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Original Article

Cleidocranial dysplasia syndrome: clinical characteristics and mutation study of a Chinese family

Shengguo Wang[1], Shu Zhang[2], Yanmin Wang[3], Yangxi Chen[3], Li Zhou[3]

[1]Department of Stomatology, Second Affiliated Hospital, Chongqing Medical University, Chongqing, China; [2]Children's Hospital, Chongqing Medical University, Chongqing, China; [3]Department of Orthodontics, West China College of Stomatology, Sichuan University, Chengdu, China

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Abstract: Cleidocranial dysplasia syndrome (CCD) is a rare autosomal dominant disease with wide range of variability. Dentists are often the first to encounter the CCD patients, some of whom do not show typical manifestations. Thus, dentists should be fully familiar with clinical manifestations and gene mutation. A 16-year-old girl was admitted for orthodontic treatment because of space in the dental arch and teeth irregularity. The introcession on the forehead and occiput suggests that she was a CCD patient. Clinical, radiological and genetic examinations were carried out in this girl and her family members and results showed delayed closure of the fontanel, hypoplastic clavicles and tooth anomalies of the girl and her mother. Genetic analysis revealed a 884C deletion in the exon 5 of the CBFA1/RUNX2 gene, which has never been reported in China. In this reported, the manifestations, diagnostic process and treatment of CCD were introduced according to the experience on the diagnosis of CCD in this family.

Keywords: Cleidocranial dysplasia syndrome, genetic analysis, family

Introduction

Cleidocranial dysplasia (CCD) is a rare autosomal dominant skeletal dysplasia with wide variability. It was first reported by Morand in 1766. The characterized manifestations of CCD are persistently open or delayed closure of the fontanel, hypoplastic or aplastic clavicles, short stature, and tooth anomalies [1-5]; sometimes many other skeletal anomalies are also observed [6]. Though CCD is an autosomal dominant disease, about one third cases were scattered and have no history of heredity [7]. Mutations in the core-binding factor α1 (CBFA1) gene, locating on chromosome 6p21, have been shown as the cause of CCD [8-11]. To date, a total of 62 types of CBFA1/RUNX2 mutations have been identified in CCD patients, including deletion, insertion, nonsense mutation, missense mutation and change in splicing site, and so on [12-14]. Since dentists are the first to encounter these cases during the routine oral examination and the CCD phenotypic spectrum is extraordinarily variable even within families, ranging from mildly affected individuals merely with dental abnormalities to severely affected patients with generalized osteoporosis [15], it is important for dentists to fully understand the clinical manifestations and gene mutation of CCD before final diagnosis. Herein, we reported a CCD family, and the clinical and radiographical manifestations were described, focusing on the oral examination and mutation analysis of CBFA1/RUNX2 gene.

Case report

A 16-year-old girl was admitted to our hospital because of several missing teeth and tooth irregularity. The introcession on the forehead and occiput and the abnormal hypermobility of the shoulders indicated a possible case of CCD, and a clinical, radiological and genetic examinations of her family members were prompted. Results revealed a CCD family including this girl, her mother (CCD) and her uncle (normal). Further ancestral analysis was impossible as the grandparents had passed away. Full clinical manifestations and findings in gene mutation analysis are described below.

