Mutational analysis of SHOC2, a novel gene for Noonan-like syndrome, in JMML

Corededdu et al recently reported the discovery of a specific SHOC2 gene mutation underlying a variant of the neuro-cardio-facio-cutaneous (NCFC) syndrome family.1 The common denominator of mutations associated with this group of disorders is their involvement in the dysregulation of the Ras–mitogen-activated protein kinase (MAPK) pathway.2 Mutant SHOC2 undergoes aberrant N-myristoylation that results in constitutive membrane targeting. This in turn is thought to sustain RAF1-stimulated MAPK activation.¹

The Ras-MAPK pathway is central also to the pathophysiology of juvenile myelomonocytic leukemia (JMML) and related myeloproliferative neoplasms.³ Leukemogenic perturbation of the Ras-MAPK pathway in nonsyndromic children results from somatic lesions of the same genes that cause NCFC syndromes when mutated in the germ line, as exemplified by PTPN11⁴ and KRAS.⁵ Moreover, some disorders of the NCFC spectrum (notably Noonan syndrome and neurofibromatosis type 1 [NF-1]) constitute a predisposition for the development of myeloproliferative neoplasms in childhood.

Together, these findings provide a strong rationale to investigate the possible occurrence of somatic SHOC2 mutations in nonsyndromic JMML. Mutations affecting Ras pathway–related genes can be defined in approximately 80% of JMML cases (PTPN11 35%, KRAS/NRAS 25%, CBL 10%, NF1 11%) and are, with very few exceptions, mutually exclusive in the same patient. We performed SHOC2 mutation analyses in a cohort of 22 JMML cases preselected for the absence of mutations in PTPN11, KRAS/NRAS or CBL and without clinical NF-1 features. All children had been enrolled in the European Working Group of Myelodysplastic Syndromes in Childhood (EWOG-MDS) studies 98 or 2006, and samples had been taken after informed consent of patients’ guardians. The entire SHOC2 coding sequence was analyzed by genomic sequencing in granulocyte DNA from bone marrow or peripheral blood of the 22 JMML patients. However, we discovered no pathologic sequence variations.

In conclusion, we found no evidence of leukemogenic SHOC2 involvement in JMML. Although the genetic link between NCFC syndromes and JMML is well established for some Ras-MAPK pathway genes such as PTPN11 and KRAS, the absence of SHOC2 mutations in JMML underscores that this phenotypic duality is not a universal feature of all Ras-related genes. We have previously reported a similar observation for SOS1.⁶ It is obvious that the leukemogenic potential of Ras-MAPK pathway mutations differs between individual genes.

References

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