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Case report

Genetic variation analysis in a Chinese Maffucci syndrome patient

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ABSTRACT

Objective: To report on the molecular genetic analysis of a Chinese patient with Maffucci syndrome.
Methods: Using the genomic DNA extracted from the patient's hemangioma sample, the coding exons and exon/intron splice junctions of the *IDH1 and IDH2* genes were amplified by polymerase chain reaction (PCR) and then sequenced. Genomic DNA was extracted from blood and a hemangioma sample from the patient, and also from her mother's blood, for chromosome microarray analysis (CMA) by Affymetrix CytoScan HD array.
Results: None of the known pathogenic mutations in the whole *IDH1* or *IDH2* genes was found in the patient's hemangioma sample. CMA detected 40 tumor-specific copy number variations (CNVs), and one copy number neutral loss of heterozygosity (LOH) region. Among the 73 known genes included in the 40 CNV regions, only 2 genes, *CHEK2* (604373) located in 22q12.1 and *EP300* (602700) located in 22q13.2, were found to be related to tumorigenesis. We did not find any CNVs at the *IDH1* and *IDH2* loci.
Conclusions: This is the first molecular genetic analysis report on a Chinese patient with Maffucci syndrome and our data enrich the understanding of the genetic background of Maffucci syndrome in different ethnic groups. The relationship between *CHEK2*, *EP300* and Maffucci syndrome needs to be further explored.

1. Introduction

Maffucci syndrome is a rare, nonhereditary and congenital mesodermal dysplasia, characterized by a combination of multiple enchondromas and hemangiomas (Pansuriya et al., 2011a). It was first described in 1881 by Maffucci, and about 200 cases have been described in the literature to date (Cai et al., 2013; Ono et al., 2012). There is neither sex preponderance nor a difference in incidence among races (Amary et al., 2011; Gao et al., 2013; Jermann et al., 2001).

In recent years, the genetic background of Maffucci syndrome has drawn great attention. It has been reported that somatic mosaic isocitrate dehydrogenase 1 (*IDH1*) and *IDH2* mutations are associated with enchondromas and spindle cell hemangiomas in Maffucci syndrome (Amary et al., 2011; Amyere et al., 2014; Pansuriya et al., 2011b). Here, we report on a Chinese female patient affected by Maffucci syndrome, with no somatic mosaic *IDH1* or *IDH2* mutations found in a hemangioma sample. A high-resolution Affymetrix CytoScan HD Array was used to detect the possible related copy number variation (CNV) as well as copy number neutral loss of heterozygosity (LOH).

2. Case report

2.1. Patient data

At first presentation, the patient was 18 years old; she weighed 40 kg and was 126 cm tall. Her left leg was 20 cm shorter than her right leg, while her left arm was 10 cm shorter than her right arm. She was born to non-consanguineous and healthy parents. Her

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mother had a history of two spontaneous abortions, and the patient was born at 28 weeks with no specified cause for the premature birth. She had a healthy younger brother. She complained of a progressive but painless mass in the submental area for more than 2 years. The patient's leg lengths had been unequal since she was one year old, and she had significantly enlarged limbs and joints and multiple purple lesions on her hands and feet since she was 3 years old (Fig. 1). The symptoms gradually worsened with age. Her first menstrual period was at 18 years old; her periods were irregular with small amounts of bleeding.

Radiographs showed multiple, irregularly shaped radiolucent areas with stippled calcification on bilateral pelvis and the left femur, humerus, ulna, radius, and index finger (Fig. 2A–D). The long bones on the left side of her body (including the femur, tibia, fibula, humerus, ulna and radius) were significantly shorter than those on the right. Computed tomographic angiography (CTA) with three dimensional reconstruction displayed the worm-eaten appearance of bone destruction involving the sternum, occipital bone, bilateral pelvis, scapula, ribs, humerus, radius and thumb, and left femur and index finger (Fig. 2E–G). Both computed tomography (CT) and CTA showed an extensive soft tissue mass of about 6.4 × 4.5 × 7.0 cm in the submental area. Multiple punctate calcification in the mass and bone involvement of the chin could also be seen (Fig. 2F and H).