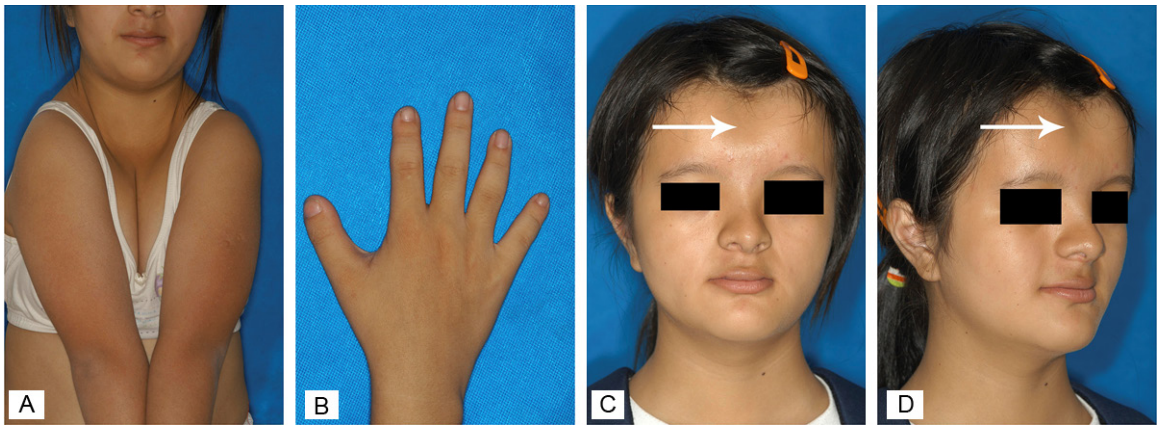

Figure 1. A: Abnormal hypermobility of the shoulders; B: Short fingers and mismatched finger to palm proportion; C, D: Introcession on the forehead, abnormally large interorbital distance and deeply inserted ears.

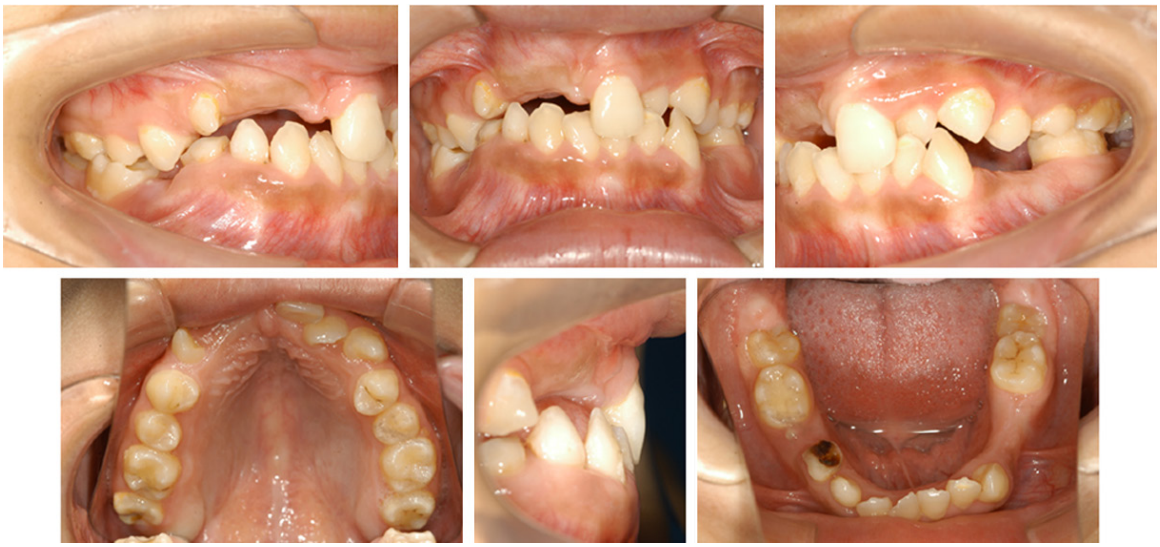

Figure 2. Intraoral manifestations and occlusion relationship.

The proband

A 16-year-old girl was admitted to our hospital for orthodontic treatment. She was of short stature (148 cm in height). Mental retardation was not found. The frontal view showed some cranial enlargement with increased interorbital distance and introcession on both occiput and forehead. The profile view showed a straight profile with prominent chin. Her short fingers compared with the palm, limped walking and abnormal hypermobility of the shoulders were the other clinical manifestations (**Figure 1**).

In the intraoral views, many permanent teeth were unerupted and some primary teeth stagnated. Class III molar relationship and irregularity in the mandibular anterior teeth, 22/32 and 15, 16/46 crossbite were also found (**Figure 2**).

A panoramic radiograph showed that there were many impacted and unerupted teeth, permanent or supernumerary, in the maxillary and mandibular (**Figure 3**). A lateral cephalogram of the skull showed dysplastic nose bone and many impacted and unerupted teeth (**Figure 3**). The orthophoria cephalometric radiographs showed delayed closure of interparietal suture and fontanels, the most obvious manifestation of CCD (**Figure 4**).

