Dental findings in 14q terminal deletion syndrome

Bryce A. Mendelsohn[a], Linda L.B. Jeng[b], Snehlata Oberoi[c,d] and Ophir D. Klein[a,c,d,e]

Departments of [a]Pediatrics, [b]Laboratory Medicine, [c]Orofacial Sciences, [d]Program in Craniofacial and Mesenchymal Biology and [e]Institute for Human Genetics, University of California San Francisco, San Francisco, California, USA

Correspondence to Ophir D. Klein, MD, PhD, Department of Pediatrics, University of California San Francisco, 513 Parnassus Ave, HSE1509, San Francisco, CA 94143, USA
Tel: + 1 415 476 4719; fax: + 1 415 476 9513; e-mail: ophir.klein@ucsf.edu

List of key features

Agenesis corpus callosum
Global developmental delay
Dandy–Walker malformation
Hypertelorism
Over-retained primary teeth
Malocclusion
Retrognathia
High arched palate

Clinical summary

The patient was a 12-year-old female who presented with delayed speech, agenesis of the corpus callosum, and dysmorphic facial and dental features. There was no similar family history. The patient was born full term at 2.9 kg (20th percentile) and began walking at 16 months. Her speech was significantly delayed and ear tubes were fitted at age 3. At age 4, an MRI showed a Dandy–Walker malformation with partial agenesis of the corpus callosum. She was recently noted by a pediatric orthopedist to have lumbar lordosis. At 12 years of age, she weighed 63.5 kg, was 170 cm in height (98th percentile), and her head circumference was 55 cm (25th percentile for height).

Facial dysmorphic features included hyperteleorism, downslanting palpebral fissures, and long lower facial height with a short neck. She did not have a high forehead. Her exam indicated severe dental crowding, retained primary teeth, and skeletal class II malocclusion with a 10 mm overjet and 3 mm overbite (Fig. 1). Both dental arches were very narrow and the palate was high arched. At rest, her lips were not competent and she displayed ∼ 30% of her maxillary incisors. When smiling, 100% of her maxillary incisors were displayed, and she was able to close her lips with difficulty. Over-retained posterior primary teeth were present but displaced by many permanent teeth, which had erupted around them.

Fig. 1

Dysmorphic features include long lower facial third, mandibular retrognathia, maxillary prognathia, narrow dental arches, high palatal vault, low-set tongue, and over-retained deciduous dentition with severe dental crowding.

Fig. 2
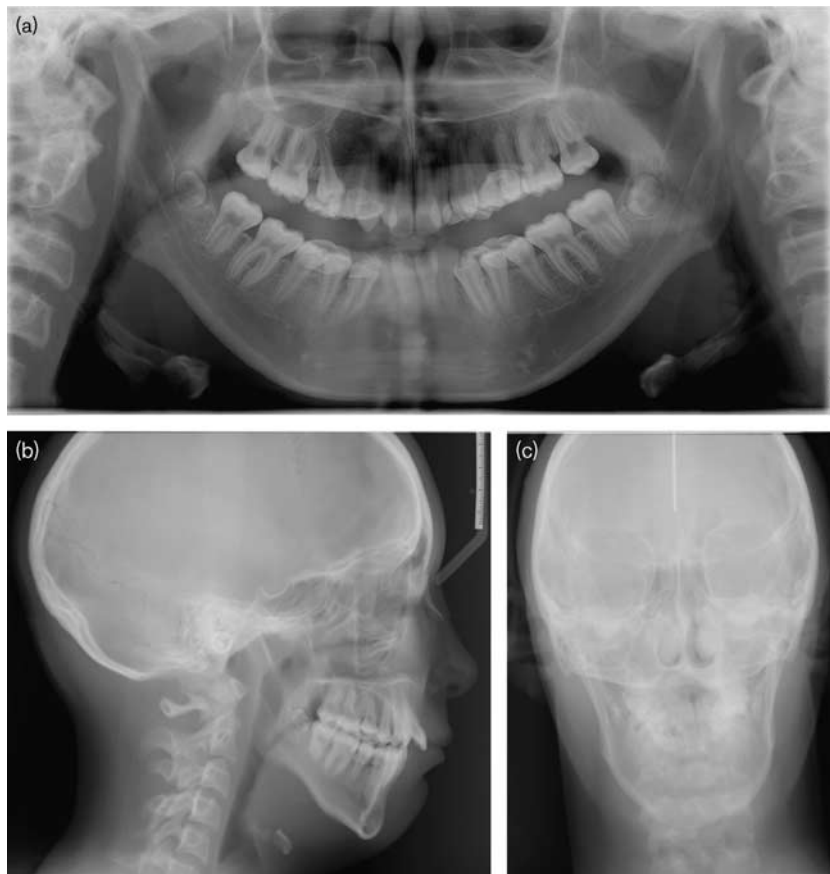
(a) Panoramic radiograph and head films show the full complement of permanent dentition with retained primary teeth, and a prognathic maxilla with a retrognathic mandible. (b) Lateral and (c) anteroposterior films of the skull and teeth.

The size of her tongue was within normal limits but was positioned low in the oral cavity. Tonsils were absent, with no report of tonsillectomy.

