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ORIGINAL ARTICLE

The original family revisited after 37 years: odontoma–dysphagia syndrome is most likely caused by a microduplication of chromosome 11q13.3, including the *FGF3* and *FGF4* genes

Thomas Ziebart · Florian G. Draenert · Danuta Galetzka · Gregor Babaryka · Ralf Schmidseder · Wilfried Wagner · Oliver Bartsch

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Abstract
Objectives Fibroblast growth factors consist of receptor tyrosine kinase binding proteins involved in growth, differentiation, and regeneration of a variety of tissues of the head and neck. Their role in the development of teeth has been documented, and their presence in human odontogenic cysts and tumors has previously been investigated. Odontoma–dysphagia syndrome (OMIM 164330) is a very rare disorder characterized by clustering of teeth as compound odontoma, dysplasia and aplasia of teeth, slight craniofacial abnormalities, and dysphagia. We have followed the clinical course of the disease in a family over more than 30 years and have identified a genetic abnormality segregating with the disorder.
Materials and methods We evaluated clinical data from nine different family members and obtained venous blood probes for genetic studies from three family members (two affected and one unaffected).
Results The present family with five patients in two generations has remained one out of only two known cases with this very rare syndrome. All those affected showed teeth dysplasia, oligodontia, and dysplasia and odontoma of the upper and lower jaw. Additional signs included dysphagia and strictures of the oesophagus. Comorbidity in one patient included aortic stenosis and coronary artery disease, requiring coronary bypasses and aortic valve replacement. Genome-wide SNP array analyses in three family members (two affected and one unaffected) revealed a microduplication of chromosome 11q13.3 spanning 355 kilobases (kb) and including two genes in full length, fibroblast growth factors 3 (*FGF3*) and 4 (*FGF4*).
Conclusion The microduplication identified in this family represents the most likely cause of the odontoma–dysphagia syndrome and implies that the syndrome is caused by a gain of function of the *FGF3* and *FGF4* genes.
Clinical relevance Mutations of FGF receptor genes can cause craniofacial syndromes such as odontoma–dysphagia syndrome. Following this train of thought, an evaluation of *FGF* gene family in sporadic odontoma could be worthwhile.

Keywords Odontoma–dysphagia syndrome · Odontoma · Dysphagia · Fibroblast growth factors · *FGF3* · *FGF4* · Autosomal dominant

T. Ziebart (✉) · F. G. Draenert · R. Schmidseder · W. Wagner
Department of Oral and Maxillofacial Surgery, University Medical Center of the Johannes Gutenberg-University of Mainz, Augustusplatz 2,
55131 Mainz, Germany
e-mail: ziebart@mkg.klinik.uni-mainz.de

D. Galetzka · O. Bartsch
Institute of Human Genetics, University Medical Center of the Johannes Gutenberg-University of Mainz,
55131 Mainz, Germany

G. Babaryka
Institute for Pathology, University Medical Center of the Johannes Gutenberg-University of Mainz,
55131 Mainz, Germany

Introduction

Localized odontoma has been described frequently in the literature [1, 2]. Odontomas are benign tumors of the upper and lower jaw and, among the odontogenic tumors, odontomas are most highly differentiated and include tissue giving rise to teeth: enamel, dentin, cementum, and pulp tissue [2]. Multiple appearances in patients are extremely rare [3, 4]. In Gardner's syndrome, a rare, highly penetrant, dominantly inherited autosomal disorder characterized by the triad of

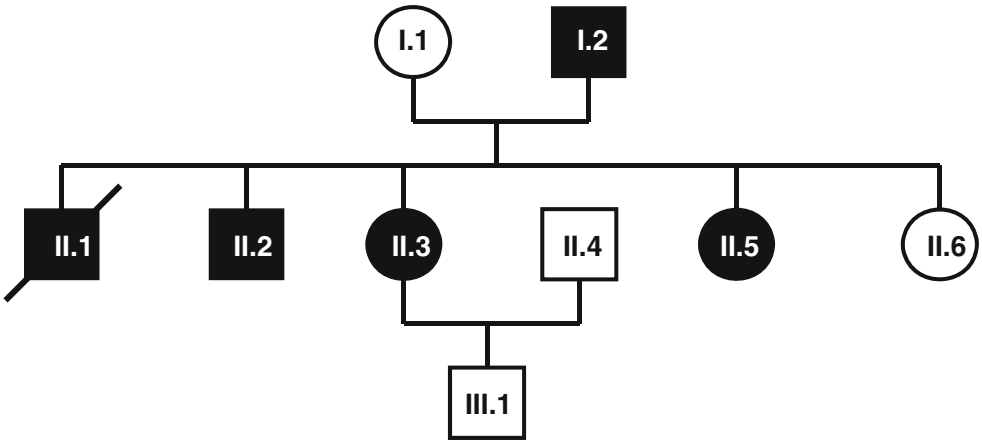


Fig. 1 Pedigree of the family. *Black symbols* indicate affected individuals. Patient II.1 died at age 6 weeks from fulminant pneumonia after odontoma resection