The chest X-ray showed the clavicles of the proband were dysplastic, which let the patient be able to approximate both shoulders in the ante-

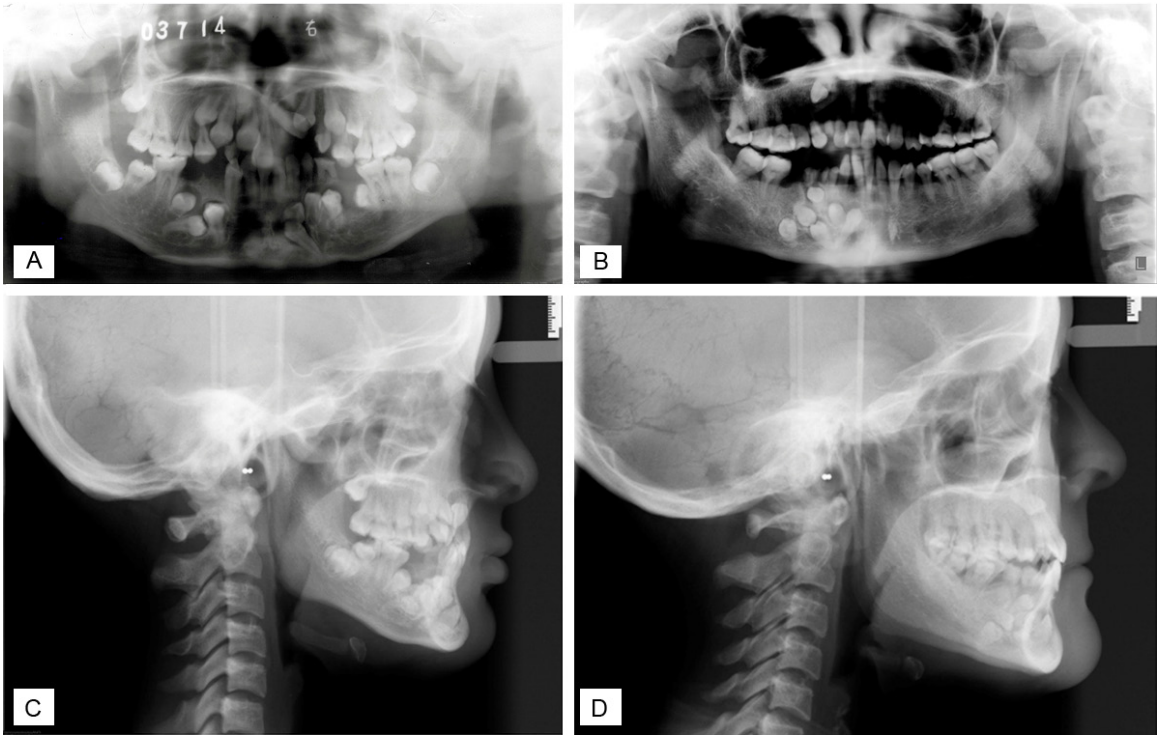

Figure 3. Panoramic radiograph showed many impacted and unerupted teeth (permanent or supernumerary), in the proband (A) and her mother (B). Cephalometric X-ray showed many impacted and unerupted teeth (permanent or supernumerary) and dysplastic nose bone in the proband (C) and her mother (D).

