectual disability syndrome characterized by macrocephaly, seizures, umbilical hernia, and facial dysmorphic features. The prevalence of SKS, with 27 patients reported so far, is still unknown. Rubinstein Taybi Syndrome Type 2 (RSTS2) is another rare genetic condition that prevalance is <1/1.000.000. It is characterized by mental and developmental retardation, dysmorphic findings.

We present a seven-year-old girl who was diagnosed with SKS and RSTS2 based on identification of a novel de novo pathogenic variant in the MTOR and EP300 genes (MIM #616638 and #613684) by Whole Exome Sequencing and supported by some characteristic clinical features.

In our patient, pathogenic mutations belonging to two different ultra-rare syndromes were found. However, the patient had clinical findings of only Smith Kingmore Syndrome among the syndromes. Although he had a pathogenic mutation, she did not have the clinical findings of Rubinstein Taybi Syndrome. This the first case presenting two different mutation of these two ultra-rare syndromes.

Keywords: ***Smith-Kingsmore Syndrome, Rubinstein Taybi Syndrome Type2, MTOR, EP300, Exome Sequencing***

Introduction

Smith-Kingsmore Syndrome (SKS) (MIM #616638); is a rare autosomal dominant syndrome that is caused by a heterozygous germline mutation in MTOR gene (MIM #601231) on chromosome 1p36. It was first described by Smith et al. in 2013 and characterized by overgrowth and intellectual disability [Smith et al., 2013]

It is also known as Macrocephaly-intellectual Disability-neurodevelopmental Disorder-small Thorax Syndrome (MINDS; ORPHA 457485).

SKS is an ultra-rare syndrome characterized by macrocephaly, seizures, umbilical hernia, and facial dysmorphic features including frontal bossing, midface hypoplasia, small chin, hypertelorism with downslanting palpebral fissures, depressed nasal bridge, smooth philtrum, and thin upper lip [Moosa et al., 2017]

The prevalence of SKS, with 27 patients reported so far, is still unknown (<1/1.000.000 in ORPHANET) [www.orpha.net]

The mTOR gene is a key regulator of cell growth, cell proliferation, protein synthesis and synaptic plasticity. The mTOR pathway is highly regulated and critical for cell survival and apoptosis [Gordo et al., 2018]. MTOR is functions via two protein complexes, mTORC1 and mTORC2, to control cell proliferation and growth [Yang et al., 2007]

Germline and somatic MTOR genetic alterations that activate mTOR signaling are found in many brain overgrowth disorders such as Focal Cortical Dysplasia (FCD), hemimegalencephaly, and diffuse megalencephaly [Mirzaa et al., 2016] intellectual disability, and seizures MTOR germline mutations in cohorts of patients with epilepsy with or without brain malformations [Moller et al., 2016]

Constitutive mTOR activation due to germline MTOR variants are associated with intellectual disability and macrocephaly [Baynam et al., 2015; Tsai et al., 2011] as well as

polymicrogyria, seizures, and café-au-lait macules [Baynam et al.,2015]

Rubinstein Taybi Syndrome Type 2 (RSTS2) is another rare genetic condition (ORPHA 353284, MIM# 613684) that prevalence is <1/1.000.000. It is characterized by mental and developmental retardation, microcephaly, highly arched palate, down slanted palpebral fissures, abnormal smile, broad thumbs and halluces. RSTS2 is often caused by mutations in the CREBBP gene (%50-70) and rarely from mutations in the EP300 gene (%3) [www.orpha.net; Tsai et al., 2011]

Materials and Methods

Case Report/Case Presentation

The index patient presented to our neurology clinic at 7 age for hiperactivity and autistic behaviour and mental and intellectuel disability. She was also diagnosed with learning disability and autistic symptoms, and attention-deficit/hyperactivity disorder. Mother (33a) and father (35a) are nonconsagineous and have three other healthy living children. In her history we found that she is the one of the 34 weeks dichorionic twins, 2800g birth weight, didn't cry at the birth without cyanosis. She discharged after a day of intensive care unit hospitalisation. She had a non-febrile convulsion at first month with recurrences till the first year of her life. She erected her neck at the age of 14th month and walked at the 20th month. She was apathic, uninterested, and neurodevelopmental impaired child. She had bizzare hand movements, swimlike arm movements and got a visual and auditory hallucinations and autistic features. She began to talk at 5th year old of her life and was receiving education in the special education group and needed speech therapy because of disarticulation and learning difficulties.

