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CLINICAL REPORT

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A family with partially penetrant multicentric carpotarsal osteolysis due to gonadal mosaicism: First reported case

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Abstract

Multicentric carpotarsal osteolysis (MCTO) is an autosomal dominant condition characterized by carpal–tarsal abnormalities; over half of affected individuals also develop renal disease. MCTO is caused by mutations of *MAFB*; however, there is no clear phenotype–genotype correlation. We describe the first reported family of variable MCTO phenotype due to mosaicism: the proband had classical skeletal features and renal involvement due to focal segmental glomerulosclerosis (FSGS), and the father had profound renal impairment due to FSGS, necessitating kidney transplantation. Mosaicism was first suspected in this family due to unequal allele ratios in the sequencing chromatograph of the initial blood sample of proband's father and confirmed by sequencing DNA extracted from the father's hair, collected from different bodily parts. This case highlights the need for a high index of clinical suspicion to detect low-level parental mosaicism, as well as a potential role for *MAFB* mutation screening in individuals with isolated FSGS.

KEYWORDS
focal segmental glomerulosclerosis, MCTO, mosaicism, multicentric carpotarsal osteolysis, v-maf musculoaponeurotic fibrosarcoma oncogene ortholog B (*MAFB*)

Anu Närhi and Andrea Fernandes contributed equally to this study as first authors.

Kristiina Avela and Emma L Duncan contributed equally to this study as senior authors.

1 | INTRODUCTION

Multicentric carpotarsal osteolysis (MCTO) is a rare skeletal disorder caused by mutations of the *MAFB* (v-maf musculoaponeurotic fibrosarcoma oncogene ortholog B) (Zankl et al., 2012). MAFB is a transcription factor; to date, all MCTO-associated mutations cluster within a narrow (18 amino acid) region of the aminoterminal transcriptional activation domain (Mehawej et al., 2013; Mumm et al., 2014; Park et al., 2018; Zankl et al., 2012).

MCTO usually presents in early childhood, with painful swelling of wrists and/or feet. Radiologically, affected individuals develop profound carpal–tarsal abnormalities, including loss of carpal and/or tarsal bones, absent or irregular ossification centers, and abnormal bone morphology including tapering ("sucked candy" appearance) of proximal metacarpals, metatarsals, and distal ends of long bones (Whyte, 2010). Over half of affected individuals also develop renal disease, ranging from mild proteinuria to end-stage renal failure requiring dialysis or transplantation. However, there is no clear phenotype–genotype correlation: both skeletal severity and renal involvement can vary within affected families and between unrelated individuals carrying the same mutation (Mehawej et al., 2013; Zankl et al., 2012).

MAFB negatively regulates osteoclast differentiation (Kim et al., 2007); however, there is surprisingly little evidence to support MCTO as an osteolytic process *per se*. Recent evidence of *MAFB* expression in sub-articular chondrocytes in regions of endochondral ossification suggests that the pathophysiology of MCTO may be abnormal maturation of carpotarsal bones (Lazarus et al., 2017), perhaps explaining the site specificity of skeletal manifestations. MAFB also influences nephrogenesis, facilitating podocyte differentiation and foot process formation (Ikenoue et al., 2018; Moriguchi et al., 2006). However, neither the mechanisms underlying renal manifestations nor those causing bony involvement are fully elucidated.

MCTO is an autosomal dominant condition, with many cases presenting sporadically due to de novo mutations. Although MCTO is usually considered to be completely penetrant, one example of reduced penetrance has been described, in which a child with classical skeletal features of MCTO heterozygous for a *MAFB* mutation (c.167C>T; p.Ser56Phe) had inherited from this variant from his mother—who lacked any clinical, radiological, or biochemical features of MCTO (Dworschak et al., 2013). No difference was evident in wild-type versus mutant allele expression between mother and child (Dworschak et al., 2013).

Here, we describe the first reported family with variable MCTO phenotype due to mosaicism.

1.1 | Case description

The proband is a 22-year-old male and the first child of unrelated Finnish parents. There was no family history of note of skeletal disease; however, his father had received a renal transplant (discussed later).

The proband was born at term, with normal measurements at birth. He learned to walk at 17 months of age. At 2 years of age, he had an orthopedic evaluation because of foot deformity, and at 3 years 8 months, he had a consultation with a pediatric neurologist. By this time, he had clumsiness, foot deformity (pes metatarsovarus adductus), ulnar deviation of wrists, small hands, and swelling of his hands and feet. He received orthopedic shoes and wrist supports. He was also noted to have dysmorphic facial features including hypertelorism, deep set eyes, down-slanting palpebral fissures, small chin, and maxillary hypoplasia. Skeletal survey detected carpal and tarsal osteolysis, leading to the clinical diagnosis of MCTO at age 4 years 6 months (radiographs and images obtained at a later age are shown in Figure 1).

