Symptomatic Mandibular Fibrous Dysplasia With Concurrent Triple X- and Premutation Stage Fragile-X-Syndrome: Case Report With Short Literature Survey

REINHARD E. FRIEDRICH¹, FELIX K. KOHLRUSCH¹ and ANDREAS M. LUEBKE²

¹Oral and Craniomaxillofacial Surgery, Eppendorf University Hospital,
University of Hamburg, Hamburg, Germany;

²Institute of Pathology, Eppendorf University Hospital, University of Hamburg, Hamburg, Germany

Abstract. *Background: Certain constitutive chromosomal abnormalities of the human X chromosome are relatively common in conspicuous neuropsychiatric findings. Although tumors or tumor-like lesions are occasionally reported in diseases of the X chromosome, they are numerically negligible, for example, in aneuploidy such as the triple X syndrome (TXS). Case Report: A 16-year-old female patient with a known TXS and premutation stage of fragile X syndrome was referred by her dentist for diagnosis and treatment of unilateral cheek swelling. The examination of the psychologically conspicuous patient revealed a unilateral mandibular tumor with dysesthesia of the mental nerve. Surgical removal of soft, crumbly spongiosa over the nerve canal resulted in sufficient pressure release of the constricted nerve and restoration of epicritic sensitivity. Imaging findings and histological and molecular genetic examination revealed monostotic craniofacial fibrous dysplasia. Conclusion: Although the data in the literature do not give reason to suppose an accumulation of neoplasms in TXS, a numb chin syndrome should be a reason for detailed diagnostics. Careful diagnosis allows for customized therapy. This is the first report on the coincidence of TXS, fragile X syndrome, and fibrous dysplasia in a single individual.*

Numerical aberrations of chromosomes are relatively common in human reproduction and viable only in certain constellations

Correspondence to: Professor R. E. Friedrich, MD, DMD, Ph.D., This article is freely accessible online.

FEBOMFS, Department of Oral and Craniomaxillofacial Surgery, Eppendorf University Hospital, University of Hamburg, Martinistr. 52, 20246 Hamburg, Germany. Tel: +49 40741053259, e-mail: rfriedrich@uke.de

Key Words: Triple X syndrome, fragile X syndrome, fibrous dysplasia, GNAS1 mutation, numb chin syndrome.

(1). Viable aneuploidy of the sex chromosomes leads to variable phenotypes with different impacts on health and quality of life (2). Triple X syndrome (TXS) is a sex chromosomal abnormality (3). TXS is a relatively common occurrence in humans, with the estimated incidence being one in 1,000 females (4-6). TXS is relatively often associated with intellectual and psychological disabilities of affected individuals (5, 6). On the other hand, affected individuals can be of normal physical and mental health (3, 5). Indeed, genotype-phenotype relationships remain to be defined (3). Most reports about TXS focus on neuro-developmental disorders (5, 7). However, other features such as malformations and metabolic alterations (7-11), and immunological diseases (8) are also part of the TXS spectrum. The relationship between TXS and neoplasms has barely been studied. Given the frequency of TXS in the general population, the low number of reports of neoplasms in this syndrome is at least notable. The few publications on TXS and neoplasms so far are case reports and concede that it might be a chance or coincidence (12-16) or consider the potential influence of mosaic or constitutional TXS status on immunological therapies (17-18).

As well as numerical aberrations, the X chromosome may show other alterations with potential effects on phenotype (19). A relatively common mutation is named after a pathognomonic cytogenetic phenomenon that can be identified in the nucleus of affected individuals during preparations to determine the karyotype (20, 21). The affected X chromosome gives the erroneous impression of a localized unstable shape and thus is called fragile X syndrome (FXS) (22, 23). The phenotype was already known from clinical studies (24) and is also known under the eponym Martin-Bell syndrome (25). FXS occurs in men and women, with lower frequency in males (26). Pathfinding symptoms of diagnosis are attention-deficit/hyperactivity disorders and learning disabilities (27, 28). However, the connection between a genetic disposition and learning difficulties is often recognized late (29, 30). FXS is a neglected cause of impaired learning disorders and, according to the general view (31), probably the most