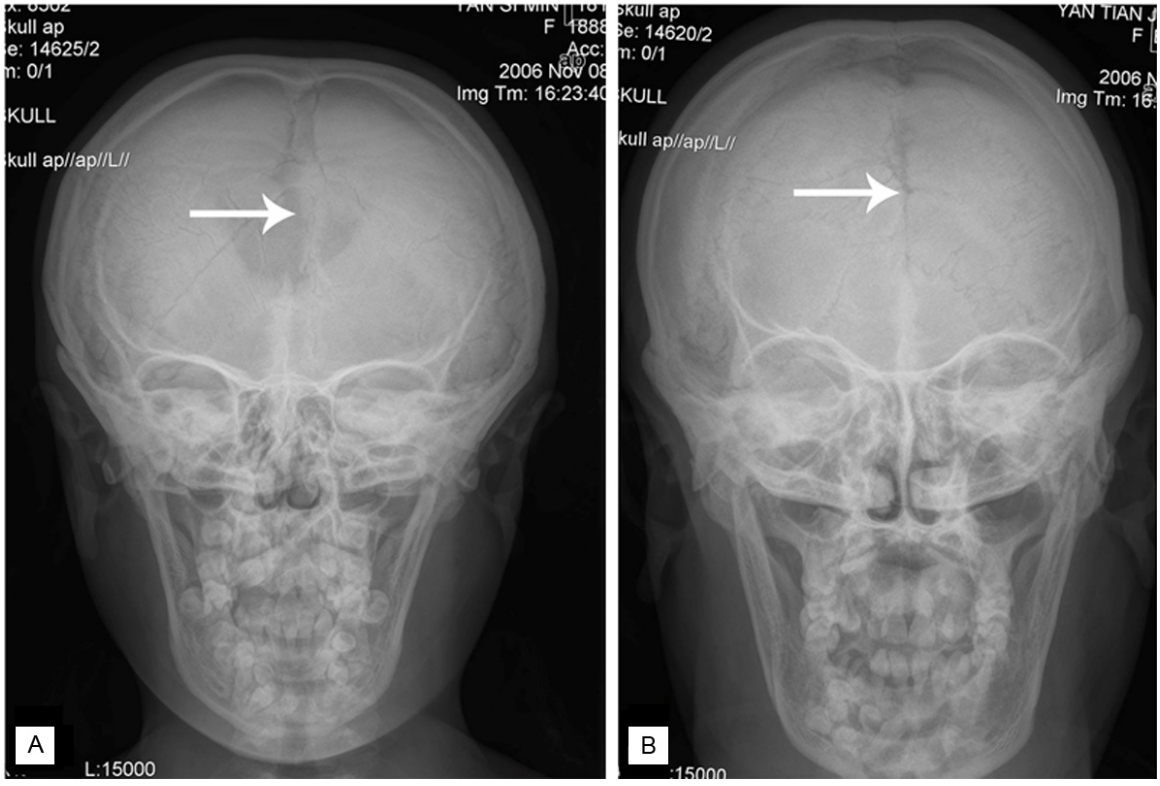

Figure 4. Orthophoria cephalometric radiographs: delayed closure of interparietal suture and fontanels in both the proband (A) and her mother (B).

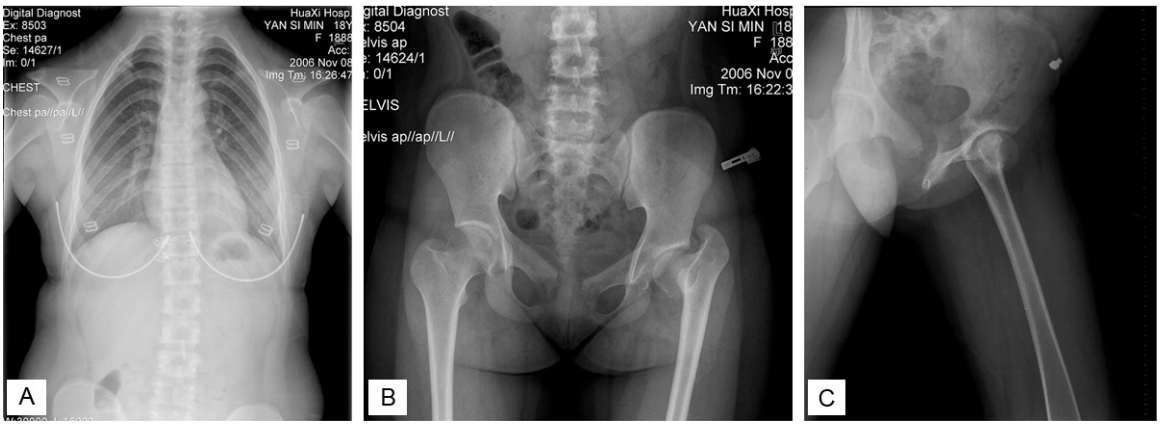

Figure 5. Thoracic plain radiographs (A): dysplastic clavicles of the proband as well as spine scoliosis and occult cleft. Plain radiographs of abdomen (B) and the hip joint (C): maldeveloped right hip joint.