Urine analysis and renal function were initially normal, but at 7 years of age, mild metabolic acidosis and mild proteinuria were noted. At 8 years of age, he was diagnosed with focal segmental glomerulosclerosis (FSGS) after renal biopsy. An angiotensin-converting enzyme inhibitor was initiated, subsequently switched to angiotensin II receptor blocker, with good control of blood pressure. His current estimated glomerular filtration rate is 68 ml/min (creatinine 128 μmol/ml) and he is eutensive.

At 10 years of age, he was found to have a mild left conductive hearing loss (40 dB). Neuropsychological performance was age-appropriate although he had some difficulties in visuospatial function. He attended normal class with the help of a personal assistant. His adult height is 183 cm, with weight 95 kg (BMI 28.4), and occipitofrontal circumference of 59.5 cm (normal range).

The proband's father, now aged 55 years, was diagnosed with FSGS on renal biopsy at age 26 years. Shortly thereafter hemodialysis was started for end-stage renal failure and he received a living-related renal transplant from a first-degree relative at age 27 years. Initially, there was acute rejection of the transplant, which settled with immunosuppression (including prednisolone). His creatinine level started to increase 12 years later; renal biopsy of the transplant kidney performed 2 years later showed glomerulosclerosis but no FSGS. Musculoskeletally, he has osteoporosis of the spine and hip and mild changes of arthrosis/degenerative osteoarthritis affecting one to two joints of each hand; but no signs of osteolysis on radiographs of either his hands or feet (Supplementary Figure S1).

2 | MATERIALS AND METHODS

This study was conducted under appropriate ethics approval (Human Research Ethics Approval HREC/12/QPAH/525); written consent was provided by both the proband and his father.

Sanger sequencing was initially performed on DNA extracted from saliva from the affected child and from blood from his parents as previously described (Zankl et al., 2012) (primers available on request). Subsequently, DNA was extracted from individual hairs collected from different bodily parts of the father (head, cheek, chest, arm, and leg), using the Qiagen EZ1 DNA Tissue Kit (Qiagen, Venlo), and further Sanger sequencing was performed (Parrini et al., 2004). Sequences were aligned and analyzed using Genalys software (Invoke Capital, London), which allows allele ratios to be visualized (Takahashi et al., 2003).