common monogenic disorder associated with impaired intellectual ability after Down syndrome (32). However, FXS has a significant range of clinical findings, and emphasis is given to marked heterogeneity (28, 31). The combination of certain physical features can substantiate the suspected diagnosis (33). Molecular genetic research has shown the cause of the cytogenetic finding is a mutation of the fragile X mental retardation 1 (*FMRI*) gene (main location: Xq27.3), leading to massive replications of a distinct base triplet (CGG) (34-38). Thus, FXS belongs to the group of trinucleotide repeat disorders (35, 36). However, the deletion of *FMRI* can also cause the FXS phenotype in rare cases (39). A lower number of replications (<59) does not appear to affect the carrier's phenotype. Individuals carrying about 59 to 200 CGG repeats define the premutation stage that is associated with diverse findings, in particular, neuropsychiatric disorders (40). Individuals with about 200 or more repetitions very likely will show the full range of findings (34). Interestingly, it has been suggested that FXS is associated with a lower risk of developing cancer (41, 42), but these relationships have been controversially discussed (43). Indeed, an increased risk of developing lip cancer in FXS was estimated (43). Furthermore, increased *FMRI* mRNA levels have a negative prognostic effect in certain forms of breast cancer (44). Other reports of FXS and malignant neoplasms are likely the results of coincidences of various genetic events (45, 46). However, those individuals reported are strikingly often children and adolescents (47-52).

Differential diagnosis of TXS before definitive karyotype results are available includes FXS, among other mutations (3). The concurrence of TXS and FXS has been reported but appears to be rare (53-55). Concerning potential bone pathologies, genetic influences on bone metabolism are of great importance in both syndromes (10, 56, 57). The coincidence of TXS or FXS with bone tumors has been registered only very rarely (12).

The following report is of a patient with known TXS and premutation stage FXS who required diagnostic and therapeutic measures due to visible and symptomatic facial tumor development.

Case Report

Medical history. The 16-year-old female patient was referred for examination and treatment an unclear swelling in the area of the right lower jaw (Figure 1A). The hardly communicative patient was accompanied by her parents for examination. The parents informed the attending surgeons that their daughter was suffering from genetically proven FXS and also TXS. The medical reports confirmed the triple X karyotype of the patient and a CGG repetition rate of the *FMRI* gene slightly higher than normal (62±2 repetitions). Evaluation of the latter genetic finding explicitly emphasized

that the patient's known behavioral disorders were not explained by the mutation status of the gene.

In the present case, a relatively short and flat forehead was noted in relation to the pronounced midface and chin region (Figure 1B). However, the sagittal relationships of a mandibular prognathism were not present (Figure 1C). The ears were slightly prominent. It was striking that it was practically impossible to establish any eye contact with the patient, and the medical contact had to be largely mediated through the parents.

For some time, the lower right cheek region had been swollen, and the patient had occasionally complained about pain. Visual inspection of the small patient revealed an inconspicuous external condition of the skin and facial motor functions. When palpating the face, the side of the right lower jaw was more prominent than the left lower jaw, in particular concerning the region of the right inferior border. The patient indicated a hyposensitive skin area that could be traced over the right cheek side distal to the nasolabial fold. The lips showed equally normal sensitivity to tactile stimuli, but the right chin region was less sensitive to touch than the left. The mandibular body showed no pain on pressure in the region of interest and symmetrical response on the mental foramina. Teeth were completely developed, had emerged to the oral cavity, and completed the dental arch in a symmetrical fashion. Teeth were well maintained, non-mobile, adequately responsive to cold stimuli, and the oral mucosa was rosy and intact. However, the mandibular body in the posterior region of the right side felt significantly enlarged to the lateral side without the oral vestibulum being elevated (Figure 1).

Radiology. A panoramic view radiography showed the vertical asymmetry of the mandibular corpus in favor of the right side (Figure 2A). On the right side of the mandible, the bone marrow was of gray-clouded radiopacity and had lost the trabecular structure. The contour of the deformed lower jaw was preserved, as well as the integrity and position of the teeth in the alveolar bone. An ill-defined radio-translucent region was depicted within the radiopaque lesion, immediately below the molars and approximately opposite the region from which the patient indicated feeling diminished sensitivity of the skin.

