Letter to the Editor

Somatic mosaicism for a FOXG1 mutation: diagnostic implication

To the Editor:

In 2005, Shoichet et al. reported a girl exhibiting severe cognitive disability with a balanced de novo translocation that disrupts the winged-helix transcription factor forhead box G1 (FOXG1) gene (1). Later, three 14q12 interstitial deletions including FOXG1 were identified in patients with intellectual disability, epilepsy, microcephaly, and facial dysmorphism (2). Finally, FOXG1-null mutations were reported in the congenital variant of Rett syndrome (RTT) in two unrelated girls (3). Up to now, 12 FOXG1 point mutations have been identified in patients suffering from typical and atypical forms of RTT (2). In all cases, FOXG1 point mutations were or appeared to be de novo.

Here, we report a 2-year-old boy with a novel FOXG1 mutation, transmitted by an unaffected mother who was found to show somatic mosaicism for the mutation. Familial occurrence and germline mosaicism for FOXG1 mutation have been reported only once, in a case of duplication (4).

This patient was born at term after uneventful pregnancy. His psychomotor development was delayed from the second month of life. He held his head at the age of 1 year but has never been able to sit unaided or walk. He never acquired spoken language and had poor eye contact. He developed infantile spasms at the second month of life. He held his head at the age of 1 year revealed growth retardation, severe generalized dyskinesia and permanent hand to mouth stereotypies. A brain magnetic resonance imaging (MRI) study showed cerebral atrophy. Conventional cytogenetic investigations were normal.

After standard DNA extraction and polymerase chain reaction (PCR) amplification, direct sequencing of FOXG1 coding sequences in patient’s DNA identified a novel heterozygous mutation in coding exon 1. The c.974_975insA mutation (p.Ser326Glufs*129) causes the loss of the JARID1B binding domain. This mutation was not observed among 200 control chromosomes. The mutation was absent from the father’s DNA. However, direct sequencing of the mother’s DNA suggested the presence of a somatic mosaicism (Fig. 1), because a very small amount of the mutated residue was detectable at different positions following c.974 position, and the signal was too weak to be considered as a heterozygous mutation.

In order to determine the level of mosaicism, we developed a real-time allele-specific PCR (AS-PCR) assay for this mutation. The mutant-specific forward primer was 5′-CCGCGCCAGCAGCATTATA-3′ and the reverse primer was 5′-ACGGTCAGCGCGTTGCGGT-3′. Quantitative detection of this mutant was developed using the SYBR Green PCR Master Mix. The melting curve analysis revealed that the mutant-specific amplicon melted at 85.59°C. The standard curve for the mutant allele was generated by a serial dilution of the proband’s DNA with the wild-type DNA on an ABI Prism 7000 sequence detection system ($R^2 = 0.98$). Levels of the mutant allele in the mother sample were calculated based on the value of delta computed tomography and the standard curve. Results showed that 35.6% of leukocytes harboured the mutation.

In order to confirm our results, mosaicism was quantified in another tissue. A skin biopsy was obtained from the mother and primary cultures of fibroblasts were performed. DNA was extracted from fibroblast culture, and similar result was obtained although the level of mosaicism was lower in fibroblasts than in peripheral blood cells. We estimated the level of the mosaicism at 9.7% in mother’s fibroblasts.

Mosaicism has been documented for chromosomal abnormalities, mitochondrial mutations, triplet repeats, and in growing number of dominant and recessive X-linked gene disorders (5). Because a proportion of cells carry the mutation not only in blood but also in other tissues deriving from other cell lineages, it must be assumed that the mutation must have occurred early during embryogenesis in a cell that contributed to both germline and somatic tissues.

We show for the first time to our knowledge that somatic mosaicism for FOXG1 mutations in individuals is not infrequent. This report has important consequences for genetic counselling. The occurrence of somatic and germ cell mosaicism represents a matter of concern to the genetic counsellor, because it causes uncertainty about the recurrence risk in parents who appear to be non-carriers using classical approaches.
Fig. 1. Sequence analysis. Arrows position the nucleotide variation at position c.974 in the proband (a), father (c) and mother’s DNAs [(b) leukocytes; (d) fibroblasts]. Circle highlights the mosaicism in mother’s DNA (b, d).
Acknowledgements

This work was supported by INSERM and Fondation Jerome Lejeune. We gratefully acknowledge the collaboration of patient’s family.

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