Physical examination; macrocephaly, tall forehead, frontal bossing, midface hypoplasia, hyper telorism, strabismus, downslanting palpebral fissures, short nose, depressed nasal bridge, smooth phyltrum, thin upper lip, high palate, macrostomia, caries, umblical hernia, short thumb and toes nails. She was consulted general surgeon for umblical hernia. (Figure 1a,b,c,d,e,f)

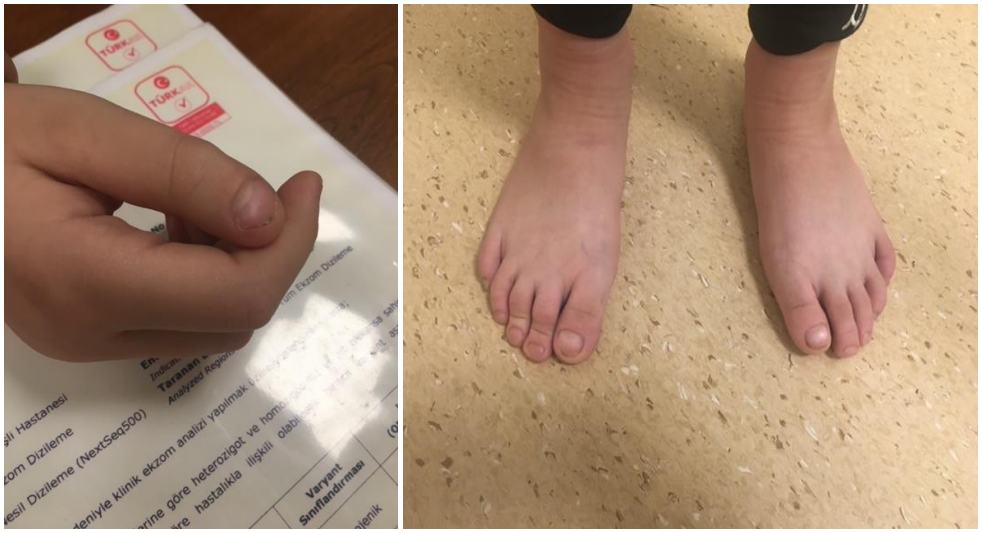

Fig. 1a, b, c, d, e, f: Shows the patient's phenotype. She has only SKS's clinical findings.

The patient has the clinical features of SKS. The clinical findings in our patient of RSTS and SKS are shown in Table 1 comparatively

Table 1: Our patient has the clinical features of both syndromes. The clinical findings in our patient of RSTS and SKS are shown in Table I comparatively