Cone-beam computed tomography of the right lower jaw showed a hyperplastic, predominantly homogeneous radiopaque cancellous bone region, which was interrupted by focal peri-radicular radiotransparent areas (Figure 2C-H). The nerve canal had a smaller diameter on the affected side than on the left side (Figure 2C-E). Both nerve channels ran horizontally at the same height (Figure 2A and C-E). Only in the area of the mental foramina, there was asymmetry of dimensions of the bone channels in which, on the lesion side, an elongation of the terminal branch of the alveolar nerve was evident in the transversal plane (Figure 2E). The

Figure 1. Facial aspect of patient. A: Enlarged interorbital distance and asymmetry of lower facial region with prominent right mandibular angle. B: Flat frontal region and relative long midfacial and lower face. C: Oral aspect reveals inconspicuous right lower alveolar process and vestibule.

increased bone volume caused by the lesion was, according to radiological findings, largely due to the expansion of the bone in the direction of the vestibular side (Figure 2F and G). The bony limitation of the nerve channel was no longer continuously detected in the area of the radiolucent region (Figure 2G and H).

Scintigraphy was performed to check whether the lesion was monostotic or polyostotic (Figure 3A-D). Scintigraphy revealed the intensified metabolism of the right side of the lower jaw as a solitary finding. The suspected diagnosis was malignant disease or osteonecrosis.

The radiological aspect of the lesion suggested fibrous dysplasia (FD), but several differential diagnoses had to be considered. Furthermore, the association of the lesion with the patient's genetic disposition was unclear.

Surgery. It was decided that a bone sample would be obtained to determine the nature of the bone lesion. The osteolytic area beneath the molars was also to be examined, and the canal relieved of compression by the lesion. Under general anesthesia, the muco-periosteum of the right lower jaw's vestibulum was lifted off. Below was an inconspicuous cortex. By means of piezo-surgery, a block of bone was removed from below the roots of the right molars (Figure 3E), and the mandibular canal was exposed. During this preparation, crumbly cancellous bone appeared below the cortex and was removed from the edge of the nerve canal. This area corresponded to the radiological transparency at the apices of the molars. The exposed alveolar nerve was intact, of normal size and, after removal of the altered bone in the remaining canal, without any adhesions to be removed. The bone barely bled during the procedure. Wound healing was unremarkable (Figure 2B). Eight weeks later, the patient described that the discomfort of the right cheek had disappeared. Likewise, the epicritic sensitivity of the lip and chin skin was intact.

Histology. The examination of the bone showed the typical features of FD (Figure 4A). In addition, the tissue was prepared for DNA extraction and amplification of the gene coding for guanine nucleotide-binding protein, alpha-stimulating activity polypeptide 1 (*GNAS1*) for mutation on codon 201 (exon 8). The lesion showed the c.602G>A (p.R201H) mutation (Figure 4B). This mutation provides evidence in the tissue sample for the phenotype called FD. Murine double minute 2 (*MDM2*) gene amplification in the bone sample was excluded (58).

Discussion

This report shows the coincidence of a somatic mutation resulting in tumor-like bone growth in an adolescent female with X-chromosomal aberrations. This coincidence of findings has not been described so far. Unusual in this case was the course of the diagnosis, because due to the knowledge of the genetic disease of the patient, it was essential to assess the clinical findings accurately as well as to take into account that the findings might have been independent of the underlying disease.

It is well-known that aneuploidy is a regular feature of the malignant phenotype arising from cells that were subjected to somatic mutation (59). In contrast to somatic aneuploidy, viable constitutional aneuploidy is rare (60). When examining the relationship of constitutive aneuploidy and the emergence of neoplasms, a careful distinction is made between autosomal and sex chromosomes. Neoplasms in constitutive aneuploidy arising in autosomes are, for example, transient myeloproliferative disorder or full-blown acute myeloid leukemia in patients with trisomy 21. In patients with sex chromosomal abnormality, the tendency to develop neoplasms is mainly due to increased tumor formation in Turner syndrome (45,X) and Klinefelter syndrome (47,XXY) (60). However, in both these X-chromosome-linked

