Clinical Features of Patients With 7p22.1 Microdeletion

With the advent of comparative genomic hybridization (CGH) technology, more patients with microduplications or micro deletions are being reported. Herein, we report an 11-year-old girl with 7p22.1 microdeletion who presented with short stature and intellectual disability. She was the second born child to non-consanguineous parents, born at full term with a birthweight of 2 kg. Ventricular septal defect and patent foramen ovale were detected after birth and cardiac surgery was undertaken at one year of age (weight 7 kg). At four years of age, she was detected with intellectual disability and short stature (height of 87 cm) with a normal karyotype (46,XX).

At 11 years, her weight was 31.3 kg (about -1 SD) height 134.5 cm (<2 SD), with distinctive facial features including long face, high forehead, arched eyebrows, long eyelashes, flat nose bridge, broad nose, upturned lip, downturned corners of the mouth and pointed chin. Small brown pigmentation, snaggle teeth, sagging shoulders and shoulder girdle muscle bulk, scar on the chest wall, flexion of the left thumb (contracture), clinodactyly and abnormal dermatogly-phics were also noted with Tanner stage 4 breast development. Wechsler intelligence scale showed intellectual disability with a score of 56.

Laboratory data showed hypertriglyceridemia (3.64 mmol/L). The levels of follicle stimulating hormone, luteinizing hormone, prolactin, progesterone and estradiol were consistent with sexual development. The level of insulin-like growth factor 1, insulin like growth factor binding protein 3, corticotrophin, cortisol, liver function, renal function and thyroid function were in normal range. An abdominal ultrasound was normal. Copy number variation (CNV) analysis (MyGenostics Gene Technology Co., Ltd. China) was performed and a 1.673 Mb microdeletion (chr7: 5 147 686-6 820 998) at chromosome 7p22.1 was found. No similar deletion was noted from her parents by CNV analysis and her parents refused for FISH analysis.

About 30 cases with 7p22.1 microdeletion have been earlier reported [1,2]. The common clinical features in these patients included intellectual disability (58.3%), distinctive facial features (44%), short stature (33.3%), microcephaly (22.2%), hernia (14.8%), hypotonia (14.8%), VSD (13%) and abnormal extremities (7.4%). Joint laxity, bilateral radial abnormalities, PFO, pulmonary artery dilatation and high palate were also reported in one case.

The specific relationship between genotype and phenotype in 7p22.1 deletion is still unknown. The deleted region in index case contained 36 genes, including *RNF216*, *AIMP2*, *RAC1*, *PMS2* and *ACTB*, which are known pathogenic genes. Mutations in *RNF216, AIMP2, RAC1* and *ACTB* are associated with intellectual disability [1-5]. The expression levels of *ACTB* are linearly correlated with the *ACTB* gene copy number and influence the amount of β-actin, which is involved in cell motility and expressed in all eukaryotic cells [1,2]. Thus, the haploinsufficiency of *ACTB* may be accountable for intellectual disability and other clinical features in 7q22.1 microdeletion [2]. Postnatal growth retardation, high forehead, hypertelorism, arched eyebrows, broad nose with large tip, hypoplastic scapulas, and congenital heart defects in index case were consistent with the features of *ACTB* gene deficiency. However, *ACTB* gene was not deleted in few cases who showed intellectual disability, implying that other genes (*e.g., RAC1* gene) or even non-coding RNA coded in this region may contribute to the clinical features of this rare condition.

In summary, 7p22.1 microdeletion syndrome should be considered in patients with intellectual disability, distinctive facial features, microcephaly, short stature, inguinal hernia, hypotonia, and congenital heart disease and confirmed with genetic testing.

Contributors: CCZ: conceived the study; HYL and JXF: manuscript writing and literatures review. All authors approved the final manuscript.
Funding: National Natural Science Foundation (81170787 & 81371215) and Zhejiang Provincial Program for the Cultivation of High-Level Innovative Health Talents (2014); *Competing interest*: None stated.

HAN-YUE LI[1], JING-XIA FANG[2], CHAO-CHUN ZOU[1]*
Department of [1]Endocrinology, The Children's Hospital, Zhejiang University School of Medicine, National Clinical Research Center for Child Health, China and [2]Pediatrics, Yongkang Fangda Ruijin Hospital, Jinhua
**zcc14@zju.edu.cn*

