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Article type : Research Letter

Dermatological signs lead to discovery of mosaic *ACTB* variants in segmental odonto-maxillary dysplasia

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/BJD.19339

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Funding: VAK, AT and the work presented in this study were funded by the Wellcome Trust (Grant WT104076MA). SP was funded by Caring Matters Now Charity and by the Newlife Foundation. The work was supported by the GOSHCC Livingstone Skin Research Centre, and by the UK National Institute for Health Research through the Biomedical Research Centre at Great Ormond St Hospital for Children NHS Foundation Trust, and the UCL GOS Institute of Child Health.

Conflict of interest: The authors state no conflict of interest.

Segmental odontomaxillary dysplasia (SOD) is a rare condition of unknown incidence, with approximately 60 cases reported (as reviewed in 2018)[1]. It presents at birth or during childhood with a constellation of ipsilateral facial signs: non-progressive/slowly-progressive overgrowth or undergrowth of soft tissues and/or bones (typically centred on the posterior maxilla, and leading to facial asymmetry), dental anomalies (missing teeth or abnormal dentition), gingival hyperplasia or abnormal gingivae, commissural lip fissures, hypertrichosis, cutaneous hyperpigmentation and/or erythema, cutaneous depression, and lip hypopigmentation. There is no predilection for one side or the other, and there is a male predominance of approximately 1.7:1[2]. Alternative names are firstly Hemimaxillofacial dysplasia[3,4], and secondly Hemimaxillary enlargement, Asymmetry of the face, Tooth abnormalities and Skin findings (HATS)[5]. SOD is a clinical entity known to Dental and Maxillofacial professionals, but virtually absent from the Clinical Genetics and Dermatology literature, despite approximately 40% of patients having cutaneous symptoms or signs.

The sporadic localized and asymmetrical nature of the disorder led us to suspect a mosaic cause, and the hypertrichosis with subtle pigmentation led to a candidate gene approach. Patients 1-3 were recruited from Great Ormond Street Children's Hospital, London, and patient 4 from University Hospital, Zurich, with appropriate approvals (**Table S1, Figure 1**). DNA from affected skin (hypertrichotic in all cases) was extracted directly from fresh or formalin-fixed paraffin-embedded tissue by standard methods, and from blood where available. Exons 4 of *ACTB* and *ACTG1* were sequenced by Sanger or ultra-deep next generation sequencing (Nextera XT, Illumina); no other genes were sequenced.

We discovered that three patients had a recurrent somatic variant in *ACTB* chr7:5568275 G>A NM_001101.3(*ACTB*_v001):c.439C>T p.(Arg147Cys), previously described in Becker's nevus. The fourth had a novel somatic variant in *ACTB*, Chr7:5528646 C>T, c.437C>T, p.A146V, not detected in blood **(Table S1, Figure 1)**, predicted pathogenic *in silico* (SIFT/PolyPhen scores 0/1 respectively) and not present in public databases (ExAc/gnomAD/100K genomes). There are no discernible differences in phenotype in the patient with the novel variant. No variants were found in *ACTG1*.

In a recent study 60% of Becker's nevus cases tested and a single case of Becker's nevus syndrome were demonstrated to carry a recurrent mosaic variant affecting codon 147 of the gene encoding Beta-actin (*ACTB)*[6]. Variants were found specifically within myocytes surrounding hair follicles within the nevi. Functional work exploring various potential avenues was not conclusive, but suggested a possible overactivation of Hedgehog signaling[6]. The same variant in *ACTB* was also recently described in a fibro-osseous maxillary lesion and astrocytoma in one patient without cutaneous features[7].

Different and germline gain-of-function *ACTB* variants have been described in Baraitser-Winter syndrome (BWS)[8], which presents with typical craniofacial features, intellectual disability, muscle wasting (particularly of the shoulder girdle), ocular coloboma, frontal pachygyria and sensori-neural hearing loss[9]. Recently germline loss-of-function deletions in *ACTB* have been associated with a novel developmental disorder, presenting with intellectual disability, growth retardation,

typical facial features and renal and cardiovascular malformations[10]. In both conditions, there are prominent craniofacial features. A systematic review of defined facial features of our patients 1-3 by a single blinded observer (RH), as part of a larger control group of childrens' faces from the same clinic, did not reveal any recurrent dysmorphic features.

We present here that the genetic cause of SOD in four of four patients tested thus far with this rare disease is post-zygotic missense variants in gene *ACTB*. We add to the mutational spectrum seen in *ACTB* mosaicism a novel variant, predicted pathogenic *in silico*, and affecting the neighbouring codon of the mutation commonly seen in Becker's naevi. Given these factors and the similarity of phenotype to the other three cases we strongly suspect this is a causal pathogenic variant.

These patients therefore share a common pathogenesis with Becker's nevus, explaining the pigmentation and hypertrichosis in some cases, but do not appear to share other features with the germline conditions BWS or the newly described developmental disorder of *ACTB* deletions. The potential to pass on these mosaic variants as heterozgous germline mutations however should be considered in future genetic counseling. Clinicians should be alerted to this broad phenotypic spectrum, and consider *ACTB* mutations when presented with cases of SOD or subtle facial under/over growth with or without pigmentary change and hypertrichosis.