Figure 2. Radiology of mandibular fibrous dysplasia. A: Panoramic view of jaws prior to surgery. No disturbance of habitual intercuspation of the teeth by the bone tumor of the right mandibular side; enlarged mandibular corpus below the roots of the teeth, central hypodense region below the right lower second molar, markedly enlarged jaw angle on the right side. The milky-glass-like radiopacity has blurred borders and extends mesially to the premolars, dorsal in the mandibular ramus. B: Panoramic view (cropped image) of the osteolysis region after decortication of the mandible on the vestibular side. C-E: A series of consecutive cone beam computed tomographs (CBCT) of the jaws prior to surgery (transverse sections through the first molar to premolar region in the posterior-anterior direction). C and D: The vertical position of the mandibular canal remains largely unchanged in its anterior-posterior course and diameter. The radiopaque tumor mass lies concentrically around the canal, which is partially bordered by a sclerotic rim. E: In contrast, the canal of the mental nerve is extended on the side of the bone tumor in the horizontal plane. F: Axial section of the lower jaw on CBCT. The dental arch remained unaffected by the bone tumor. Central, irregularly shaped, hypodense areas are scattered within the lesion and in contact with the tooth roots of the right molar, premolar and canine. The cortical layer of the bone is preserved in the tumor area in continuity. G: Axial section of right mandibular side on CBCT a little further caudal than shown in Figure F (cropped image). Moth-eaten-like transition zone of hyperdense tumor border with conserved nerve canal to the more distal area of extensive osteolysis. However, in the central hypodense area the nerve canal is not completely recognizable. H: Sagittal projection of the hypodense zone of the right side of the lower jaw. The nerve canal's caudal border is missing in the area of the second molar. The tooth roots have a natural shape and are intact.

syndromes, the study also showed a lower incidence of certain neoplasms in patients with gonosomal aneuploidy compared to the respective control group (60). TXS patients are not listed in the discussion of cancer and other tumors and sex chromosomal constitutive aneuploidy (60).

Fibrous Dysplasia

Genetics. FD is a non-tumorous bone disorder that is characterized by the overproduction and deposition of a poorly organized fibro-osseous matrix, slowly replacing the normal cancellous bone (61, 62). The disorder is caused by a mutation of the *GNAS1* gene on chromosome 20 (63-65). It is believed that the disease is viable in humans only as a somatic mutation. It follows that in a patient with this mutation, the more cells the mutation captures, and thus potentially the more organs, the earlier the defining genetic

change has occurred in ontogenesis (66, 67). The phenotype is correspondingly variable (68). McCune-Albright syndrome is based on *GNAS1* mutation happening early during embryogenesis and resulting in a phenotype characterized by significant endocrine dysregulation in addition to metabolic bone and pigmentation disorders (69). For skeletal manifestations of the *GNAS1* mutation, an influence of the bone metabolism by gene product Gs alpha on the parathyroid receptor is assumed (64). In osteoclasts, adenylyl cyclase is activated, and consequent increased production of cyclic adenosine monophosphate stimulates the proliferation, differentiation, and overproduction of poorly organized fibro-osseous tissues (70-72).

Radiology. Radiographic imaging of craniofacial FD is considered typical, showing a radiopaque lesion described with different metaphors such as sclerotic, ground-glass, or

Figure 3. Bone scintigraphy and specimen. A: Whole-body bone scintigraphy with monostotic findings. Selected scintigraphs of the skull depict the mandibular lesion in frontal (B), axial (C), and lateral (D) views. E: Resected specimen of the lower jaw with millimeter scale. Typical cancellous, easy-to-cut bone with a fibrous cut surface.

Figure 4. Histological and molecular genetic findings. A: Hematoxylin-eosin stained specimen of the mandibular lesion shows a lesion of immature woven bone trabeculae that seem to arise directly from a moderately cellular stroma of spindle cells with bland, tapered nuclei, and an inconspicuous, eosinophilic cytoplasm. The cells did not display any atypia. B: Ancillary molecular testing revealed a characteristic mutation at codon 201 within exon 8 of the guanine nucleotide-binding protein, alpha-stimulating activity polypeptide 1 (GNAS1) gene located on chromosome 20q (c.602G>A;pR201H).

peu d'orange appearing. The lesion's margins are ill-defined. Cortex is usually absent in FD. In mandibular cases, FD affects predominantly the post-mental region (73). Cyst-like lesions within a bone are well-known in FD (66). Nuclear-medical diagnosis of FD is not unique (74-76). Scintigraphy was an effective diagnostic measure in the presented case for

classifying FD as monostotic. Indeed, scintigraphy is a strategy for locating polyostotic FD (73). However, no decision was made based on scintigraphy in assessing whether the lesion was benign. The differential diagnosis of inflammatory or neoplastic bone changes may be difficult in cases of FD (76-81). Malignant degeneration of FD is rare

(82-91). However, reports of malignancy arising from FD suggest the affected body region should be under long-term monitoring (90, 91). Patients with FD have an increased risk of developing breast cancer (92).

