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Haploinsufficiency of the *MYT1L* gene causes intellectual disability frequently associated with behavioral disorder

To the Editor: We read with great interest the research article by De Rocker et al.[1] on the *MYT1L* gene and its role in intellectual disability (ID). Based on a series of 22 patients with different aberrations affecting this gene (deletions, mutations, and partial duplications), the authors describe the main clinical features associated with *MYT1L* haploinsufficiency as ID (22/22), speech delay (22/22), behavioral problems (19/22), and overweight (17/19). Apart from duplications, whose consequences may differ depending on their position, orientation, and other factors, only four of these patients present alterations affecting the *MYT1L* gene exclusively : two de novo point mutations and two de novo deletions. To contribute to this description, we would like to add one patient with a de novo intragenic deletion of *MYT1L* detected by comparative genomic hybridization array (arr(hg19) 2p25.3(1,843,177x2,1,844,493-1,983,593x1,2,000,941x2)dn).

Our patient is the first daughter of an unrelated healthy couple; the girl was born at 40 weeks of gestation via a natural delivery and had a birth weight of 2,700 g (10th to 25th percentile) and neonatal hypotonia. At the time of examination (at 4.5 years of age), she weighed 18 kg (50th percentile), was 109 cm tall (90th percentile), and presented microcephaly. Neurologically, she presented psychomotor developmental delay; she walked at 31 months and spoke her first words at 18 months, she does not control her sphincters overnight, and she attends a special education center. Behavioral problems fit those of autistic spectrum disorders (aggressiveness toward others, avoidance of eye contact, echolalia, hand and oral stereotypies, and hyperactivity). She also shows convergent strabismus, myopia, recurrent otitis, and seizures.

In relation to the association of *MYT1L* alteration with obesity proposed by De Rocker et al.,[1] our patient, with a weight in the normal range (50th percentile) in spite of a height in the 90th percentile (body mass index of 15.5 kg/m^2), does not fit this criterion. Although overweight in patients with *MYT1L* haploinsufficiency was previously described as an early-onset feature,[2] we cannot reject the possibility that our patient will develop obesity in late childhood, as occurs in other patients.[1] On the other hand, taking into account the World Health Organization definition of overweight and obesity based on both weight and body mass index,[3] it is remarkable that of the four patients with alteration affecting exclusively *MYT1L* who were described by De Rocker et al.,[1] only patient 10, with a body mass index > 30 kg/m^2, strictly meets these criteria.

Conversely, behavioral problems in our patient are strikingly similar to those reported by De Rocker et al,[1] including hyperactivity, aggressiveness toward others, avoidance of eye contact, echolalia, and hand and oral stereotypies. It is also of interest that, in addition to the two DECIPHER database–identified patients mentioned in the article (nos. 314 and 141), a third patient (255731) with a 0.47-Mb deletion affecting exclusively *MYT1L* has ID and autism as the only clinical descriptors.

More patients would be needed to better characterize the resulting phenotype, but, given the clinical similarities between patients with deletion or point mutation of the *MYT1L* gene, it is becoming clear that haploinsufficiency of this gene causes ID frequently associated with behavioral disorders.

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DISCLOSURE

The authors declare no conflict of interest.

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A *PMS2*-specific colorectal surveillance guideline

To the Editor: We read the review by Goodenberger et al.[1] on colorectal surveillance guidelines for *PMS2* mutation carriers with great interest. However, we would like to address two issues by adding data from our cohort consisting of 415 confirmed *PMS2* mutation carriers (the majority of which were recently published (n = 367) but not included in the article by Goodenberger et al.[1]) to offer further perspective on *PMS2* specific guidelines.[2]

First, we would like to emphasize the difference between index carriers and mutation-positive family members when assessing the appropriateness of surveillance guidelines. As the authors rightly point out, colorectal cancer (CRC) at less than 30 years of age could be due to digenic inheritance or a modifier gene because young CRC patients appear to have a relatively low incidence in *PMS2* families. Indeed, the authors note that none of the index carriers with CRC at more than 30 years of age reported a positive family history for CRC diagnosed at younger than 30 years. All colorectal cancers diagnosed at an age younger than 30 (n = 7) except one belonged to an index carrier. In the family in which a nonindex individual developed CRC before age 30, the patient died soon after diagnosis and before a *PMS2* mutation in the index was identified. There is thus no evidence in either of the two cohorts, with a combined number of ~300 families, that family members have a high or even moderate risk of developing CRC before age 30, even in this group of highly selected families. Therefore, surveillance starting at age 25—as advised by Goodenberger and colleagues—is not appropriate in our opinion. However, we do agree with the authors that first-degree family members of a young patient with CRC should be counseled accordingly about the possibility of another mutation in a modifier gene and given appropriate surveillance advice, i.e., start surveillance 2–5 years earlier than the age at which the index carrier was diagnosed.

Second, the authors note that the group of mutation carriers with CRC diagnosed before age 30 appears to be a distinct group, indicating the possibility of an additional—second—germ-line mutation. One notable finding herein is that in their cohort all cases had left-side CRC, a nontypical location for Lynch syndrome–associated CRC. Even though this finding was statistically significant, we advise caution in the interpretation of these findings because in our cohort 57% (4/7) of the young CRC patients presented with right-side CRC. This difference illustrates the need for very large cohorts, which can be achieved only through global collaboration.

In conclusion, we believe that, although patient preference should always be taken into account, the combined data from Goodenberger and colleagues' study and ours provide enough evidence to support starting CRC surveillance in monoallelic *PMS2* mutation carriers at age 30. First-degree relatives of index carriers (siblings and children) who presented with CRC before age 30 should be exempt from this rule and start 2–5 years earlier than the age at which this index was diagnosed with CRC.

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Response to ten Broeke and Nielsen

To the Editor: Thank you for the opportunity to respond to the letter from ten Broeke and Nielsen[1] regarding our review article "*PMS2* Monoallelic Mutation Carriers: The Known Unknown."[2] We were delighted to see the publication of data from 98 mostly unpublished families with germ-line *PMS2* mutations, including 2,548 family members with 377 proven carriers, by ten Broeke et al.[3] while our review was in press. Their study greatly expands the number of known families with *PMS2* mutations.