REFERENCES

1. Palumbo O, Accadia M, Palumbo P, Leone MP, Scorrano A, Palladino T, *et al*. Refinement of the critical 7p22.1 deletion region: haploin sufficiency of ACTB is the cause of the 7p22.1 microdeletion-related developmental disorders. Eur J Med Genet. 2018;61:248-52.
2. Shimojima K, Narai S, Togawa M, Doumoto T, Sangu N, Vanakker OM, *et al*. 7p22.1 microdeletions involving ACTB associated with developmental delay, short stature, and microcephaly. Eur J Med Genet. 2016;59:502-6.
3. Husain N, Yuan Q, Yen YC, Pletnikova O, Sally DQ, Worley P, *et al*. TRIAD3/RNF216 mutations associated

with Gordon Holmes syndrome lead to synaptic and cognitive impairments via Arc misregulation. Aging Cell. 2017;16:281-92.
4. Shukla A, Das Bhowmik A, Hebbar M, Rajagopal KV, Girisha KM, Gupta N, *et al*. Homozygosity for a nonsense variant in AIMP2 is associated with a progressive neurodevelopmental disorder with microcephaly, seizures, and spastic quadriparesis. J Hum Genet. 2018;63:19-25.
5. Reijnders MRF, Ansor NM, Kousi M, Yue WW, Tan PL, Clarkson K, *et al*. RAC1 missense mutations in developmental disorders with diverse phenotypes. Am J Hum Genet. 2017;101:466-77.

Vinblastine-induced Acral Hyperpigmentation

A 5-year-old girl, diagnosed with multi-system langerhans cell histiocytosis (bone, liver, bone marrow and pituitary involvement), was started on induction chemotherapy (weekly cycles of vinblastine/ prednisolone for 12 weeks). Two months later, she developed progressive bluish-black discolouration over the nose and fingertips along with darkening of the nail beds without any itching, pain, redness, numbness, trauma or sun exposure.

Several differentials were considered, Chikungunya fever is well reported for causing an acute, brownish-black, centrofacial hyperpigmentation [1]. It can persist for three to six months after resolution of infection [1]. However, our child had no fever, arthralgia or cytopenias to suggest an infectious aetiology. Addisonian hyperpigmentation, which commonly involves mucous membranes, flexures, palmar and plantar creases, the areola, genitalia and pressure points (elbows and knees), was ruled out clinically, as well as by the absence of hyponatremia, hyperkalemia and acidosis [1]. Hyperpigmentation in thyroid disorders also has a similar distribution as in Addison disease [2]; however, the thyroid function test was normal. Exogenous ochronosis, secondary to topical hydroquinone use, responsible for bluish-black hyperpigmentation of the sun-exposed areas of the face, was also ruled out as there was no history of such application; neither was henna applied locally [1,2]. She had no preceding redness, scaling, pain, injury or cutaneous eruptions to suggest post-inflammatory hyperpigmentation [3]. Acanthosis nigricans, although classically noted over the nape of the neck, axilla and groin, can also develop over the face [4]. However, our child had neither hyperglycemia nor obesity and the lesion in question lacked the characteristic velvety thickening of acanthosis nigricans [3]. The involvement of distal phalanges, interphalangeal joints and oral mucosa, characteristic of Vitamin B_{12} deficiency, was absent in our child [2]. Moreover, her red blood cell indices were normocytic and normochromic, ruling out this possibility. Drug-induced acral hyperpigmentation was considered after ruling out other differentials and vinblastine was discontinued, following which the hyperpigmentation faded over a period of 3 weeks, but did not disappear completely.

Vinca alkaloids are notorious for causing extravasation injury [4]. Supravenous hyperpigmentation has been reported with the ABVD regimen which includes vinblastine (however, the causative drug was not implicated) [5]. Vinorelbine, a vinca alkaloid, in high doses is known to cause acral erythema [6]. Although drug-induced hyperpigmentation is responsible for 10-20% cases of acquired hyperpigmentation [2], it has not been reported with either vinblastine or prednisolone. Possible mechanisms of drug induced acral hyperpigmentation

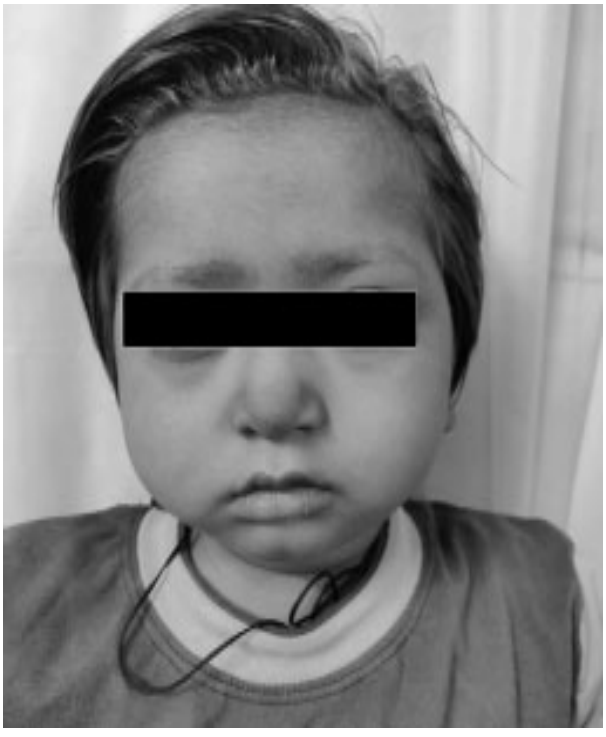

Fig.1