SMITH KINGSMORE SYNDROME		RUBINSTEIN-TAYBI SYNDROME 2; RSTS2	
Caused by mutation in the mechanistic target of rapamycin gene (MTOR, 601231.0001)		Caused by mutation in the 300-KD E1A-binding protein gene (EP300, 602700.0003)	
HEAD & NECK			
- Macrocephaly - Tall forehead - Large anterior fontanel - Frontal bossing - Midface hypoplasia - Small chin	+ + + + + +	-Microcephaly - Micrognathia - Retrognathia	- + +
Eyes			
- Hypertelorism - Downslanting palpebral fissures - Strabismus	+ + +	- Heavy, arched eyebrows - Long eyelashes - Downslanting palpebral fissures, mild	- + +
Nose			
-Short nose - Depressed nasal bridge	- +	- Prominent nose - Beaked nose - Long columella extending below the alae nasi	- - -
Mouth			
- Macrostomia - Open mouth posture - Long philtrum - Smooth philtrum - Thin upper lip	+ + + + -	- Narrow palate - High-arched palate -Dental malocclusion - Overbite - Dental caries- -Grimacing smile	- + + + - +
ABDOMEN-CHEST			
Diastasis recti Umbilical hernia- Small thorax	- + +	- Malrotation (in some patients) - Feeding/swallowing issues beyond the neonatal period (in some patients)	- +
SKELETAL			
Hands			
-Deep palmar creases - Short proximal phalanges - Short distal phalange	- - +	- Broad thumbs - Square distal fingertips- - Broad great toes	? - +
NEUROLOGIC			
- Intellectual disability - Seizures (in some patients) - Mild prominence of the ventricular system - Hypogenesis of the body and the splenium of the corpus callosum - Generalized white matter loss - Small mesencephalon, pons and medulla - Perisylvian polymicrogyria - Heterotopic gray matter in the right frontal lobe	+ + + + +	- Mental retardation, mild to moderate - Autism spectrum disorder (in some patients) - Delayed psychomotor development - Delayed gross motor development - Speech delay - Hypotonia	+ + + + + + +
Behavioral Psychiatric Manifestations			
-Autistic features	+	- Hyperactivity - Behavioral difficulties	+ +

Material and Method

After obtaining written informed consent, blood samples were taken from the patient for genetic study. Genomic DNA was isolated from peripheral blood leukocytes using a QIAamp DNA Blood Mini kit® (Qiagen GmbH, Hilden, Germany) and Clinical Exomes sequencing was performed using Illumina NextSq500 system (Illumina, Inc.). To obtain a clear clinical diagnosis quickly, the patient was screened for causal variants using WES. The candidate variants were first screened with the criterion of a minor allele frequency <1% against the 1,000 Genomes Project, the NHLBI exome variant server or in 50 HapMap control exomes. The area of analysis included each exon and ~20 bp of exon-intron boundaries.

Discussion/Conclusion
Results

It was identified de novo mutations in MTOR gene (c.5663T>G (p.Phe1888Cys) and EP300 gene (c.6627_6638delCCAGTTCCAGCA (p.Asn2209_Gln2213delinsLys) heterozygot deletion-insertion by performed WES. Both variants were described to be disease-causing and patogenic by ClinVar [Handoko et al., 2018]. Sanger confirmation and segregation analysis revealed that all variants occurred de novo, suggesting that they are pathogenic. All other biochemical, immunological and metabolic findings were normal.

Radiology and EEG

EEG was normal. Cranial MRI showed macrocephaly, hyper telorism, cerebral polymicrogyry, mild dilatation of the perivascular system and generalized mild white matter loss. The cerebellum was normal (Figure 2a,b,c)

