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CORRESPONDENCE

# Correspondence on "Clinical spectrum of MTOR-related hypomelanosis of Ito with neurodevelopmental abnormalities," by Carmignac et al.

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**To the Editor:**

We read with great interest the article by Carmignac et al. [1], which offers an unexpected hint about the group of conditions caused by *MTOR* pathogenic variants. Among them, Smith–Kingsmore syndrome (SKS, OMIM 616638) is better characterized. SKS is an autosomal dominant disorder caused by pathogenic heterozygous germline activating variants in *MTOR* and characterized by macrocephaly, megalencephaly, intellectual disability, seizures, and clear-cut dysmorphic features [2]. Somatic variants in *MTOR* have been found in patients showing mild SKS features, such as subtle dysmorphisms, inconstant intellectual disability of variable degree, seizures, hemimegalencephaly or focal cortical dysplasia/polymicrogyria. In such cases, patchy hypopigmentation of the skin (i.e., hypomelanosis of Ito [HI])—a feature that coincides with somatic mosaicism—has sometimes been described [3–5]. Based on these assumptions, it is clear that somatic pathogenic variants of *MTOR* can cause a spectrum of phenotypes resembling SKS and characterized by segmental or nonsegmental distribution, according to the mosaicism patterning (i.e., group B, according to the most recent mosaicisms classification [6]).

In Carli et al. [7] we reported the case of a 7-year-old boy with hemimegalencephaly, generalized seizures, mild developmental delay, HI, and lateralized overgrowth (LO) of the entire left side of the body. This represents the first report demonstrating that LO can be one of the features associated with somatic pathogenic *MTOR* variants. We take this opportunity to describe a case, similar but more severe in presentation than the one of our first report. This patient, first child of healthy nonconsanguineous Arab parents, was born at term by vaginal delivery after an unremarkable pregnancy along with normal birth parameters. At 4 months of age, he presented with seizures, characterized by hypertonia and ocular deviation. Electroencephalogram (EEG) revealed abnormal electrical activity in the posterior left hemisphere. Brain magnetic resonance image (MRI) demonstrated focal cerebral hypertrophy of the whole left hemisphere, consistent with hemimegalencephaly, a thin frontal horn, a short corpus callosus, and left ventricle dysmorphisms. Poor gray/white matter differentiation consistent with retarded myelinization and frontal-precentral polymicrogyria were also evident. At physical examination, he showed macrocephaly (+2.0 SDS), downward palpebral fissures, telecanthus, strabismus, nevus simplex on nasal root and forehead, and anteverted nostrils. LO with S/V-shaped and whorled patterned hypopigmentation, along Blaschko's lines, was evident along the left side of the body. Neuropsychomotor development was slightly retarded, with development of social smile, head control, sitting position at 6, 7, and 9 months of age, respectively. A deep next-generation sequencing (NGS) on DNA extracted from dermal fibroblasts in normal and hypopigmented skin revealed a mosaic *MTOR* c.5917A>T (p.Ile1973Phe) pathogenic variant (Supplementary Fig. 1A). This variant was previously reported only in the COSMIC Database for breast, bladder, and kidney tumor tissue samples. In the patient's dermal fibroblasts, derived from the biopsy of hypopigmented skin, we investigated *MTOR* activity by assessing AKT and p70S6K phosphorylation status. Immunoblot experiments showed increased levels of phosphorylated AKT (ser473) and p70S6K (thr389) in primary cultured fibroblast, harboring the p.(Ile1973Phe) *MTOR* variant compared to controls, resulting in a constitutive MTOR (mTORC1/2) activation and a suppression of melanogenesis (Supplementary Fig. 1B). These results confirmed the pathogenetic role of the p.(Ile1973Phe) *MTOR* variant identified, corroborating what emerged in cell-based assays [8].

These reports, with some patients described in the paper of Carmignac et al. [1], demonstrate that cases with mosaic *MTOR* variants and lateralized or patchy distribution of the SKS features are increasingly recognized and diagnosed, and have been likely underestimated in the past. However, in their paper, Carmignac et al. [1]. approached these disorders from a different perspective, starting from a group of patients with HI and *MTOR* variants. They demonstrated that a subset can have neurologic findings (8/15), facial dysmorphisms (9/15), and/or LO (6/15) as additional features, or can present with isolated HI (2/15). From this view, we want to emphasize that cases described by Carmignac et al. [1] do not represent a different disease entity, but rather the mild end of phenotypes described in mosaic *MTOR* variants. Besides not describing a new condition or association, their report further corroborates that germinal and mosaic *MTOR* variants create a range of phenotypes depicting a wide spectrum, which largely depends on tissue extension and levels of somatic mosaicism as observed in several related disorders (e.g., *PIK3CA*-related overgrowth spectrum). SKS represents the severe end of the spectrum, while isolated HI represents the mild one, at the other end of the spectrum. Our two cases, characterized by similar features of varying severity, represent bridge cases between SKS and phenotypes described by Carmignac et al. [1] Clearly, there is no need to define a separate disease entity in patients with HI + LO/neurological findings. Given these observations, it is obvious that there is instead a need to improve disease classification and terminology uniformity. Separation of these disorders based on their phenotype rather than molecular anomalies is fundamentally misleading, whereas grouping them based on a common molecular mechanism (i.e., gain-of-function pathogenic variant in *MTOR*) would be preferable. However, the *MTOR* mutational status—i.e., mosaic or germinal—is insufficient to separate typical SKS from highly overlapping segmental phenotypes: it is rather more comprehensive and exhaustive grouping all phenotypes together, regardless of *MTOR* mutational status, to avoid misleading discrepancies. The separation of mosaic and germinal cases, as well as a precise definition of the mosaic level and extension, is anything but easy in clinical practice and—apart from implications of inheritance—is sometimes academic, representing an end in itself.

We must adopt a shared terminology to group all phenotypes due to somatic or germline pathogenic variants in *MTOR* under a common definition—as "MTOR-related disorders" [9]—or alternatively, to adopt an umbrella acronym such as "MROS"

(MTOR-related overgrowth spectrum), to be parallel with strongly similar conditions, such as PIK3CA-related overgrowth spectrum (PROS).

## DATA AVAILABILITY

All data supporting this correspondence are included.

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## ETHICS DECLARATION

Written informed consent to perform genetic testing with additional studies was obtained from the family, using a form approved by the Ethics Committee of Azienda Ospedaliero Universitaria C. Policlinico di Bari, Italy, in line with principles of the Declaration of Helsinki and other applicable local ethical and legal requirements.

## COMPETING INTERESTS

The authors declare no competing interests.

## ADDITIONAL INFORMATION

**Supplementary information** The online version contains supplementary material available at https://doi.org/10.1038/s41436-021-01256-0.

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