colonic polyposis, multiple osteomas, and mesenchymal tumors of the skin and soft tissues, some 50% of the patients present with odontomas [5, 6]. Gardner's syndrome is caused by mutations of the adenomatous polyposis coli (*APC*) gene on chromosome 5q22, and more than 1,000 different mutations of the *APC* gene have been reported. Fibroblast growth factors (FGF) play an important role in growth, differentiation and regeneration of a variety of tissues. Their presence in human benign tumors has been previously investigated [7]. Apart from its role in angiogenesis and tumor angiogenesis, FGF signaling plays an essential role in skeletal development [8]. Over 20 different members of the fibroblast growth factors family have been identified [9, 10]. All FGFs show structural homology and can bind heparan sulphates [11]. FGF-1 and FGF-2 can induce growth in various mesenchymal and neuroectodermal tissues. FGF-2 and FGF-3 have been identified in odontogenic lesions [11]. FGF-4 could be detected in primary and secondary enamel knots of the enamel organ at the cap and bell stages [10, 12, 13]. Furthermore, FGF-3 and FGF-10 were identified in the mesenchyme of the dental papilla in the cap and bell stages [10].

The first case report in 1967 of an odontoma syndrome described a girl suffering from multiple odontoma of the upper and lower jaw [21]. The tumors were excised for the first time 18 days after birth. In the following 5 years, odontomas were excised twice. At the age of 6 years, the girl died after an operation for stenosis of the oesophagus. Autopsy confirmed the oesophageal stenosis and additionally revealed aortic stenosis, bronchiectases, chronical pyelonephritis, and interstitial hepatic sclerosis [21].

In 1973, Schmidseder and Hausamen described for the first time the odontoma dysphagia syndrome in a report on the present family [3]. Schönberger et al. examined the clinical dysphagia of the syndrome and suggested autosomal dominant inheritance in this family [22].

Here we aimed to identify the genetic defects underlying the odontoma–dysphagia syndrome. We revisited the family, performed a retrospective analysis including nine members of the family over more than 30 years, and undertook a genome-wide search in three family members, including one unaffected and two affected individuals.

Material and methods

Patients

We studied a German family with autosomal dominant transmission of dysplasia and oligodontia of the teeth and dysplasia of the upper and lower jaw. Figure 1 shows the