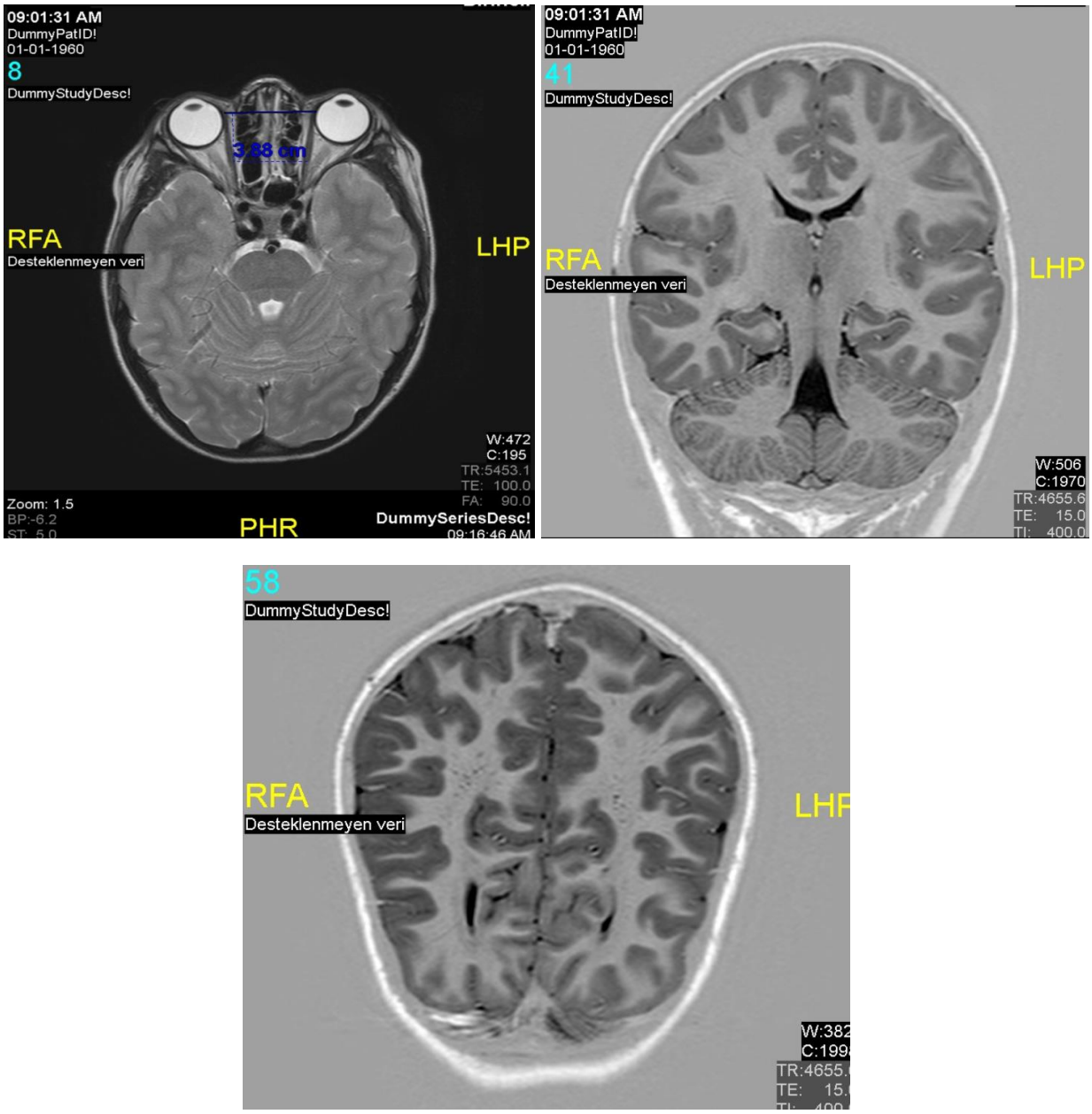

Fig. 2a, b, c: Shows the patient's MRI. She has macrocephaly, hypertelorism, polymicrogyria

Results and Discussion

The first case presenting two pathogenic variants in two ultra-rare syndromes (SKS and RTS-2) and has only one's clinical findings.

This study confirms the important role of somatic MTOR mutations in the pathogenesis of FCD, and jointly with previous reports shows that germline MTOR mutations may contribute to a broad phenotypic spectrum, ranging from focal epilepsy without

MRI-detectable brain abnormalities and normal development, to hemimegalencephaly, intellectual disability, and epilepsy [Handoko et al., 2018]

The treatment effectiveness in these patients with mTORC1 pathway inhibitors needs further evaluation, but meanwhile, screening of MTOR in a broad range of focal epilepsies is warranted.

In this article we observed that our case has the same point with identical twins patients published before (10a-b) This twins has the mutation c.5663A>C/p.Phe1888Cys instead of our patient has c.5663T>G

In this article Moller et al. described patients with the same mutation. But our case presented patogenic variant of RTST2 (EP300 gene) besides the MTOR mutation. Our patient has the two patogenic variants in two different gene but only SKS's clinical findings. In Table 2 shown that comparison of the characteristics of our patient with other published cases of the mosaic MTOR p.Thr1977Ile variant.