Dentition. Although craniofacial FD may cause malocclusion of the teeth, and some teeth may be displaced by the growth of FD (93), changes in dental arch curvature are not a regular sign of this entity (94).

Disorders of the cranial nerves. The most important complication of craniofacial FD in terms of functional impairment of cranial nerves is the compression of altered and growing bone on the optic canal with consequent obstruction (95). However, it has been pointed out that compression of the nerve canal does not necessarily lead to a reduction in vision. Rather, many cases with craniofacial FD and orbital involvement show that the vision can remain unaffected over a long period of time (96). From this experience, it has been concluded that decompression of the optic canal must be considered very carefully because the risk of iatrogenic nerve damage is inherent to the surgical procedure (96). For the mandibular nerve, isolated hyperesthesia has been described in mandibular FD (97). However, reports of pain in patients with FD are much more common in axial skeletal locations. Pain in craniofacial FD occurs in about 30% of cases (92). The reduced sensitivity in the terminal branches of the mandibular nerve is unusual in connection with an FD in the bone surrounding the nerve. Rather, this finding should be regarded as a sign of malignant neoplasm if no local findings can adequately explain other causes of this symptom (98-102).

Treatment is overwhelmingly surgical, with modeling osteotomies being preferred over extensive resections (103-108). Alternative drug therapies aim to stop rapidly progressive FD (109) but still need long-term evaluation of risks and benefits of anti-resorptive therapy.

Histology. The histological evaluation of the FD is unambiguous in the majority of cases and allows the diagnosis of the disease based on characteristic features under conventional light microscopy (70). However, borderline cases of osteo-pathological assessment have been reviewed in the literature, including manifestations of the jaws (110). The molecular genetic identification of typical mutations of the GNAS1 gene ensures histological diagnosis (64, 111).

TXS

Risk of cancer. Some case reports on the diagnosis and treatment of malignant neoplasm in TXS have been published (12). Therapy and prognosis do not seem to differ

from that of a normal population. Bone tumors are extremely rare in TXS patients developing cancer (12). It can be concluded from the few publications on the subject that the diagnosis of TXS was known in a few cases of cancer.

Craniofacial morphology. Targeted analyzes of TXS patients have detected a number of malformations in this group (7, 10). Facial malformations of TXS include cleft lip and palate. However, it was explicitly pointed out that the majority of TXS patients are not diagnosed at all, and the frequencies of the findings in the presented study were considerably influenced by the recruitment method, which necessarily led to a collection of difficult cases (7). Some cephalometric parameters differ in TXS patients and controls. From this, it was deduced that TXS may develop midfacial hypoplasia, becoming evident in the analysis of the sagittal dimension. Likewise, sagittal underdevelopment ('length') of the mandible was found to be more common in TXS than in controls (11). It is possible that TXS patients have a shorter skull base than controls (112). However, anthropometric signs are not so pronounced that a typical phenotype can be derived from these findings.

Dentition. Few studies include oral findings in TXS. The focus of clinical investigations is on the assessment of dental status. Dental disorders were observed in almost half of all TXS patients (7). Here, the need for treatment of many patients is stressed, mainly the rehabilitation of carious dentition. The disorder of facial development with numerical aberration of the dentition is apparently extremely rare in TXS (113), as well as changes in tooth form (114).

FXS

Risk of cancer. Some reports on the diagnosis and treatment of malignant neoplasm in FXS have been published. A recent survey presented 40 cases (115). Another study describes an increased risk for the development of lip cancer in FXS (43). Therapy and prognosis of FXS patients do not seem to differ from that of a normal population. Bone tumors are extremely rare in FXS patients developing cancer (115). The individual reports of an increased risk of breast cancer in patients with FXS (44) [or FD (92)] suggest that the patient should be advised to undergo regular gynecological examinations at an early age.