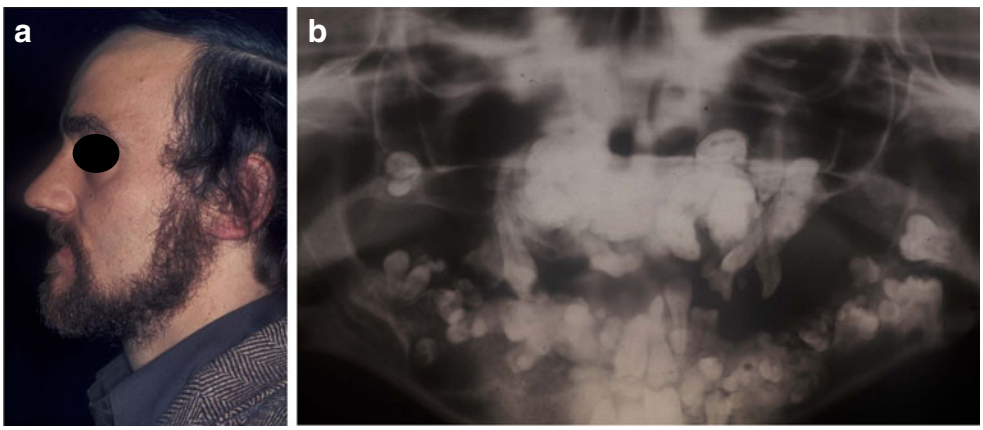
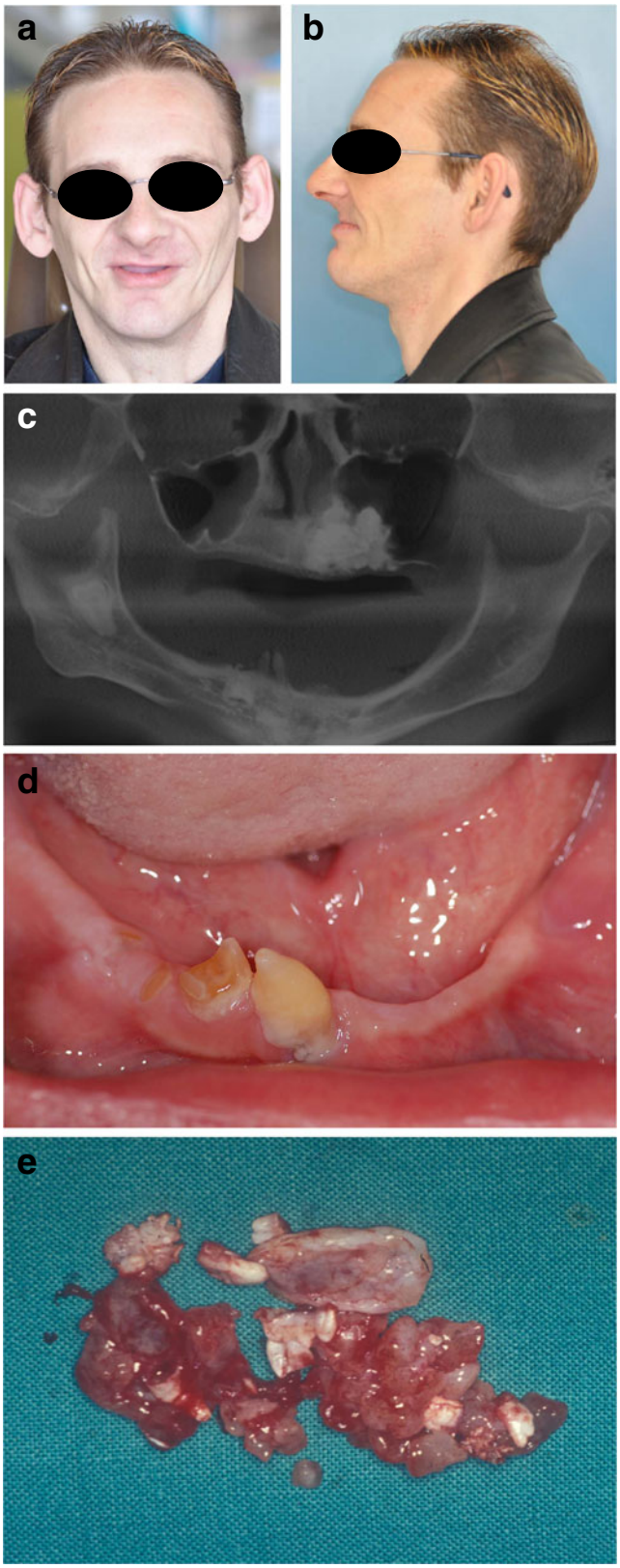


Fig. 2 Patient I.2. **a** Facial profile, note dysplasia of upper and lower jaw. **b** OPTG, note multiple odontoma and displaced teeth **c**



◀ **Fig. 3** Patient II.2. **a**, **b** Facial profiles showing mandibular and maxillary atrophy and dysplasia. **c** OPTG view of digital volume tomography before last operation: odontoma in regions 21–26 and impacted tooth in region 48. **d** Intraoral view regions 34–44, note oligodontia, atrophic mandible, and tooth defects. **e** Resected compound odontoma with multiple teeth-like structures

pedigree of the family. Three individuals provided written consent to further studies, including cytogenetic and molecular genetic studies. Their examinations included clinical documentation by photography, X-ray analysis (panoramic tomograms) and analysis of the upper and lower jaw (Figs. 2, 3, 4, and 5). Venous blood samples, 10 ml volume, were collected from two affected siblings, II.2 and II.3, and from III.1, the healthy son of II.3.

Cytogenetic analysis and DNA extraction

Conventional karyotyping was performed and DNA was extracted from peripheral blood leukocytes according to standard procedures.

Molecular karyotyping

DNA from patients II.2 and II.3 and from their healthy nephew, III.1, was hybridized on Affymetrix genome-wide human single-nucleotide polymorphism (SNP) Array 6.0 (Affymetrix, USA), which contains ~1,850,000 probes with an average distance of 1.3 kb between neighboring probes according to the manufacturer. Analyses were performed using the GeneChip Genome-Wide SNP Assay Kit 6.0 (Affymetrix) and the Genotyping Console 3.0.1 (Affymetrix) software. All CNVs required a minimum of ten consecutive array probes detected and CNVs needed to be called by at least two algorithms.

