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CORRESPONDENCE

Response to Resta et al.

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We are grateful to Dr. Resta and collaborators for bringing to our attention two additional case reports of patients with postzygotic *MTOR* variants [1]. Their findings are in keeping with our recently published case series, both at the clinical and molecular level. Mosaic activating *MTOR* variants, p.Cys1483Tyr (previously reported and also found in our series) and p.Ile1973Phe were found in skin DNA from their patients, whereas they were consistently absent from blood DNA.

It is not unexpected that some of these *MTOR* mosaic patients share common clinical findings with Smith–Kingsmore syndrome (SKS), caused by constitutional heterozygous *MTOR* activating variants. Yet, in our opinion, SKS cannot be diagnosed clinically, neither in the patient reported by Carli et al. [2] in the absence of increased birth length, macrocephaly, or typical facial features—nor in most patients in our series, even though seizures/macrocephaly/(hemi)megalencephaly were common, and typical facial dysmorphic features suggestive of SKS were occasionally present. The only constant finding was hypomelanosis of Ito (HI), since we ascertained patients on skin manifestations suggestive of mosaicism.

Although HI has long been considered a nonspecific manifestation of mosaicism, here we consider it specifically related to the *MTOR* variant, as in mosaic *RHOA* or *TFE3* patients [3, 4]. In four mosaic *MTOR* patients, we have found a reduction in melanosomes in the epidermis, as in hypochromic ash-leaf macules in tuberous sclerosis complex. This suggests that hypopigmentation is a direct consequence of mTORC1 activation. This could have been supported by findings by Resta et al. [1], who report "constitutive MTOR (mTORC1/2) activation and a suppression of melanogenesis" in primary cultured fibroblasts from their patient. Unfortunately, we are not aware of any melanogenesis process in skin fibroblasts, and we did not find any evidence for their claim about melanogenesis in their Supplementary Fig. 1B.

We agree that the diagnosis of these syndromes with variable overgrowth requires identification of an *MTOR* variant, but, despite a common molecular basis, we do not think that *MTOR*-related HI and SKS belong to a common clinical overgrowth spectrum. First, their skin phenotypes are strikingly different. Second, in contrast with *PIK3CA*-related overgrowth spectrum (PROS), overgrowth is not a common finding in these patients. Other examples exist in the field of skin mosaicism. For instance, an identical heterozygous *HRAS* p.Gly12Ser variant has been found either in the germline in most cases of Costello syndrome [5], and in a mosaic state in epidermal nevi, sometimes with associated visceral tumors [6], yet their clinical expressions differ radically, and they cannot be considered parts of the same clinical spectrum, although both are rasopathies.

Despite our recent advances in the genetic characterization and understanding of HI, most cases remain elusive. In our pigmentary mosaicism cohort, a majority of patients were not found to carry postzygotic single-gene variants in their skin, in any of the genes reported so far. Yet, from a diagnostic perspective, all these patients should initially be considered clinically under the umbrella term of HI, before undergoing a molecular diagnosis approach guided by careful analysis of associated clinical signs.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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