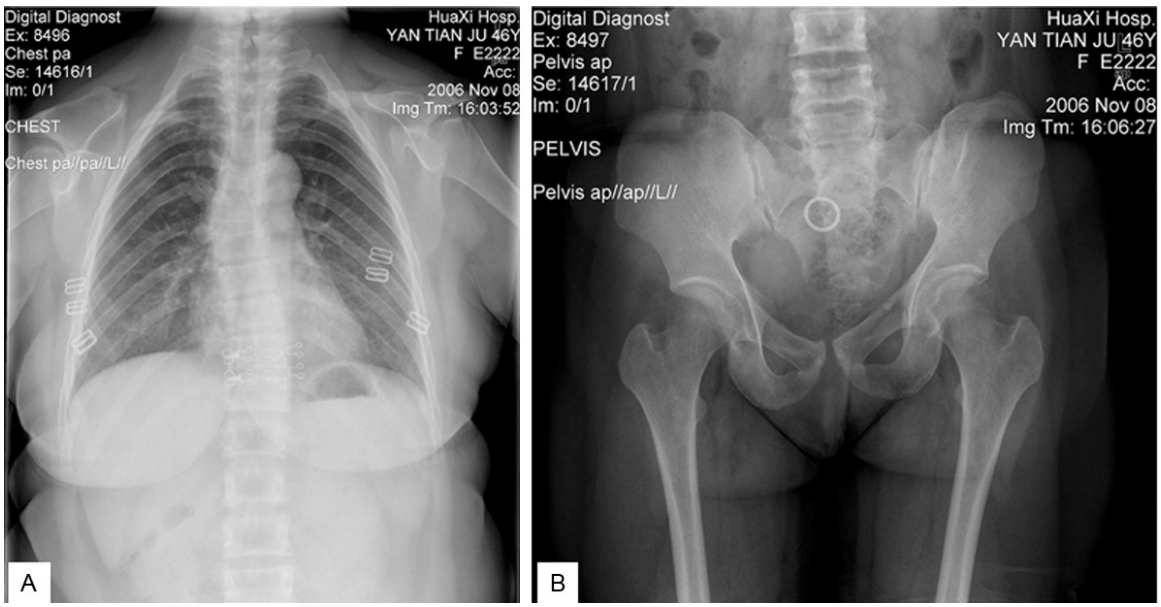

Figure 6. Plain radiographs: dysplastic clavicles, spine scoliosis, occult cleft and asymmetric flank bone in the mother. A: Chest; B: Abdomen.

rior plane, a characteristic sign of CCD. Owing to the dysplasia of the right hip joint, the patient walks limped. Scoliosis, occult cleft of the spondylous (**Figure 5**) and short finger and toe bones were also found on the plain radiographs.

The mother

Signs of CCD syndrome were also observed in her mother: introcession on both occiput and forehead, increased interorbital distance, hyperfunction of the shoulder, many unerupted permanent teeth and a lot of stagnated primary teeth (**Figure 8**).

Delayed closure of interparietal suture and fontanels, dysplastic nose bone and clavicles, scoliosis, occult cleft of the spondylous, and short finger and toe bones were seen on the plain radiographs (**Figures 3**, **4**, **6**, **7**).

The uncle

The uncle was healthy. He has no introcession on the forehead or occiput, normal shoulders, and no stagnated primary teeth. His children were also healthy.