Sample preparation and H.E. staining

Tissue samples were fixed in 4% formalin in phosphonate buffer for 24 h. EDTA solution was used for the

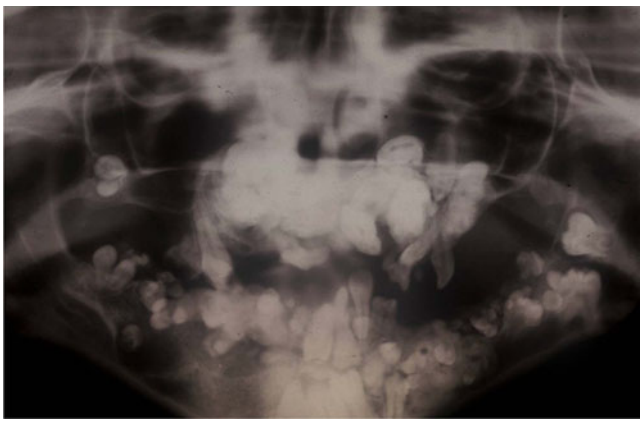


Fig. 4 Patient II.3. OPTG demonstrating development disorder of the jaw with crowding of teeth and odontoma in the upper and lower jaw

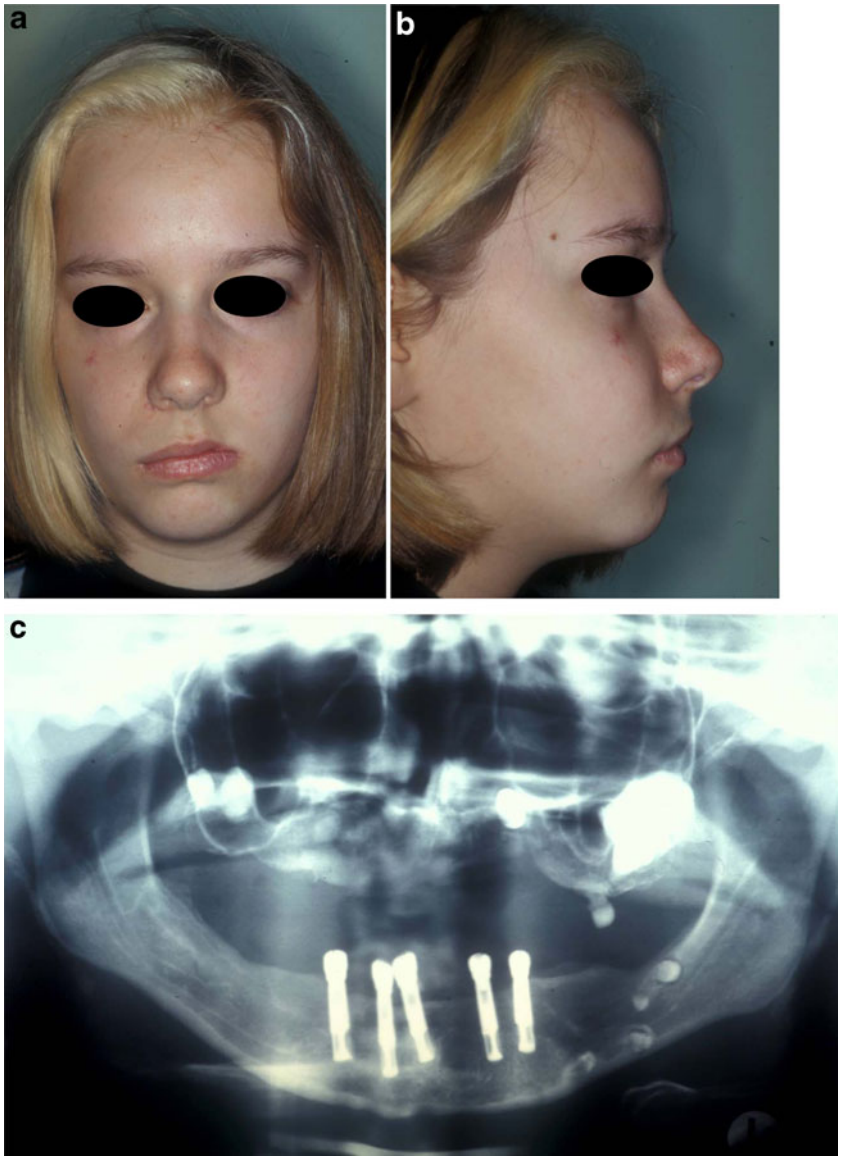


Fig. 5 Patient II.5. **a**, **b** Frontal and lateral facial views. **c** OPTG after first surgery interventions: Residual odontoma in regions 25–28 and implant insertion in regions 33–43. **d** Intraoral status: dysgnathia of the upper and lower jaw, teeth development disorder and crowding of teeth. **e** Resected compound odontoma. **f**, **g** Enamel and dentin-like structures of the compound odontoma

demineralization of the hard tissue samples. The samples were cut by microtome and stained by the hematoxylin-eosin method. Microscopic evaluation was carried out on light microscopy in the magnifications ×40 (Fig. 5f) and ×100 (Fig. 5g).