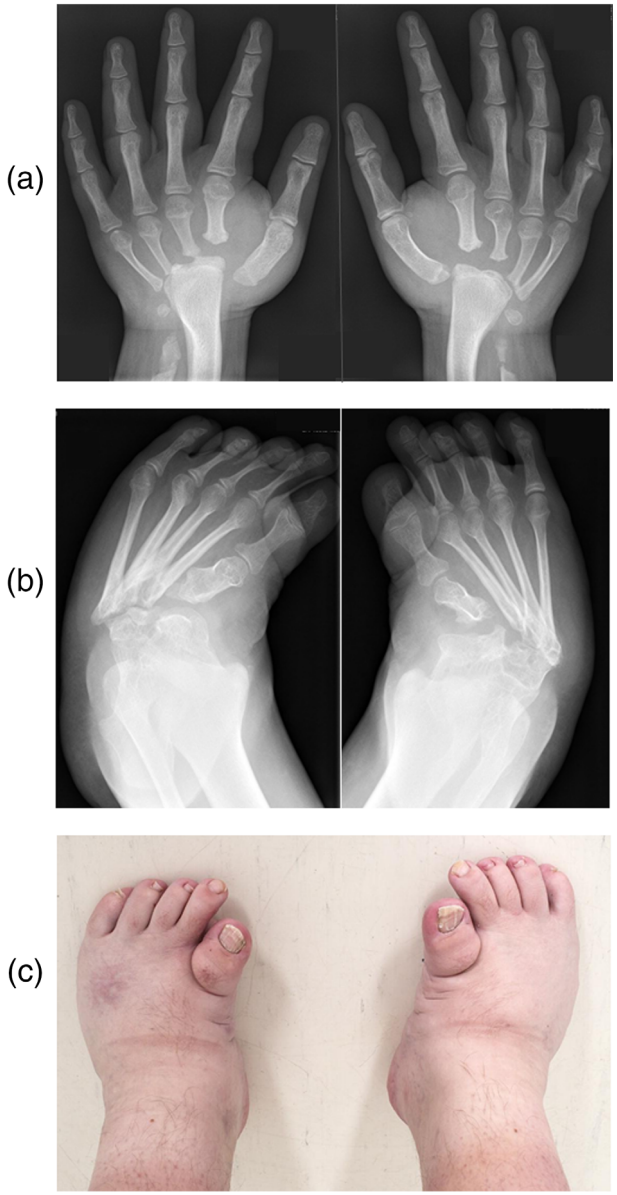

FIGURE 1 Radiographs of the proband's hands and feet. (a) Radiographs of the proband's hands at 14 years of age, showing osteolysis with loss of distal ulna, the proximal tapering of the second to fifth metacarpal bones and the loss of proximal portion of the middle phalanx of the left fifth finger. The bowing of the deformed distal radius and the first metacarpal bone and the absence of all carpal bones other than os pisiforme is noted. (b) Radiographs of the proband's feet at 14 years of age, showing metatarsus adductus foot deformity, tapering loss of the proximal metatarsals, abnormally shaped talus, and calcaneal bone, as well as the absence of navicular and cuneiform bones. (c) Photograph of the proband's feet [Color figure can be viewed at wileyonlinelibrary.com]

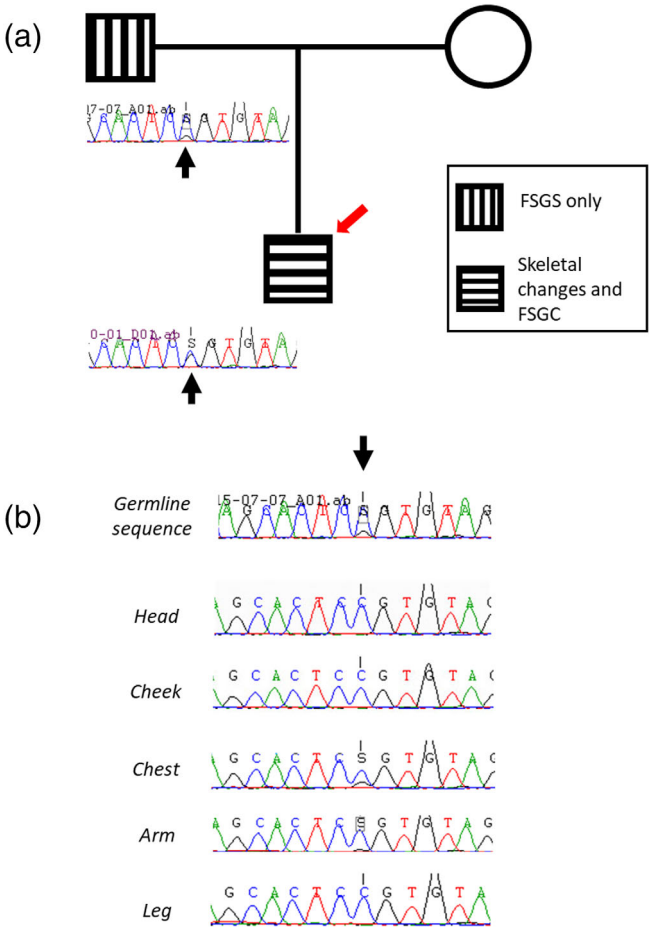

FIGURE 2 Pedigree and sequencing images. (a) Pedigree of proband and parents. Red arrow indicates proband. Black arrow identifies the c.188C>G p.Pro63Arg63 variant in both parent and child. (b) Chromatographs using DNA obtained from different bodily parts of the proband's father showing variation in peak ratios and germline sequence from father for reference (arrow identifying the c.188C>G p.Pro63Arg63 variant) [Color figure can be viewed at wileyonlinelibrary.com]

3 | RESULTS

3.1 | Sequencing results

A mutation in *MAFB* previously associated with MCTO (Mehawej et al., 2013; Zankl et al., 2012) was identified in both the proband and his father (*MAFB* (NM_005461.3) c.188C>G (p.Pro63Arg) (Figure 2(a)). The proband's sequencing chromatograph performed on DNA from buccal swab showed an equal ratio of wild-type to mutant allele, whereas the father's chromatograph showed an unequal ratio (Figure 2(a)). Sequencing of DNA from the father's hairs obtained from different bodily sites showed varying ratios of wild-type to mutant allele(Figure 2(b)), suggesting somatic mosaicism.

This *MAFB* variant (c.188C>G; p.Pro63Arg) is situated in the mutation cluster region of the aminoterminal transcriptional activation domain. Both this variant (Mehawej et al., 2013; Zankl et al., 2012) and another affecting the same base and amino acid but with a different missense change (c.188C>T, p. Pro63Leu) (Mehawej et al., 2013; Stajkovska et al., 2018) have been reported previously in MCTO. The variant is absent from control populations in gnomAD (https://gnomad.broadinstitute.org/; accessed November 17, 2020) and is predicted damaging and/or deleterious by in silico prediction programs Polyphen (Adzhubei et al., 2010), SIFT (Vaser et al., 2016), and

MutationTaster (Schwarz et al., 2014), also detailed in previous reports (Mehawej et al., 2013; Zankl et al., 2012); and fulfills criteria for "likely pathogenic"(Richards et al., 2015).