The subcutaneous lesions in her hands and feet were diagnosed as venous malformation by physical examination and Doppler ultrasonography. No obvious change was found in the comprehensive metabolic panel (including general tests, electrolytes, and assessment of renal and hepatic function). Pathological examination after surgical resection of part of the lesions showed that the lesions in the tongue and submental area were venous malformations (Fig. 3A); and a biopsy showed that the lesion in the left humerus was an enchondroma (Fig. 3B). On the basis of these findings – the development of multiple enchondromas in the extremities and the presence of subcutaneous vascular lesions – the diagnosis of Maffucci syndrome was established.

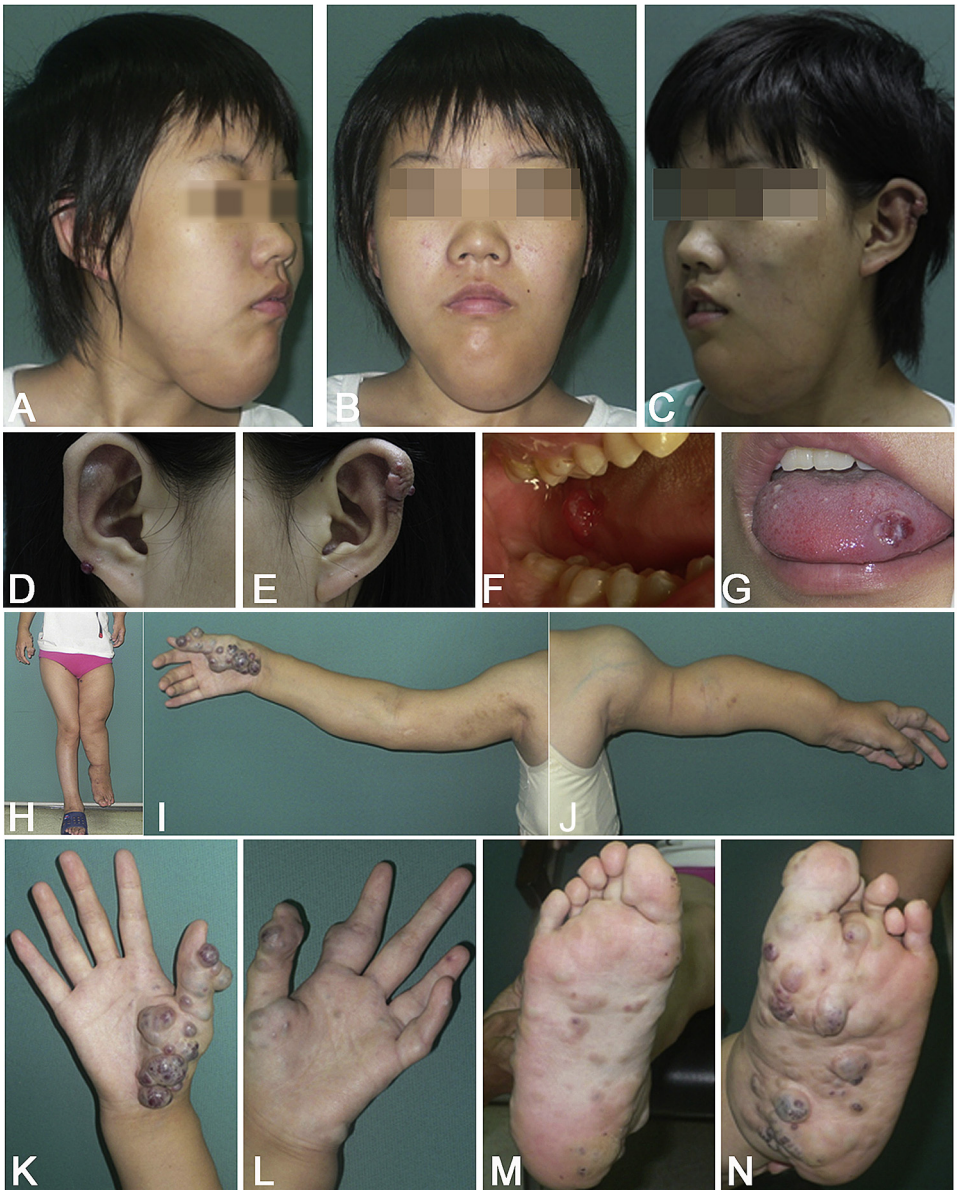

Fig. 1. Clinical features of the patient: The patient had obvious submandibular swelling on anterior and lateral views (A–C); small vascular malformations on her ears (D and E), buccal mucosa (F) and tongue (G); unequal leg lengths (H); and multiple vascular malformations on her hands and feet (I–N).