Gene analysis

To further support the diagnosis of CCD and help the prenatal diagnosis in the proband in the future, genomic DNA of the proband, her mother and uncle were isolated from whole

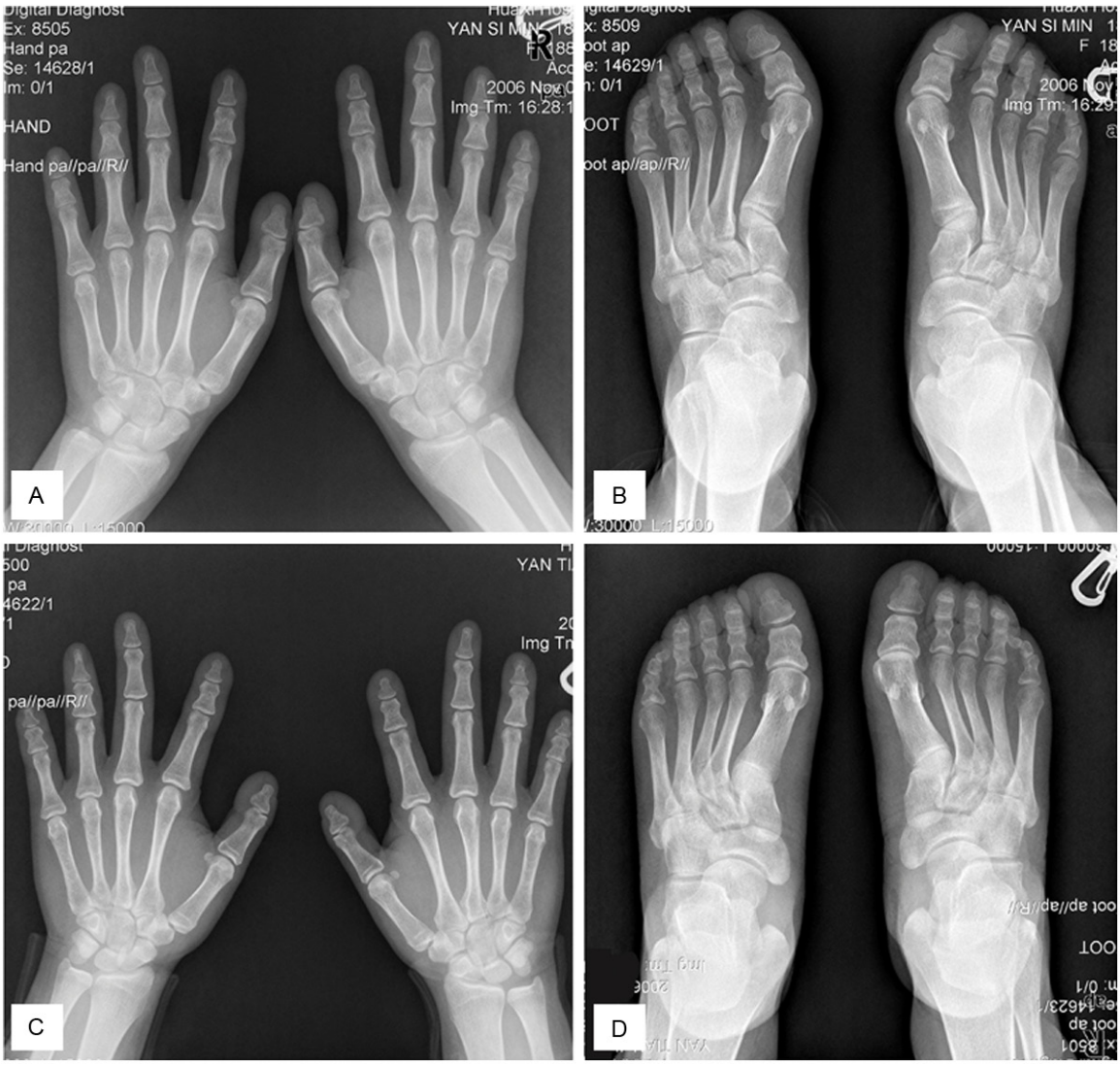

Figure 7. Short finger and toe bones in the proband (A, B) and her mother (C, D).

blood after informed consent was obtained. The mutation analysis of *CBFA1/RUNX2* gene was carried out with polymerase chain reaction (PCR) and two-way direct sequencing. In order to confirm the known mutations, the amplicon were cloned in plasmid and direct sequenced (**Figure 8**).

Gene mutation analysis supported the diagnosis of CCD. A frameshift mutation 884delC corresponding to the cDNA sequence was found in exon 5 of *CBFA1/RUNX2* gene of the proband and her mother, the uncle showed a "wild type" sequence in this region. The mutation identified by direct sequencing may result in premature termination after the runt domain.