The patient's panoramic radiograph indicated that all permanent teeth were present and developing in both jaws (Fig. 2a). The anteroposterior radiograph showed a slight deviation of the nasal septum and narrow upper and lower dental arches, with increased lower face height (Fig. 2b). The lateral head film showed a prognathic maxilla and retrognathic mandible (Fig. 2c). The upper incisors showed increased inclination, and there was increased clockwise rotation of the mandible, thereby increasing face height.

Investigations
Prenatal amniocentesis indicated a normal karyotype. At age 12, array-based comparative genomic hybridization (aCGH) analysis of the patient's DNA was carried out using a 180K-feature whole-genome microarray (ISCA v1 Clinical Design; Agilent Technologies, Santa Clara, California, USA). Data were analyzed using BlueFuse software (BlueGnome, Cambridge, UK) and compared with whole-genome sequencing and variation data from the Database of Genomic Variants (DGV, *http://projects. tcag.ca/variation*), the Database of Chromosomal Imbalance and Phenotype in Humans Using Ensembl Resources (DECIPHER, *http://decipher.sanger.ac.uk/*), and the International Standards for Cytogenomic Arrays database (ISCA, *https://www.iscaconsortium.org*).

The aCGH analysis showed a terminal loss within 14q32.31q32.33 (chr14:102,744,764-107,287,476, hg19) of 4.543 Mb compared with a pooled, normal, sex-matched DNA sample (Fig. 3). A total of 229 genes are included within this region, establishing the diagnosis of 14q terminal deletion syndrome as the cause of this patient's developmental and craniofacial abnormalities. This deletion was likely *de novo* as her parents lacked any features of this syndrome, but parental chromosome studies were unavailable.

Discussion
Here, we report a 14q terminal deletion syndrome patient with several dental anomalies, including skeletal class II

Fig. 3
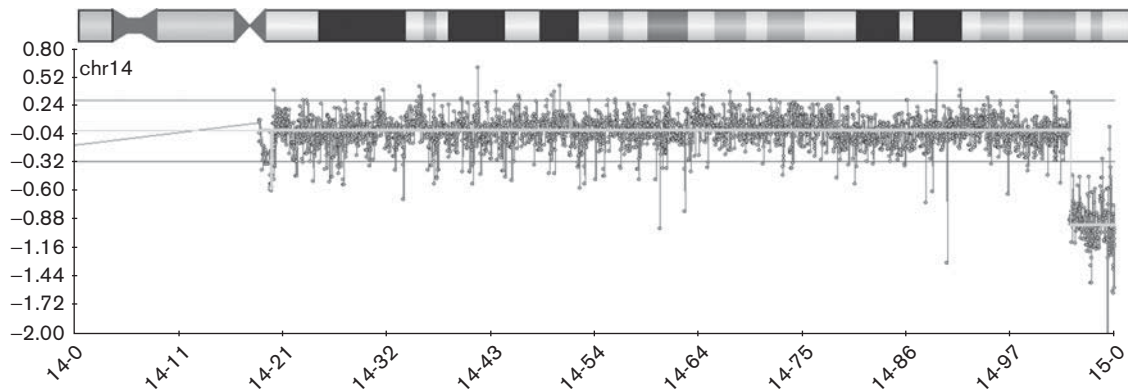
Whole chromosome aCGH plot showing a single 4.543 Mb copy loss within 14q32.31q32.33. Chromosome 14 ideogram is at the top of the image. Oligonucleotide probes were plotted by Megabase on the *x*-axis and as a normalized $\log_2$ ratio of patient : control signal intensity on the *y*-axis.

malocclusion with narrow arches and severe crowding, as well as over-retained primary teeth, which has not been reported previously in the literature. Past reports of 14q terminal deletion have noted dental abnormalities such as missing incisors (Karnitis *et al.*, 1992), and some patients report that primary teeth may require removal (14q deletions from 14q32.2 and 14q32.3, 2007; Unique, *http://www.rarechromo.org*).

Two patterns of dysmorphic craniofacial features have been described in 14q terminal deletion patients, and these seem to be divided between deletions that do or do not include material proximal to ~1.68 Mb from the terminus (Engels *et al.*, 2012). *JAG2*, a component of the Notch signaling pathway, lies near this junction. Homozygous deletions of *JAG2* in mice cause severe craniofacial abnormalities (Jiang *et al.*, 1998), and whereas heterozygous mice appear normal, DECIPHER (Firth *et al.*, 2009) assigns *JAG2* a haploinsufficiency index of 5.7%, strongly suggesting that dosage effects are different in humans compared with mice. We propose that heterozygous deletion of *JAG2*, perhaps in combination with more distal genes, may contribute toward the craniofacial phenotype of 14q terminal deletion syndrome.

Impaired apoptosis, which has been suggested to play a role in pulp elimination during root resorption (Rodrigues *et al.*, 2009), may contribute toward primary tooth over-retention because of haploinsufficiency of proapoptotic genes in the deleted region. *SIVA1*, *APOPT1*, *BAG5*, and *PPP1R13B*, all deleted in this patient, are known or hypothesized to function in apoptosis. *SIVA1* in particular has been shown to induce apoptosis in a caspase-dependent manner

(Py *et al.*, 2004), and caspase activity has been detected in resorbing primary tooth pulp (Rodrigues *et al.*, 2012).

In many cases of rare genomic variants, some features are not present nor noted in all patients. We suggest that dental findings should be included in future descriptions of the 14q terminal deletion phenotype, and patients with overlapping 14q deletions should obtain appropriate dental and orthodontic evaluation.

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