4 | DISCUSSION

To our knowledge, this is the first reported case of mosaicism in MCTO. Mosaicism was first suspected in this family because of unequal allele ratios in the sequencing chromatograph of the initial blood sample of proband's father (Figure 2(a)). Subsequent sequencing of DNA from hairs drawn from multiple body sites confirmed the presence of two cell populations (one with and the other without the *MAFB* mutation), and, when present, evident in both forward and reverse electrophoretogram traces (Supplementary Figure S2). Our results are consistent with a postzygotic mutational event prior to germ cell formation in the father, allowing the mutation to be transmitted to his child through his germ line.

Somatic mosaicism is the presence of genetically distinct cell lines within one individual, such that a genetic mutation is only evident in a subset of cells, and includes single nucleotide polymorphisms (SNPs), copy number variation, abnormal chromosomal structure, and aneuploidy (Biesecker & Spinner, 2013). The most obvious example is the development of cancer. However, somatic mosaicism is increasingly recognized as a cause of non-Mendelian inheritance and phenotypic variability for many conditions, including skeletal dysplasias (Freed et al., 2014). Variable expressivity and/or reduced penetrance of a mutation can also result in apparent non-Mendelian inheritance (Dworschak et al., 2013); however, in this situation, both parent and progeny carry equally the same mutation in all cells.

In the family reported herein, the proband has classical skeletal features and FSGS with mild renal impairment. In contrast, his father does not have osteolysis but typical—and profound—renal disease. It is possible that the father's renal disease is due to a separate disease process; however, his carriage of a *MAFB* mutation is highly suggestive that this is the cause. FSGS has been observed in individuals with Duane retraction syndrome, who carry mutations in *MAFB* affecting the DNA-binding domain (Sato et al., 2018). In contrast, individuals with MCTO have mutations in *MAFB* affecting the transcriptional domain. To date, no other individual has been reported with mutations affecting the transcriptional domain of *MAFB* and isolated renal disease (i.e., without skeletal features of MCTO); however, *MAFB* is not commonly screened in isolated FSGS.

Although conventional Sanger sequencing was used in this family, the transition to massively parallel sequencing has greatly increased both our understanding of and ability to detect somatic mosaicism. Even low-level somatic mosaicism can be detected with the high read depths typically achieved with these technologies (Cao et al., 2019; Dou et al., 2018; Freed et al., 2014). Moreover, extreme read depth allows a more quantitative assessment of "allele dose," as would quantitative PCR. We acknowledge that Sanger sequencing is not a quantitative methodology, although Sanger sequencing performed on samples with mosaicism identified through exome sequencing can show similar and consistent electropherogram peak height changes (Cao et al., 2019). Small peaks can be observed artifactually in Sanger sequencing; however, the analysis program used here was designed in part to optimize detection of varying allele dose distinct from artifactual noise (Takahashi et al., 2003); and it would be unusual to see variability in both forward and reverse reactions in different samples drawn from a single individual (Supplementary Figure S2). We would have liked to have assessed for mosaicism in DNA from other body fluids and sites; however, transporting tissue samples (particularly liquid samples) from Finland to Australia was difficult (in contrast to transporting germline DNA and labeled hairs).

The presence of parental mosaicism has clear implications for genetic counseling; and the shift toward massively parallel sequencing for diagnostic screening will improve the confidence with which mutations can be truly termed de novo and improve the accuracy of advise given to parents regarding future offspring.

5 | CONCLUSIONS

Genetic mosaicism can cause phenotypic variability in MCTO. In diseases usually attributed to de novo mutations, low-level parental somatic mosaicism should be considered when non-Mendelian inheritance patterns or genotype/phenotype discrepancy is observed. Our results also suggest that screening of *MAFB* in individuals with isolated FSGS may be warranted.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Andrea Fernandes: writing – original draft preparation (equal). Anu Närhi: writing – original draft preparation (equal). Sanna Toiviainen-Salo: writing – review and editing. Jessica Harris: conceptualization; data curation; formal analysis; supervision; methodology; writing – review and editing. Aideen McInerney-Leo: investigation; writing – review and editing. Syndia Lazarus: conceptualization; data curation; formal analysis; supervision; methodology; writing – review and editing. Kristiina Avela: conceptualization; data curation; investigation; writing – review and editing. Emma Duncan: conceptualization; data curation; formal analysis; funding acquisition; resources; supervision; investigation; methodology; writing – original draft preparation; writing – review and editing.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as all new data created or analysed has been included in the manuscript and supplementary information.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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