Mosaic *SMO* mutation in a patient with linear basal follicular hamartomas confirms Happle-Tinschert Syndrome as a variant of Curry-Jones Syndrome

Lovgren ML, Twigg SRF[2], Wilkie AOM[2], Moss C.
[2]Clinical Genetics Group, MRC Weatherall Institute of Molecular Medicine, University of Oxford, John Radcliffe Hospital, Oxford OX3 9DS, UK

Happle-Tinschert syndrome (HTS) is a rare sporadic, multisystem disorder characterised by basaloid follicular hamartomas in a linear distribution suggestive of mosaicism. HTS is phenotypically similar to mosaic Gorlin syndrome and Curry-Jones Syndrome (CJS; OMIM 601707). Mosaicism for a recurrent mutation in *SMO*, encoding the hedgehog signal transducer smoothened, is responsible for CJS. We therefore investigated *SMO* in a patient with HTS.

A 9-year-old boy, born to consanguineous parents of Pakistani origin, had multiple asymmetric congenital anomalies predominantly on the left. Skeletal abnormalities included hypoplastic, duplicated and fused digits and a shortened leg. Skin lesions following Blaschko's lines included whorled, macular, hypopigmented lesions on the trunk and arm, some atrophic and others raised; round, depressed hyperpigmented lesions on the plantar surface, and patchy naevoid hypertrichosis. He had relative microcephaly, but development was normal apart from mild speech delay; an MRI brain scan was normal. He had an undescended testis but no dysmorphic facial features, eye or hearing problems. The family history was unremarkable.

A major lifelong symptom was intractable constipation with massive abdominal distension. Barium meal excluded malrotation and rectal biopsy excluded Hirschsprung's disease.

Biopsies from both hyper- and hypopigmented skin revealed basaloid follicular hamartomas (BFH) confirming the clinical diagnosis of HTS. Genetic analysis of DNA extracted from the skin biopsies revealed a mutation in *SMO* c.1234C>T, p.Leu412Phe which was absent in unaffected skin.

This recurrent mosaic mutation, also found in CJS, basal cell carcinoma, ameloblastoma, and medulloblastoma, causes constitutive activation of the hedgehog-patched-GLI pathway (Twigg SRF *et al*. A Recurrent Mosaic Mutation in *SMO*, Encoding the Hedgehog Signal Transducer Smoothened, Is the Major Cause of Curry-Jones Syndrome. *Am J Hum Genet* 2016;98(6):1256-65). The cause of HTS was previously unknown, but a recent paper reports the same finding as ours (Zenker M *et al.* A postzygotic SMO Mutation Caused the Original Case of Happle-Tinschert Syndrome. *Acta Derm Venereol* 2018 in press).

CJS resembles HTS in the skin lesions and acral skeletal anomalies but differs in manifesting craniosynostosis and gastrointestinal abnormalities (malrotation, dysmotility, myofibromas, and smooth muscle hamartomas). Our patient with severe constipation, not previously reported in HTS but well described in CJS, demonstrates further phenotypic as well as genetic overlap between the two syndromes. Inappropriate activation of hedgehog signalling also explains the similarity of HTS and CJS to mosaic Gorlin syndrome. This genetic finding offers new therapeutic possibilities including with vismodegib, an inhibitor of SMO.