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Exploration of genetic factors determining cleft side in a pair of monozygotic twins with mirror-image cleft lip and palate using whole-genome sequencing and comparison of craniofacial morphology

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ABSTRACT

Objective: The aim of the present study is to explore genetic factors determining difference of cleft side using whole-genome sequencing and evaluation of craniofacial morphology using cephalometric analysis between Japanese monozygotic (MZ) twins with mirror-image cleft lip and palate (CLP).
Design: We selected a Japanese MZ twin pair (MZ-A and MZ-B) affected with unilateral CLP who are discordant for cleft side (left/right) and conducted whole-genome sequencing to identify genetic factors determining cleft side. Moreover, we compared their craniofacial morphologies using cephalograms.
Results: Whole-genome sequencing results suggested that no discordant DNA variants were found between MZ-A and MZ-B. The comparison of craniofacial morphology between the MZ twins revealed that MZ-B had maxillary deficiency and slightly more mandibular protrusion than MZ-A.
Conclusions: It is indicated that environmental factors might be a critical factor that influences the determination of difference of cleft side in orofacial clefts. In addition, we found some differences in craniofacial morphology between MZ-A and MZ-B. Our findings suggest that various environmental factors, such as epigenetics, might be a critical factor that influences the determination of difference of cleft side in CLP rather than inherited genetic factors.

1. Introduction

Orofacial clefts, including nonsyndromic cleft lip with or without cleft palate (NSCL/P), are the most common birth defects of the craniofacial region (Carlson et al., 2017). Orofacial clefts are genetically complex traits caused by the interaction of multiple genetic and environmental risk factors (Vierira, 2012), include conditions such as cleft lip, cleft palate, or both together, cleft lip and palate (CLP) (Allori, Mulliken, Meara, Shusterman, & Marcus, 2017). CLP can be further classified into unilateral (left or right side) or bilateral. In most cases, cleft types are unilateral and frequently on the left side rather than the right side. The underlying causes of this left-right bias are still unclear.

The formation of the lip and palate at the embryonic stage is dependent on the migration of neural crest-derived cells into the craniofacial region and is influenced by coordinated signaling that controls the spatial and temporal pattern of morphogenesis of the facial prominences (Cohen, 2002). Embryonic morphogenesis occurs along three orthogonal axes, namely anterior-posterior, dorsal-ventral, and left-right axes. The left-right axis has just begun to be investigated at the molecular level. The mechanisms that secure proportional left-right asymmetry of organs, such as the heart, viscera, and brain, indicate a link between biomolecular chirality and human perception (Levin, 2005).

Mirror-image asymmetry in twins has been reported in congenital

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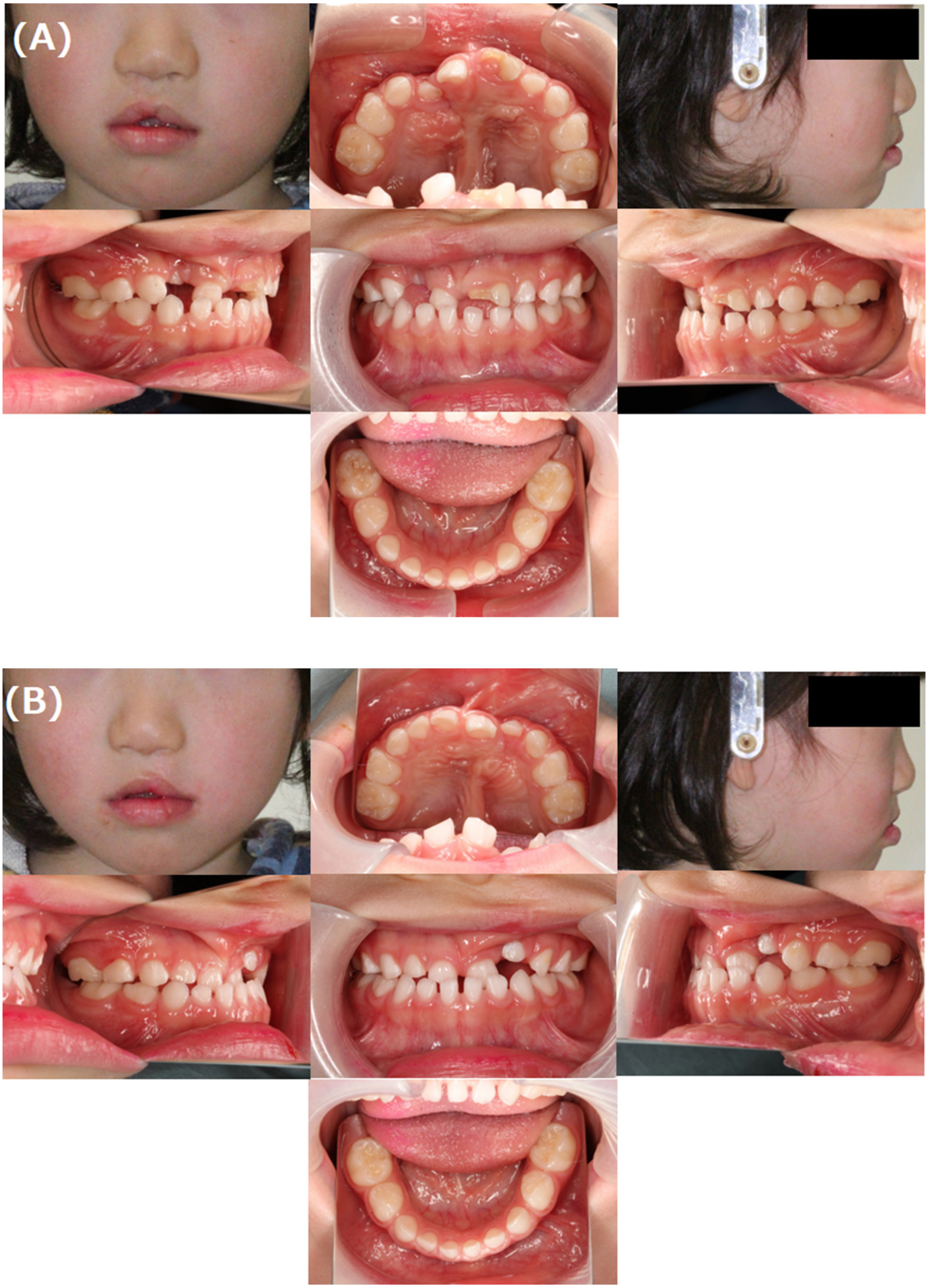

Fig. 1. Intra-oral and facial photographs of Japanese monozygotic twin boys (MZ-A and MZ-B). (A) MZ-A with unilateral, right-sided cleft lip and palate, (B) MZ-B with unilateral, left-sided cleft lip and palate.

disorders (Brent, 2011; Sperber, Machin, & Bamforth, 1994; Thacker, Gruber, Weinberg, & Cohen, 2009) and indicated as a confirmatory sign of monozygosity (Markovic, 1970). It is considered that mirror-image asymmetry occurs between days 9 and 12 after fertilization in embryogenesis (Burn, 1991), however, the exact mechanism remains unclear.

The elucidation of processes involved in mirror-image asymmetry is important for the understanding of birth defects and genetic syndromes, such as orofacial clefts. Although many studies have reported various candidate genes associated with orofacial clefts in humans, the mechanisms involved in the formation of clefts and the developmental