Table 2: Comparison of the characteristics of our patient with other published cases of the mosaic MTOR p.Thr1977Ile variant

Characteristics	**Our Patient (MTOR- EP300 mutation)**	**Handoko et al.,2018 Patient 10a MTOR**	**Handoko et al., 2018 Patient 10b MTOR**
Sex/age		F/23	F/23
Variant Cdna protein	c.5663T>G (p.Phe1888Cys)-MTOR c.6627_6638delCCAGTTCCAGCA (p.Asn2209_Gln2213delinsLys) EP300	c.5663A>C p.Phe1888Cys-MTOR	c.5663A>C p.Phe1888Cys-MTOR
Inheritance	Germline de novo	Germline de novo	Germline de novo
Family history of seizures	No	Identical twin sister same phenotype	Identical twin sister same phenotype
Age at seizures onset	2 month	4y	6y
Seizures description	Generalized tonic-clonic or Giddy laughing with hyperactivity	Irresponsive preceded or followed by detached laughing; TCS; convulsive status epilepticus	Giddy laughing with hyperactivity; TCS; convulsive status epilepticus (age 8)
EEG	Normal	Persistent diffuse sharp and slow wave activity, most prominent over right hemisphere	Mild slow background, diffuse and left centro-temporal epileptiform discharges
Epilepsy syndrome	Generalized tonic-clonic	Focal epilepsy, probably frontal or temporal lobe	Focal epilepsy, probably frontal or temporal lobe
MRI Findings	Polymicrogyry, mild prominence of the ventricular system,hypertelorism, generalized white matter loss.	Ventricular prominence with mild extra ventricular enlargement at 6 mo (1.5T)	Mild ventricular prominence at 6 mo (1.5T)
Cognition before onset sz	Delayed	Delayed	delayed
Cognition and behavior after sz onset	Moderate ID, Autism, hallucination, self mutilation	Moderate ID, aerophagia, autism	Moderate ID, autism
Neurologic Examination		Hypotonia, nonverbal, shuffling gait	Hypotonia, nonverbal, shuffling gait
Dysmorphic features, including head circumferences	Macrosefali, tall forehead, frontal bossing, midface hypoplasia, hyper telorism, strabismus, downslanting palpebral fissures, short nose, depresse nasal bridge, smooth phyltrum, thin upper lip, high palate, macrostomia, long thin extremities, umblical hernia, broad-great toes, short thumb and toes nails.	Macrocephaly:HC: 61.3 cm at 12 y (15.8 SD). Facial dysmorphy: prominent forehead, low-set ears, gingival hyperplasia, frontal bossing, kyphosis, micrognathia, long thin extremities	

Gordo et al. has published first 23 patients with SKS, Handoko et al added 24th case, Garcia et al.,(2019) added 25th case with an ant phospholipid syndrome on the same patient. Plaza's case (2020) was the 26th SKS case. Our case will be the 27th case. But the importance of this case who presents a pathogenic variant and clinical findings of another rare syndrome, RTST2. Than it is the first case presenting two different mutations of these two rare syndromes. This case recall us two rare syndrome could be overlapped on a poor child.

Ethics approval and consent to participate

The paper is exempt from ethical committee approval, because it is not clinical research paper. Written informed consent was obtained from the patient for publication of this case report and any accompanying images. If your manuscript does not report on or involve the use of any animal or human data or tissue, please state "Not applicable" in this section.

Data Availability

All data generated or analyzed during this study are included in this article [and/or] its supplementary material files. Further enquiries can be directed to the corresponding author.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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None

Authors' contributions

Yesim Ozdemir, conception of the work, drafting the work, final approval of the publication, the acquisition and analysis of genetic results of WES, agreed the accountability for all aspects

Murat CAG, drafting the work for surgical aspect of the content, final approval of the publication

Munis Dundar, design of the work, the acquisition and analysis of genetic results of WES, final approval of the publication

Aslihan Kiraz, design of the work, the acquisition and analysis of genetic results of WES, final approval of the publication

Cihan Meral, interpretation of data for the work, drafting the work for neurological aspect of the content

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