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Germline Mutations of Mitogen-Activated Protein Kinases Pathway Signaling Pathway Genes in Children

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Abstract : Background and Aims: Cardiofaciocutaneous syndrome (CFC) is an autosomal dominant disorder with the vast majority of cases arising by a new mutation of BRAF, MEK1, MEK2, or rarely, KRAS genes. Here, we report a rare Tunisian case of CFC syndrome for whom we identify SOS1 mutation. Methods: Genomic DNA was obtained from peripheral blood collected in an EDTA tube and extracted from leukocytes using the phenol/chloroform method according to standard protocols. High resolution melting (HRM) analysis for screening of mutations in the entire coding sequence of PTPN11 was conducted first. Then, HRM assays to look for hot spot mutations coding regions of the other genes of the RAS-MAPK pathway (RAt Sarcoma viral oncogene homolog Mitogen-Activated Protein Kinases Pathway): SOS1, SHOC2, KRAS, RAF1, KRAS, NRAS, CBL, BRAF, MEK1, MEK2, HRAS, and RIT1, were applied. Results: Heterozygous SOS1 point mutation clustered in exon 10, which encodes for the PH domain of SOS1, was identified: c.1655 G > A. The patient was a 9-year-old female born from a consanguineous couple. She exhibited pulmonic valvular stenosis as congenital heart disease. She had facial features and other malformations of Noonan syndrome, including macrocephaly, hypertelorism, ptosis, downslanting palpebral fissures, sparse eyebrows, a short and broad nose with upturned tip, low-set ears, high forehead commonly associated with bitemporal narrowing and prominent supraorbital ridges, short and/or webbed neck and short stature. However, the phenotype is also suggestive of CFC syndrome with the presence of more severe ectodermal abnormalities, including curly hair, keloid scars, hyperkeratotic skin, deep plantar creases, and delayed permanent dentition with agenesis of the right maxillary first molar. Moreover, the familial history of the patient revealed recurrent brain malignancies in the paternal family and epileptic disease in the maternal family. Conclusions: This case report of an overlapping RASopathy associated with SOS1 mutation and familial history of brain tumorigenesis is exceptional. The evidence suggests that RASopathies are truly cancer-prone syndromes, but the magnitude of the cancer risk and the types of cancer partially overlap.

Keywords : cardiofaciocutaneous syndrome, CFC, SOS1, brain cancer, germline mutation
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