Craniofacial morphology. Examinations of the skull in FXS are focused on findings that characterize the phenotype (33). Similarly to TXS, studies on FXS emphasize the reduced facial depth, as well as hypoplasia of the nasal bone cartilage interface, narrow mid-facial width, and exaggerated ear prominence (33). However, even these mild findings are often very discreet, not adequately consistent enough to prove

all findings in the same patient, and the coincidence of medical findings is also often not very conspicuous. In fact, it was acknowledged that the facial characteristics of FXS are often very subtle (33). In contrast, previous studies on craniofacial anthropology in FXS highlighted the shortened upper face height and increased jaw length compared to sex and age-matched controls (116-118). Further studies provide evidence for cleft lip and palate arising somewhat more frequently in FXS than in the normal population (119).

Sella turcica malformation was reported in two fetuses with FXS (120). The authors detailed a deep *sella turcica*, notching in the anterior wall, very short *dorsum sellae*, and irregularly arranged remnants of the notochord in the *dorsum*. A further study on this subject was performed on lateral cephalograms of FXS patients, revealing normal bone in all five cases of study. However, *sella turcica* was of normal shape in only one case. Two of the individuals showed deformities of the anterior wall or reduced *dorsum* height (121). In the case we presented, the anterior wall of the *sella turcica* was also clearly oblique.

Dentition. In one study, numerical and structural changes in teeth were demonstrated in FXS (122). The dental findings are abnormalities of root morphology, the comparatively early emergence of molars, and a larger jaw angle. However, the correlations of the findings were generally low (122). Earlier studies had shown significantly more frequent malocclusions but no differences in jaw relations and palatal dimensions in FXS (123). Taurodontism was demonstrated in a study in both FXS and TXS (114).

FXS and cherubism. In a case with FXS, a cherubism phenotype was detected (125). This case is interesting because there are overlaps of the phenotype in FD of jaws and cherubism. Cherubism is caused by a mutation of a gene coding for the sarcoma homology 3 domain-binding protein 2 (SH3BP2). SH3BP2 is a protein encoded by a gene located on chromosome 4 (126). FD is a unilocular or multilocular disease with origin in a somatic mutation that potentially affects every bone. On the other hand, cherubism is a hereditary disease with different penetrance but skeletal findings being preferentially located in the jaws. The patient's phenotype with cherubism is characterized by bilateral, spongy hyperplasia of jaws (127). However, unilateral cases of cherubism are also known (126). Therefore, the clinicoradiological findings of unilateral mandibular hyperplasia of the presented case do not exclude cherubism in principle. The histological findings in cherubism and FD are sometimes difficult to distinguish from each other (110). Indeed, cherubism has been called the familial form of FD (127) before the genetic delineation to FD was known. Another monogenetic disease, neurofibromatosis type 1 (NF1), can lead to a cherubism phenotype (128).

TXS, FXS, and FD and other syndromic diseases. Coincidences of NF1 with FXS (129), TXS (130) or FD (131) have been published as case reports. In cases with gonosomal disease and NF1, metabolic and developmental disorders were predominant findings but not the characteristic of *NF1* as a tumor-suppressor gene or phakomatosis. The presented patient had no clinical findings pointing to a coincidence with NF1 according to established diagnostic criteria. In patients with FD and NF1, the skin hyperpigmentation pattern differed markedly from the aspect expected in McCune–Albright syndrome. The coincidence of FXS and other syndromes has been reported, *e.g.* for trisomy 21 (132, 133), and Robin sequence (134).

Conclusion

FD of the jaw is a rare condition in which the focus is on differentiation from other lesions and tumors. The coincidence of FD with other syndromic diseases is known from individual reports. Therapy is symptomatic and carried out after careful examination of the patient.

Conflicts of Interest

The Authors declare that there are no conflicts of interest regarding publication.

Author's Contributions

REF treated the patient, researched the literature, and wrote the article. FKK checked the scientific literature and wrote the article. AML provided morphological and molecular genetic findings and checked the article. All Authors gave final approval for publication.

