CLINICAL/SCIENTIFIC NOTES OPEN ACCESS

Expanding the phenotype of *MTOR*-related disorders and the Smith-Kingsmore syndrome

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Neurol Genet 2020;6:e432. doi:10.1212/NXG.0000000000000432

Heterozygous germline mutations in mammalian target of rapamycin (*MTOR*) (OMIM 601231) are known to underlie Smith-Kingsmore syndrome (SKS; OMIM 616638), an infrequent entity with autosomal dominant inheritance, also known as macrocephaly-intellectual disability-neurodevelopmental disorder-small thorax syndrome (ORPHA 457485).[1] Among the clinical features of SKS, the most common features include intellectual disability, macrocephaly, epilepsy, and facial dysmorphism. The aim of this case is to raise awareness of a distinct phenotypical presentation of SKS manifesting with bilateral cataracts and no history of seizures.

Case presentation

A 5-year-old boy with macrocephaly and a history of developmental delay that included lag in motor and language milestones presented to our clinic. He is the firstborn of nonconsanguineous parents with unremarkable medical and family histories. His mother underwent adequate prenatal control and preeclampsia. During the third trimester, macrocephaly was diagnosed on ultrasound suspicious of hydrocephalus. The baby was born by elective cesarean section at 38 weeks because of preeclampsia and oligohydramnios. Birth weight and length were 3,960 g (P90) and 53 cm (P80), respectively. Head circumference referred to be normal although it was not recorded. Diagnosis of cryptorchidism prompted bilateral orchidopexy at 10 months of age. Brain MRI was performed showing left temporal lobe cyst (figure, A and B). At 5 years of age, physical examination was remarkable for macrocephaly and prominent and downward oblique eyes with telecanthus, strabismus, and bilateral cataracts (figure, C and D). In addition, nevus flammeus on nasal bridge and tip, anteverted nostrils, and a long philtrum were also observed. No visceromegalies were palpable, and no other notable features were found. Somatometry showed a weight of 20.5 kg (P50-75), height of 113.5 cm (P75), head circumference of 56 cm (+3 SD), inner intercanthal distance of 4 cm (>2 SD), philtrum of 2 cm in length (+2 SD), palpebral fissures of 3.2 cm in length bilaterally (+1 SD), auricular pavilions of 6 × 4 cm (P50), hand of 13 cm (P75-97), and middle finger of 6 cm (P75-97). On cranial X-rays, increased anteroposterior diameter (dolichocephaly) was observed with no other evident abnormalities. With clinical suspicion of SKS, an exome sequencing was performed.

Results

The clinical exome was made, resulting in the diagnosis of a monogenic disorder, clinically indistinctive from Smith-Kingsmore, Weaver, and Marshall syndromes. According to the American College of Medical Genetics and Genomics (ACMG) classification, a likely pathogenic variant was identified in heterozygosis in the *MTOR* gene, c.5663T>G (p.Phe1888Cys). The reported variant was not found in gnomAD exomes nor genomes. However, in silico analysis (Functional Analysis through Hidden Markov Models, MutationAssessor, MutationTaster, and

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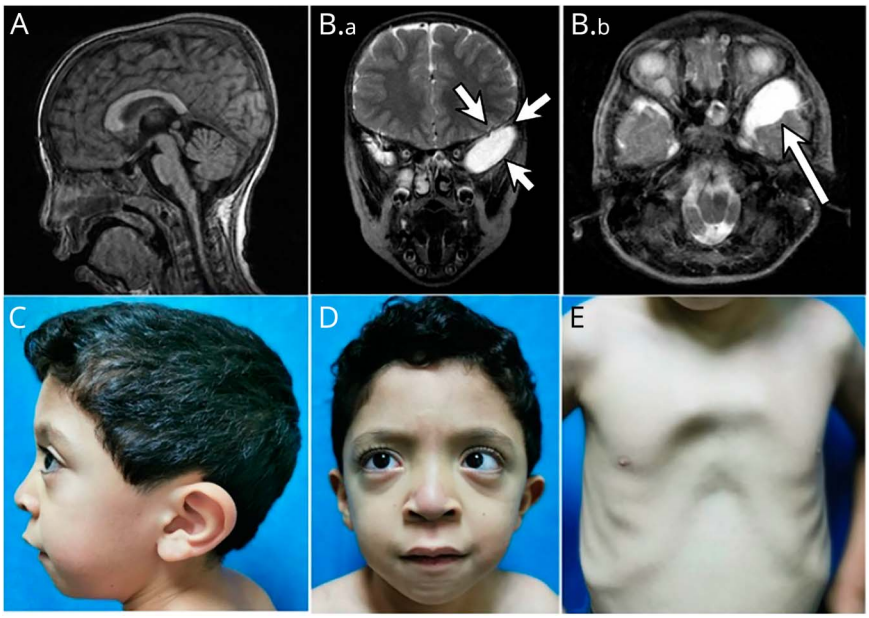
The Article Processing Charge was funded by the Authors.