Results

Clinical reports (Table 1)

Clinical features are summarized in Table 1.

I.2, a man, was the oldest known affected member of this family. His parents and all siblings were healthy [22]. He was treated in our clinic for massive odontoma of the lower and upper jaw (Fig. 2a, b) [15, 16]. Together with his unaffected wife I.1, he had five children. His oldest son II.1 died at age 6 weeks from fulminant pneumonia after odontoma resection of the upper jaw. His second son II.2 was also diagnosed with the syndrome. At age 8 weeks, he showed failure to thrive, retardation of growth, increased levels of bilirubin, atresia of the oesophagus and was treated with balloon dilatation twice. At age 14 weeks, multiple odontoma were diagnosed and resected in our clinic (Fig. 3e). He also had oligodontia and dysplasia of the upper and lower jaw (Fig. 3a–d). Histological investigations showed enamel and dentin like structures compatible with a compound odontoma. Additional findings included a congenital stenosis of the aortic isthmus (aortic coarctation), which was operated on at the age of 14 years. The third sibling, a girl II.3, also presented with oligodontia and odontoma and was operated on in our clinic. The orthopantomogram (OPTG) (Fig. 4) showed multiple odontomas and numerous rudiment teeth. She also had an aortic coarctation and a pulmonary stenosis of a bronchus, which was treated

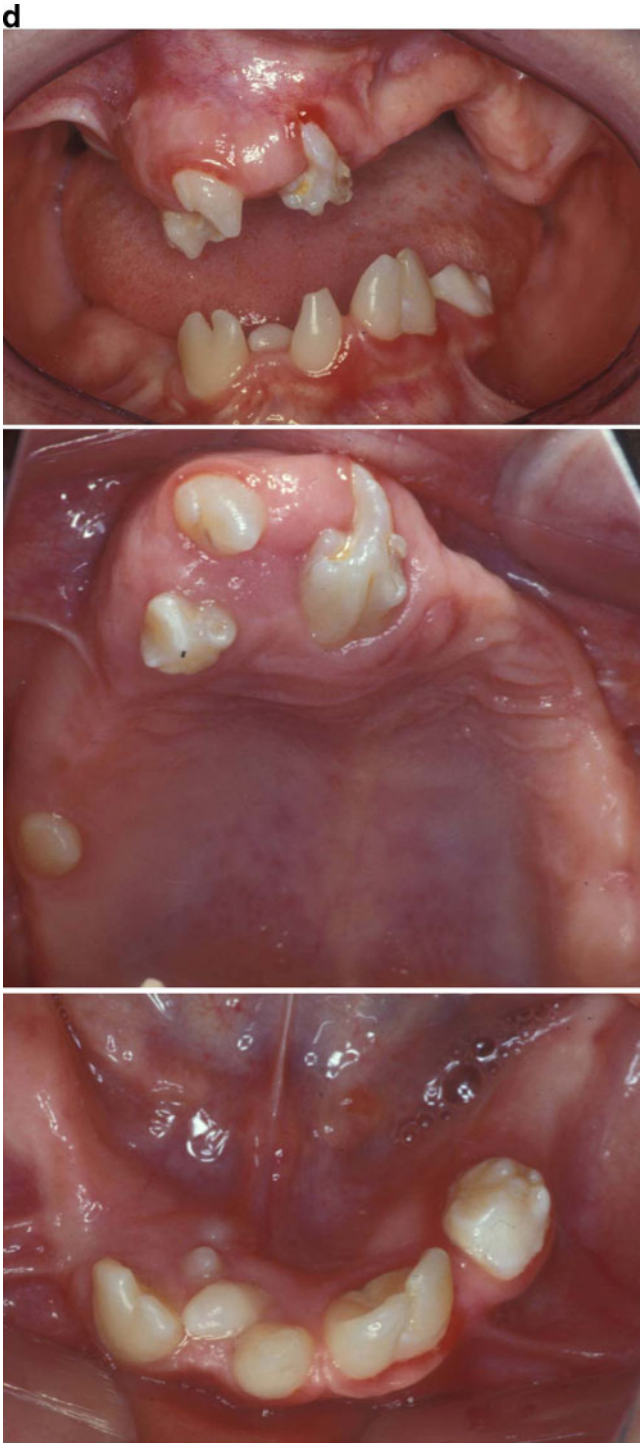


Fig. 5 (continued)