Acknowledgement

We gratefully acknowledge the participation of all patients and families in this study, and research coordination by Mrs Jane White.

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Figure legends

Figure 1

Clinical features in Segmental Odontomaxillary Dysplasia

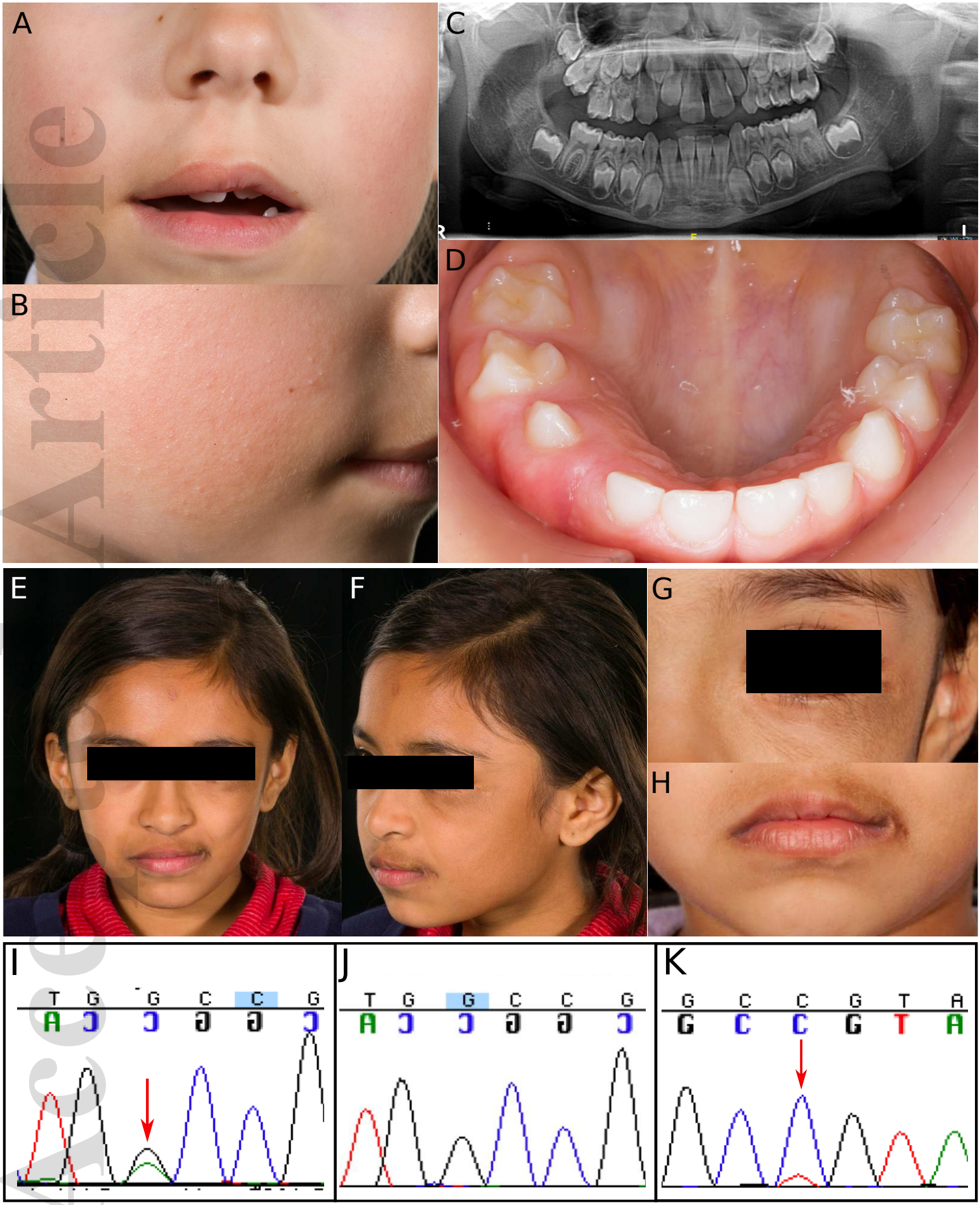
Patient 1 – Subtle facial asymmetry with a thickened right upper lip and a right sided area of subtly increased pigmentation with a strict midline cutoff **(A)**. Area on the right lower cheek with increased follicularity **(B)**. Orthopantomogram showing increased radiolucency of right maxillary bone **(C)**. Overgrowth of right upper gums and increased spacing between the teeth **(D)**.

Patient 3 - Left facial undergrowth, with a left sided commissural lip fissure, and hypertrichosis of the left upper lip and under the left eye **(E-H)**.

Sanger Sequencing from patient 3 showing a novel somatic variant in *ACTB*, Chr7:5528646 C>T, c.437C>T, p.A146V, in skin **(I)** not present in blood **(J)**. Sanger sequencing from patient 4 showing a somatic variant in *ACTB* chr7:5568275 G>A NM_001101.3(*ACTB*_v001):c.439C>T p.(Arg147Cys), previously described in Becker's nevus **(K)**.

Supplementary Table 1 (available at Figshare DOI 10.5522/04/12489140)

Phenotypic and genotypic features of patients with clinical Segmental Odontomaxillary Dysplasia and *ACTB* mosaicism.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