Discussion

Through two generations of this Chinese family received examination, the daughter and her mother were CCD cases, and her uncle and her uncle's children were healthy. While classic clinical manifestations of CCD were seen in the mother and the daughter, an involved hip joint was also seen in the daughter. Furthermore, mutation of *CBFA1/RUNX2* gene was found in the mother and the daughter. To date, 62 types of *CBFA1/RUNX2* gene mutations, which have been shown to be the cause of CCD, have been identified in CCD patients [12-14]. However, few cases and mutation analysis of CCD have been reported in China. Thus, the mutation spectrum

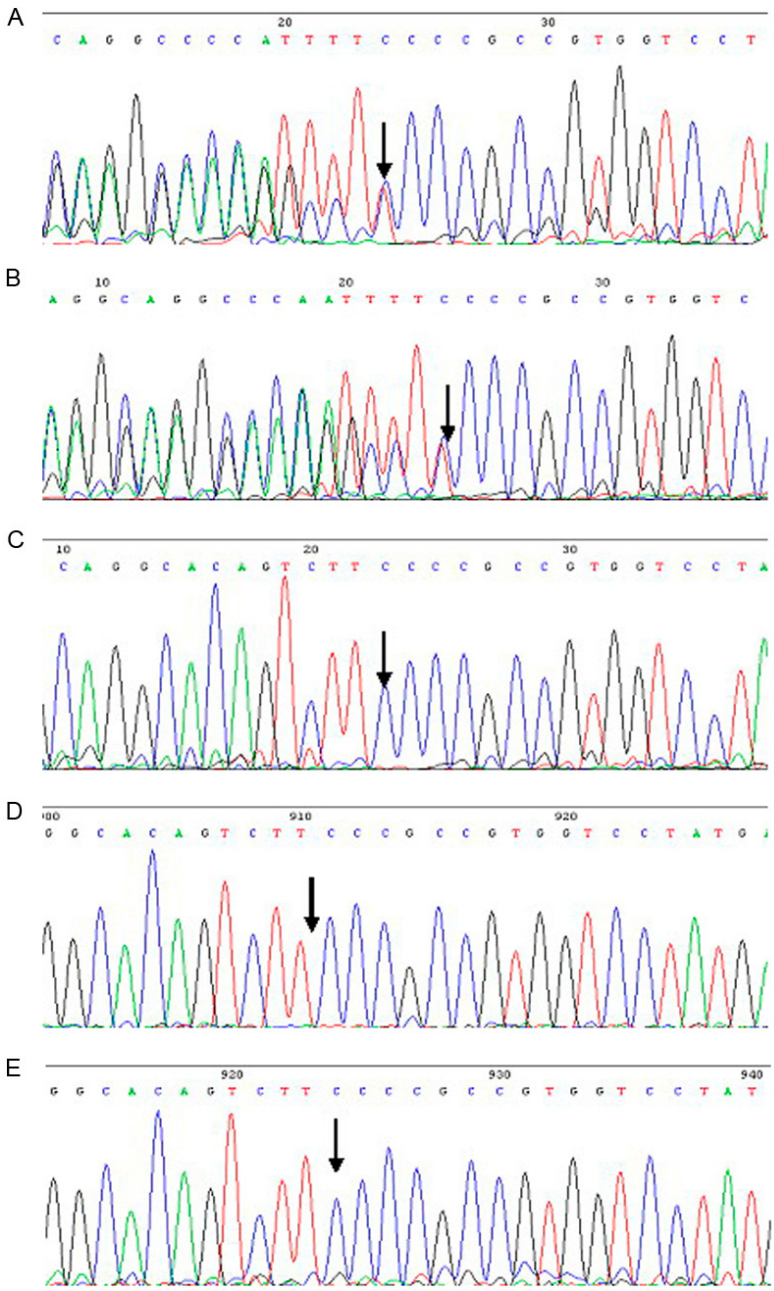

Figure 8. A: Direct sequencing of exon 5 amplicon in the CBFA1/RUNX2 gene of the proband. A C deletion in exon 5 (arrow) was found; B: Direct sequencing of exon 5 amplicon in the CBFA1/RUNX2 gene of the mother. A C deletion in exon 5 (arrow) was also found; C: Direct sequencing o exon5 of CBFA1/RUNX2 gene. Normal sequence was found in this region (No C deletion in exon 5 of CBFA1/RUNX2 gene); D: Plasmid sequencing of exon 5 in the mutation allele of CBFA1/RUNX2 gene of the proband. A C deletion was found in the exon 5 of CBFA1/RUNX2 gene; E: Plasmid sequencing of exon 5 in the wild allele of CBFA1/RUNX2 gene of the proband, the exon 5 of CBFA1/RUNX2 gene was normal as in her uncle.

of Chinese CCD patients is still poorly understood. In this CCD family, genetic analysis revealed, for the first time, a frameshift mutation of 884delC resulting in a truncated protein in exon 5 of *CBFA1/RUNX2* gene in Chinese CCD individuals, which was consistent with the findings in a previous report on Caucasians [15] and provided further support on the functional mutation leading to CCD.

While the family members studied exhibited typical manifestations of CCD, there are still some CCD cases without above manifestations (such as delayed closure of the fontanel and tooth anomalies without hypoplastic clavicles or dental anomalies) due to the wide range of variability [15]. It has been reported that there are four types of CCD: The first has typical clinical manifestations and a history of heredity; the second has typical clinical manifestations without a history of heredity; The third has atypical clinical manifestations and a history of heredity; The fourth has neither typical clinical manifestations nor a history of heredity [7, 15]. It is not difficult to diagnose the former two types of CCD, but it is difficult to identify accurately the latter two, especially the fourth type on the basis of only clinical manifestations and radiograph findings. When dental anomalies are found, CCD should be considered, particularly when family members have similar clinical symptoms; if final diagnosis can not be made on the basis of clinical manifestations and radiograph findings, genetic analysis may be necessary.