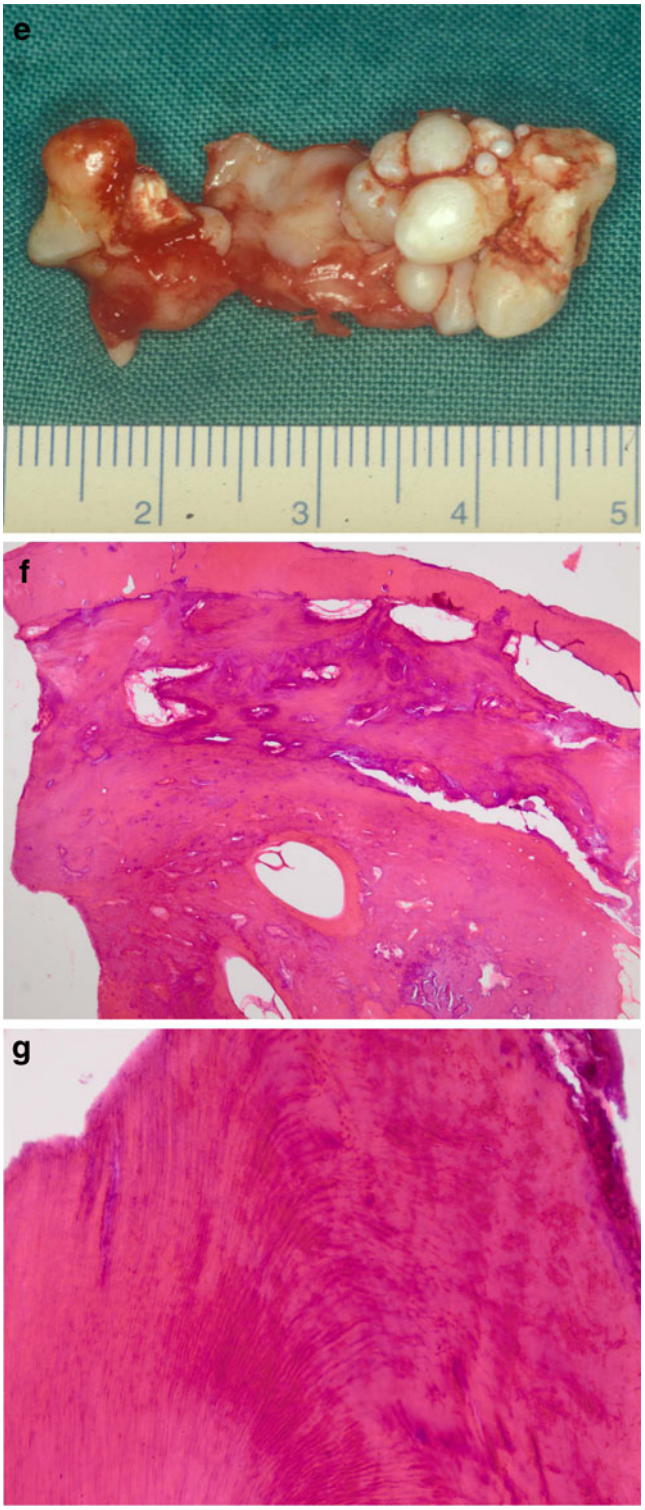


Fig. 5 (continued)

by segmental lung resection showing signs of a chronic inflammation of the segment. In contrast to her brother, no oesophagus stenosis or atresia and heart disease were found. Her husband II.4 was healthy and unaffected, as was their son III.1. Sibling II.5 demonstrated a milder form of the syndrome with oligodontia and odontoma, but no pathologic findings of the heart or oesophagus (Fig. 5a–c). Figure 5d shows the oral status before surgery with dysgnathia and development disorder of the teeth. The resected tissue (Fig. 5e) has the macroscopic sign of an odontoma with teeth-like structures (Fig. 5f, g). After multiple odontoma resections, dental implants were placed in the lower jaw for