Figure Physical examination and radiologic images



(A) Brain MRI in T1 sagittal sequence identifying megalencephaly. (B) Brain MRI in T2 sequence, (B.a) coronal and (B.b) axial both showing an arachnoid cyst in the left temporal pole (Galassi classification type I) (arrows). (C) Macrocephaly: low implantation and dysplastic ear pavilions with prominent antihelix. (D) Oblique downward palpebral fissures of 3.2 cm each (>1 SD) with hypertelorism. Strabismus and bilateral cataracts: flammeus nevus on bridge and nasal tip, anteverted nasal wings, and long philtrum (Likert III). (E) Pectus excavatum and nipples of low implantation with teletelia.

Sorting Intolerant from Tolerant) predicts this variant as pathogenic. The result obtained is compatible with the genetic diagnosis of the Smith-Kingsmore syndrome. Neither of the parents were tested for this variant because they presented with no clinical suspicion for SKS.

Discussion

The first SKS case reported was a girl with megalencephaly and intractable seizures, in which an exome sequencing showed a phenotypically relevant heterozygous de novo variant, c.4448G>T (p.Cys1483Phe) in *MTOR*.[2] Except for the seizures, our patient did show common characteristics of SKS, although cataracts have never been described. The detected variant in the *MTOR* gene has been previously reported in a pair of twins, who presented with seizures, cognitive delay, intellectual disability, behavioral disorders, hypotonia, and macrocephaly.[3] It is classified as likely pathogenic (Class 2) according to the recommendations of the ACMG.

It is well known that mammalian target of the rapamycin (mTOR) pathway integrates both intracellular and extracellular signals. As such, it serves as a regulator of cell metabolism, growth, proliferation, and survival. The mTOR protein is a 289-kDa serine/threonine kinase and belongs to the phosphoinositide 3-kinase (PI3K)–related kinase family. This kinase positively regulates cell growth and proliferation by promoting many anabolic processes, including biosynthesis of proteins, lipids, and organelles.[4] Mutations in genes in the PI3K/Akt/mTOR pathway have also been described in multiple (hemi)megalencephaly-associated syndromes, including megalencephaly-polymicrogyria-polydactyly-hydrocephalus and megalencephaly capillary malformation syndrome.[5] In 2017, 4 patients with SKS were described, claiming that it belongs to the group of "mTORopathies," a term introduced to describe neurologic disorders characterized by the altered cerebrocortical architecture, abnormal neuronal morphology, and intractable epilepsy as a consequence of mTOR signaling hyperactivation, suggesting a histopathologic substrate for epileptogenesis.[6] A recently published article reported a de novo *MTOR* gain of function variant in a patient with SKS and antiphospholipid syndrome, expanding both the genetic and phenotypic spectra of *MTOR*-associated diseases.[7]

Conclusion

To date, only 10 *MTOR* gene variants have been described in 28 families with SKS. We hereby describe an unusual presentation of the spectrum of mTORopathies. In this particular case, the patient presented with bilateral cataracts and remarkably no history of seizures in a 5-year lapse.

Study funding

No targeted funding reported.

Disclosure

A. Elizondo-Plazas, M. Ibarra-Ramírez, A. Garza-Báez, and L.E. Martínez-de-Villarreal report no disclosures relevant to the manuscript. Go to Neurology.org/NG for full disclosures.

Publication history

Received by *Neurology: Genetics* December 25, 2019. Accepted in final form April 9, 2020.

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Marisol Ibarra-Ramírez, MD	University Hospital "Dr. José E. Gonzalez," UANL	Data collection and revision of the manuscript
Azalea Garza-Báez, MD	University Hospital "Dr. José E. Gonzalez," UANL	Imaging interpretation and data analysis
Laura Elia Martínez-de-Villarreal, MD	University Hospital "Dr. José E. Gonzalez," UANL	Revision for intellectual content

References

1. Moosa S, Böhrer-Rabel H, Altmüller J, et al. Smith-Kingsmore syndrome: a third family with the MTOR mutation C.5395G>A p.(Glu1799Lys) and evidence for paternal gonadal mosaicism. Am J Med Genet A 2016;173:264–267.
2. Smith L, Saunders CJ, Dinwiddie DL, et al. Exome sequencing reveals de novo germline mutation of the mammalian target of rapamycin (MTOR) in a patient with megalencephaly and intractable seizures. J Genomes Exomes 2013;2:63–72.
3. Møller RS, Weckhuysen S, Chipaux M, et al. Germline and somatic mutations in the MTOR gene in focal cortical dysplasia and epilepsy. Neurol Genet 2016;2:e118.
4. Laplante M, Sabatini DM. MTOR signaling at a glance. J Cell Sci 2009;122: 3589–3594.
5. Baynam G, Overkov A, Davis M, et al. A germline MTOR mutation in aboriginal Australian siblings with intellectual disability, dysmorphism, macrocephaly, and small thoraces. Am J Med Genet A 2015;167:1659–1667.
6. Gordo G, Tenorio J, Arias P, et al. MTOR mutations in Smith-Kingsmore syndrome: four additional patients and a review. Clin Genet 2018;93; 762–775.
7. Rodríguez-García ME, Cotrina-Vinagre FJ, Bellusci M, et al. A novel de novo MTOR gain-of-function variant in a patient with smith-kingsmore syndrome and antiphospholipid syndrome. Eur J Hum Genet 2019;27:1369–1378.