KRAS G12D mosaicism in a patient with linear epidermal naevus and features of Neurofibromatosis Type 1

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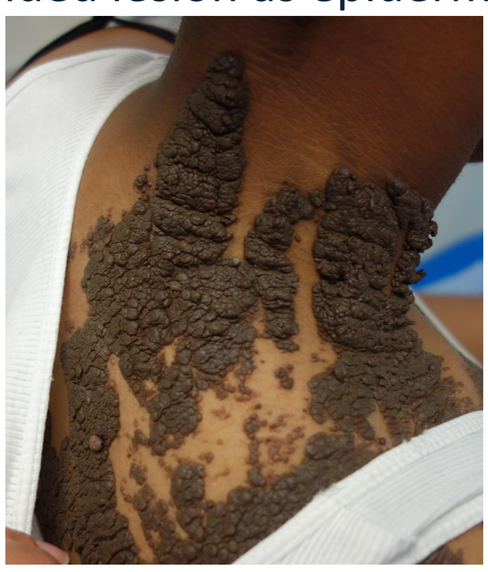
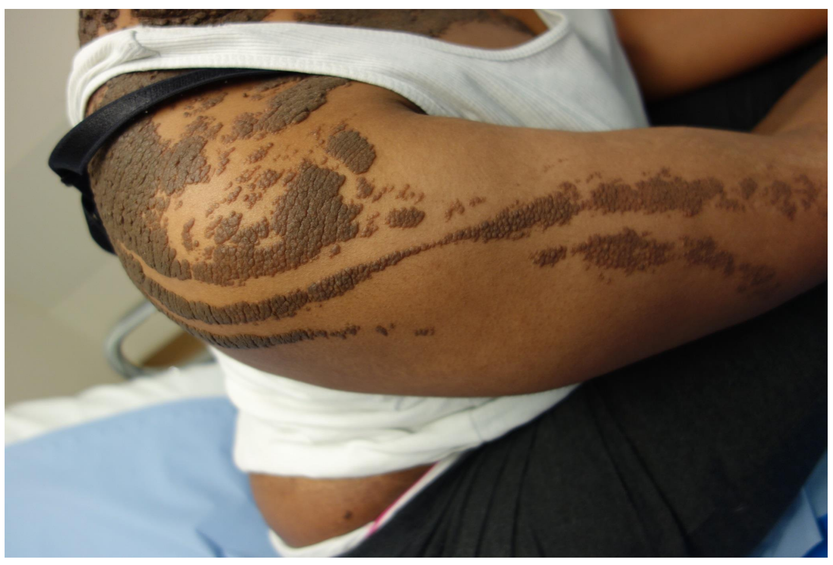
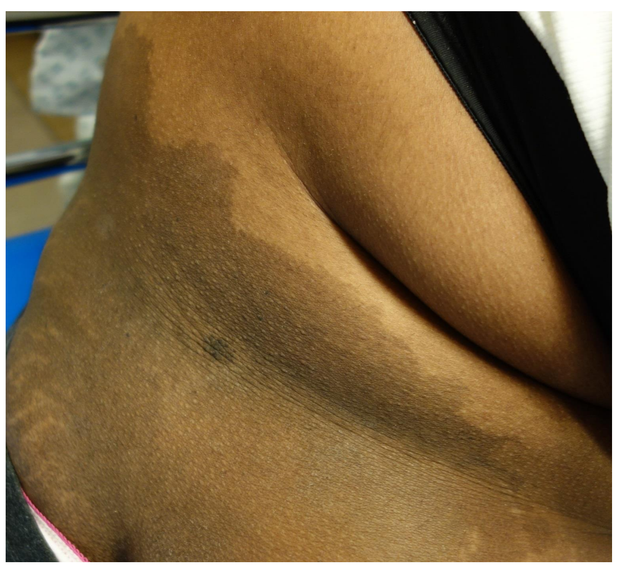
Ras proteins play a central role in cellular signalling process through the two most important Ras-dependent pathways, Ras-Raf-MEK-ERK and PI3K-Akt signalling pathways resulting in activation of these pathways which influences apoptosis, proliferation and differentiation in various tissues. Three highly conserved proto-oncogenes code for the classical Ras proteins: *HRAS, KRAS, NRAS* and any mutations disrupting their function results in many human disorders. These oncogenic mutations in *RAS* genes are activating somatic mutations found in about 30% of human cancers and are absent in non-cancerous tissues of the patients (*KRAS* 21%; *NRAS* 8%; *HRAS* 3%).

RASopathies are a group of developmental syndromes with partly overlapping clinical symptoms that are caused by germline mutations of genes within the Ras/MAPK signaling pathway. The term Mosaic Rasopathies was coined for this group of congenital cutaneous disorders and to distinguish them from germline Rasopathies.