Table 1 Clinical features of the syndrome

	Patient I.1	Patient I.2	Patient II.1	Patient II.2	Patient II.3	Patient II.4	Patient II.5	Patient II.6	Patient III.1
Gender	F	M	M	M	W	M	F	F	M
Rare or uncommon features									
Heart failure	−	NK	NK	+	+	−	−	−	−
Atresia of esophagus	−	NK	NK	+	+	−	−	−	−
Lung disease	−	NK	+	+	−	−	−	−	−
Typical features									
Odontoma	−	+	+	+	+	−	+	−	−
Oligodontia	−	+	+	+	+	−	+	−	−
Dysplasia of jaw	−	+	+	+	+	−	+	−	−
Dysplasia of teeth	−	+	+	+	+	−	+	−	−

NK not known

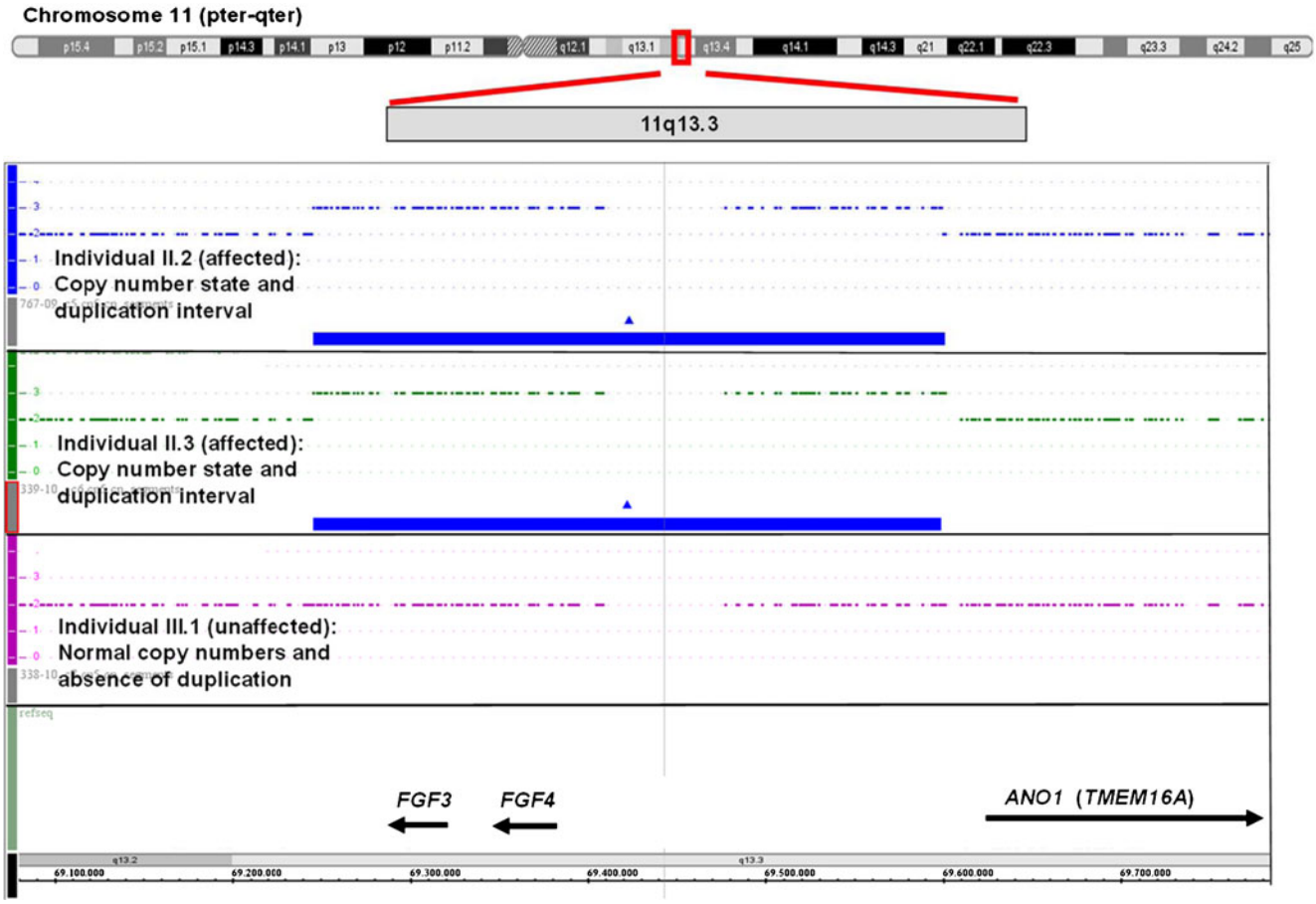


Fig. 6 Microarray data of chromosome 11 of patients II.2 and II.3. *Top*, ideogram of chromosome 11 showing the area of the microduplication identified by the microarray. *Middle*, microarray results of patients II.2 and II.3 (*blue boxes*) indicating a 355-kb duplication from 69,246,102 to 69,600,647 bp on chromosome 11q13.3. *Bottom*, schematic illustration of positions of genes on chromosome 11q13.3, note *FGF3* at ~69,300,000 basepairs (bps) and *FGF4* at ~69,340,000 bps. The gene for transmembrane protein 16 A (*TMEM16A*, alias anoctamin1, *ANO1*) is located distal to the duplication area. In the affected subjects II.2 and II.3, molecular karyotyping with a high-resolution SNP array (Affymetrix 6.0) revealed a gain from 69,246,102 to 69,600,947 bp on chromosome 11 (NCBI build 36, March 2006). This gain corresponds to a 355-kb duplication in 11q13.3 and includes two genes, both in full length, *FGF3* and *FGF4*. The microduplication of chromosome 11q13.3 was absent in the healthy subject III.1

dental rehabilitation (Fig. 5c). The youngest of the five siblings, II.6, was healthy and showed no pathological findings.

Results of cytogenetic analysis and molecular karyotyping

Chromosomal analysis showed normal karyotypes at a 450 banding level in all three probands (II.2, II.3, and III.1) (not shown). In the affected individuals II.2 and II.3, molecular karyotyping with a high-resolution SNP array (Affymetrix 6.0) revealed a gain from 69,246,102 to 69,600,947 bp on chromosome 11 (NCBI build 36, March 2006) (Fig. 6). This gain corresponded to a 355-kb duplication in 11q13.3 and was found to include two genes, both in full length, *FGF3* and *FGF4* (Fig. 6). The microduplication of chromosome 11q13.3 was absent in the healthy individual III.1.

Discussion

After 37 years, we revisited a family with a very rare hereditary syndrome including dysplasia and oligodontia of the teeth and dysplasia of the upper and lower jaw in all five of those affected, and esophageal abnormalities and aortic coarctation in a subset of two individuals (II.2 and II.3). The disorder showed an autosomal dominant inheritance. All affected individuals underwent surgical treatment for odontoma replacement followed by implantation to increase mastication function.