As CCD is an autosomal dominant disease, there is a 50 percent chance for the offsprings to inherit it from their parents. Thus, it is impor-

tant to incorporate the genetic analysis described above in the prenatal diagnosis aiming to identify potential CCD cases. In terms of dental anomalies in CCD, the therapeutic approaches include: a) Prosthetic treatment. Following extraction of the impacted teeth [16-20] or not [19, 21-27], the space in the dental arch is replaced with artificial teeth. In some cases, the impacted teeth are exposed or dental implants are inserted to support the overdentures [4, 28-31]. b) Surgical treatment. Before surgical repositioning or transplantation of the permanent teeth, the supernumerary teeth should be removed [28, 32-34]. c) A combination of surgical and orthodontic treatment. After surgical removal of the deciduous teeth and imbedded supernumeraries, orthodontic treatment proceeds allowing eruption of the impacted permanent teeth and adjustment of the occlusion [35, 37-40]. As the mother had many impacted and unerupted teeth, easy eruption of the teeth was not expected and a more conservative treatment was selected. For the proband, simple orthodontic treatment and prosthetic replacement by means of dentures were used. At one year after orthodontic treatment, significant movement of the impacted teeth was observed. Thus, the proband may attain ideal occlusion through a combination of surgical and orthodontic treatment with the aim of actively erupting and aligning the impacted permanent teeth. Treatment is currently proceeding.

Conclusion

CCD is a rare autosomal dominant disease with a wide range of variability, and characterized by delayed closure of the fontanel, hypoplastic clavicles, short stature, and tooth anomalies. In this Chinese CCD family, hip joint maldevelopment in the proband was evident in addition to the characteristic manifestations of CCD. Furthermore, a frameshift mutation of 884delC corresponding to the cDNA sequence was found in exon 5 of *CBFA1/RUNX2* gene this Chinese family, which has never been reported before in China, providing support that the mutation results in CCD. Lastly, the orthodontic treatment may improve the movement of impacted teeth and the combination of surgical and orthodontic treatment produce a relatively ideal occlusion.

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Address correspondence to: Shengguo Wang, Department of Stomatology, Second Affiliated Hospital, Chongqing Medical University, Chongqing, China. Tel: +8615823458851; E-mail: wangshengguo95@163.com

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