Acknowledgements

The Authors would like to thank the patient and her parents for permission to publish the case report.

References

- 1 Hassold T and Hunt P: To err (meiotically) is human: The genesis of human aneuploidy. *Nat Rev Gen* 2: 280-291, 2001. PMID: 11283700. DOI: 10.1038/35066065
- 2 Hall H, Hunt P and Hassold T: Meiosis and sex chromosome aneuploidy: how meiotic errors cause aneuploidy; how aneuploidy causes meiotic errors. *Curr Opin Genet Dev* 16: 323-329, 2006. PMID: 16647844.
- 3 Tartaglia NR, Howell S, Sutherland A, Wilson R and Wilson L: A review of trisomy X (47,XXX). *Orphanet J Rare Dis* 5: 8, 2010. PMID: 20459843. DOI: 10.1186/1750-1172-5-8
- 4 Hamerton JL, Canning N, Ray M and Smith S: A cytogenetic survey of 14,069 newborn infants. I. Incidence of chromosome abnormalities. *Clin Genet* 8: 223-243, 1975. PMID: 1183067. DOI: 10.1111/j.1399-0004.1975.tb01498.x
- 5 Otter M, Schrander-Stumpel CT and Curfs LM: Triple X syndrome: A review of the literature. *Eur J Hum Genet* 18: 265-271, 2010. PMID: 19568271. DOI: 10.1038/ejhg.2009.109