Following molecular karyotyping, we could identify a chromosomal microduplication including two genes, *FGF3* and *FGF4*, present in two affected individuals (II.2 and II.3) and absent in an unaffected individual (III.1) from this family.

Growth factors of the FGF family have important functions in the vertebrate development. They play a crucial role in the mesoderm formation, and they regulate and control the development of several organs [17]. The *FGF3* and *FGF4* genes are located as a cluster on chromosome 11q13.3. The interval between *FGF3* and *FGF4* is small, only approximately 35 kb (Fig. 6). There has been no previous report of duplication of the *FGF3* and *FGF4* genes, respectively, in patients with or without odontoma. FGF-3 is expressed in dental mesenchyme during the cap and bell stage of tooth development [18]. In an animal model, a dog breed with a characteristic dorsal hair ridge (Rhodesian ridgeback dog) was found to carry a heterozygous or homozygous chromosomal microduplication (on dog chromosome 18, which is syntenic to the long arm of chromosome 11 in the human) comprising the *FGF3*, *FGF4*, *FGF19*, and *ORAOV1* genes [24]. Neural tube defects but not odontoma have been described in a subset of ridgeback dogs; however, it is hard to say whether these observations are transferable to humans. Microdeletions of chromosome 11q13 containing the *FGF3* gene have been implicated in causing oto-dental syndrome (OMIM 164950) [23].

FGF-4 expression could also be identified during tooth development. Jernvall et al. demonstrated that FGF-4 is a regulator gene of the tooth form [19]. Mutations of FGF receptor genes could be identified in craniofacial syndromes such as craniosynostosis [20], and Jehee et al. reported duplications involving bands 11q11 and 11q12 in patients with syndromic multiple craniosynostoses [14].

Taken together, there have been numerous observations suggesting a role of FGF-3 and FGF-4 in tooth development. Therefore, we believe it is likely that in this family the partial duplication of chromosome 11 resulted in increased function with increased doses of FGF-3 and/or FGF-4, causing the very rare odontoma–dysphagia syndrome. Following this train of thought, an evaluation of FGF-3 and FGF-4 and/or the *FGF3* and *FGF4* genes in sporadic odontoma could be worthwhile.

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Conflicts of interest The authors declare that they have no conflict of interest.

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