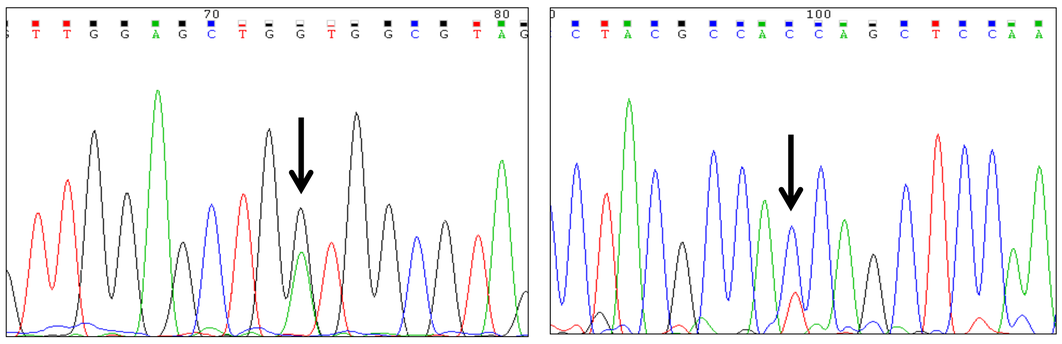
An 18 year old female patient presented with extensive skin lesion on the right side which was noted at birth. At the age of two, she was noted to have a limp with limb length discrepancy. She subsequently had eleven operations to lengthen the right leg which left her with an unusable right leg. On examination, bulky raised verruciform lesion extending from the right arm to the hand following a Blaschkoid distribution and extensive hyperpigmented large *café au lait* patch on the back was observed. In addition, marked scoliosis and small right leg with no movement (held in flexion with no reflexes) was also observed. Investigations revealed vitamin D deficiency with raised parathyroid hormone, bone lesions, multiple neurofibroma on MRI and biopsy confirmed the right sided lesion as epidermal naevus.



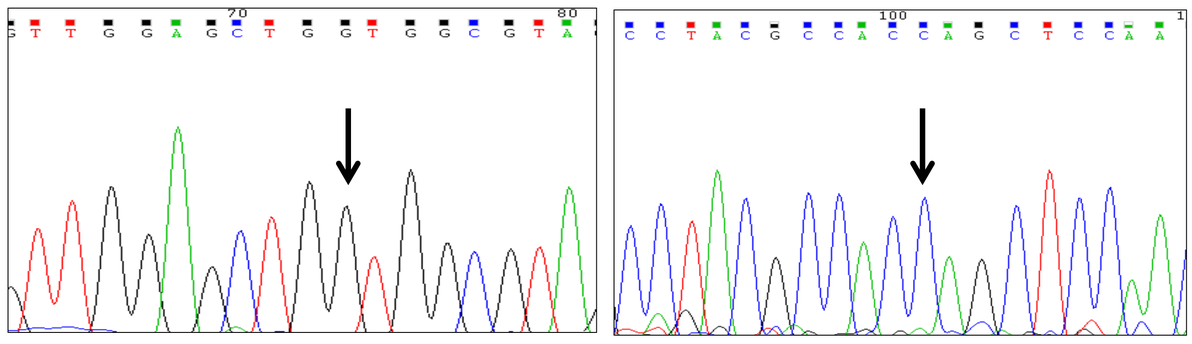




DNA was extracted from the skin obtained from the affected area to screen for mutations in 23 genes within the Ras-MAPK pathway using Ion Torrent's PGM. We detected a pathogenic missense variant c.35G>A p.(Gly12Asp) in *KRAS* proto-oncogene. To confirm the origin of this missense variant, we then tested DNA extracted from blood but did not detect and therefore the variant is thought to be somatic. This pathogenic variant was previously reported in mosaic rasopathies.



DNA extracted from affected areas of skin showing the variant c.35G>A p.(Gly12Asp) in *KRAS* gene



DNA extracted from blood did not carry the variant c.35G>A p.(Gly12Asp) in *KRAS* gene

Mosaic rasopathies are rapidly expanding group of disorders ranging from simple nevoid skin lesions to their systematized forms and multiorgan involvement. Somatic *KRAS* mutations frequently occur in lung, colorectal and pancreatic cancer and rarely in biliary tract and ovaries. The most common somatic mutations in *KRAS* occur at positions 12, 13 and 61, 12 being the most frequent *KRAS* mutation in human cancers in COSMIC database and not observed in human germline cells. *KRAS* G12D has been reported in nevus sebaceus, linear nevus sebaceous syndrome and non-organoid keratinocytic epidermal nevus. Functional studies suggest that germline G12D is lethal when present as germline but nonlethal in a mosaic state.