- 6 Tartaglia NR, Ayari N, Hutaft-Lee C and Boada R: Attention-deficit hyperactivity disorder symptoms in children and adolescents with sex chromosome aneuploidy: XXY, XXX, XYY, and XYYY. *J Dev Behav Pediatr* 33: 309-318, 2012. PMID: 22333574. DOI: 10.1097/DBP.0b013e31824501c8
- 7 Wigby K, D'Epagnier C, Howell S, Reicks A, Wilson R, Cordeiro L and Tartaglia N: Expanding the phenotype of triple X syndrome: A comparison of prenatal *versus* postnatal diagnosis. *Am J Med Genet A* 170: 2870-2881, 2016. PMID: 27644018. DOI: 10.1002/ajmg.a.37688
- 8 Goswami R, Goswami D, Kabra M, Gupta N, Dubey S and Dadhwal V: Prevalence of the triple X syndrome in phenotypically normal women with premature ovarian failure and its association with autoimmune thyroid disorders. *Fertil Steril* 80: 1052-1054, 2003. PMID: 14556833. DOI: 10.1016/s0015-0282(03)01121-x
- 9 Stagi S, Di Tommaso M, Scalini P, Sandini E, Masoni F, Chiarelli F, Verrotti A, Giglio S, Romano S and de Martino M: Cross-sectional study shows that impaired bone mineral status and metabolism are found in nonmosaic triple X syndrome. *Acta Paediatr* 106: 619-626, 2017. DOI: 10.1111/apa.13744
- 10 Haverty CE, Lin AE, Simpson E, Spence MA and Martin RA: 47,XXX associated with malformations. *Am J Med Genet A* 125A: 108-111, 2004. PMID: 14755479. DOI: 10.1002/ajmg.a.20393
- 11 Ferrazzo KL, Payeras MR, Ferrazzo VA and Mezomo MB: Craniofacial and dental manifestations of triple X syndrome associated with congenital hypothyroidism: A case report. *Spec Care Dentist* 34: 156-159, 2014. PMID: 24117978. DOI: 10.1111/scd.12050
- 12 Patiño-García A, López de Mesa R, de Alava E and Sierrasesúmaga L: Clinical and molecular features of Ewing sarcoma in a patient with triple-X syndrome. *Cancer Genet Cytogenet* 113: 188-190, 1999. PMID: 10484990.
- 13 Lee JH, Kim KS and Cho YG: A case of torsion of a mucinous cystadenoma in triple-X syndrome with pure gonadal dysgenesis. *Arch Gynecol Obstet* 274: 174-177, 2006. PMID: 16408186. DOI: 10.1007/s00404-005-0116-9
- 14 Sahinturk S, Ozemri Sag S, Ture M, Gorukmez O, Topak A, Yakut T and Gulen T: A fertile patient with 45X/47XXX mosaicism. *Genet Couns* 26: 29-34, 2015. PMID: 26043504.
- 15 Iskender C, Tarım E, Cok T, Yalcinkaya C, Kalaycı H and Sahin F: Fetal axillary cystic hygroma: a novel association with triple X syndrome. *Birth Defects Res A Clin Mol Teratol* 94: 955-957, 2012. PMID: 23109196. DOI: 10.1002/bdra.23083
- 16 Kemp B, Hauptmann S, Schröder W, Amo-Takyi B, Leeners B and Rath W: Dysgerminoma of the ovary in a patient with triple-X syndrome. *Int J Gynaecol Obstet* 50: 51-53, 1995. PMID: 7556861. DOI: 10.1016/0020-7292(95)02395-s
- 17 Becher R, Mahmoud HK, Schaefer UW and Schmidt CG: Transplantation of bone marrow with constitutional chromosomal anomalies. Cytogenetic studies and clinical implications. *Blut* 53: 341-346, 1986. PMID: 3530353. DOI: 10.1007/bf00320894
- 18 Sharapova SO, Valochnik AV, Guryanova IE, Sakovich IS and Aleinikova OV: Novel biallelic ATM mutations coexist with a mosaic form of triple X syndrome in an 11-year-old girl at remission after T-cell acute leukemia. *Immunogenetics* 70: 613-617, 2018. PMID: 29492593. DOI: 10.1007/s00251-018-1056-4
- 19 Hall DA and Berry-Kravis E: Fragile X syndrome and fragile X-associated tremor ataxia syndrome. *Handb Clin Neurol* 147: 377-391, 2018. PMID: 29325626. DOI: 10.1016/B978-0-444-63233-3.00025-7
- 20 Lubs HA: A marker X chromosome. *Am J Hum Genet* 21: 231-244, 1969. PMID: 5794013.
- 21 Sutherland GR: Routine diagnostic detection of the fragile X. *J Med Genet* 21: 74-75, 1984. PMID: 6694192. DOI: 10.1136/jmg.21.1.74-a
- 22 Sutherland GR and Richards RI: Unusual inheritance patterns due to dynamic mutation in fragile X syndrome. *Ciba Found Symp* 197: 119-126, 1996. PMID: 8827371. DOI: 10.1002/9780470514887.ch7
- 23 Sutherland GR: The fragile X chromosome. *Int Rev Cytol* 81: 107-143, 1983. PMID: 6347931. DOI: 10.1016/s0074-7696(08)62336-0
- 24 Martin JP and Bell J: A pedigree of mental defect showing sex-linkage. *J Neurol Psychiatry* 6: 154-157, 1943. PMID: 21611430. DOI: 10.1136/jnnp.6.3-4.154
- 25 Rocchi M, Archidiacono N and Filippi G: X-linked mental retardation. I. Martin-Bell syndrome (report of 18 families). *J Genet Hum* 35: 351-379, 1987. PMID: 3437265.
- 26 O'Byrne JJ, Sweeney M, Donnelly DE, Lambert DM, Beattie ED, Gervin CM, Barton DE and Lynch SA: Incidence of fragile X syndrome in Ireland. *Am J Med Genet A* 173: 678-683, 2017. PMID: 28157260. DOI: 10.1002/ajmg.a.38081
- 27 Schwartz CE, Phelan MC, Pulliam LH, Wilkes G, Vanner LV, Albiez KL, Potts WA, Rogers RC, Schroer RJ, Saul RA, Prouty LA, Dean JH, Taylor HA and Stevenson RE: Fragile X syndrome: Incidence, clinical and cytogenetic findings in the black and white populations of South Carolina. *Am J Med Genet* 30: 641-654, 1988. PMID: 3177476. DOI: 10.1002/ajmg.1320300165
- 28 Laxova R: Fragile X syndrome. *Adv Pediatr* 41: 305-342, 1994. PMID: 7992687.
- 29 Simko A, Hornstein L, Soukup S and Bagamery N: Fragile X syndrome: recognition in young children. *Pediatrics* 83: 547-552, 1989. PMID: 2927995.
- 30 Wheeler AC, Wylie A, Villagomez A, Bishop E and Raspa M: Health care for individuals with fragile X Syndrome: Understanding access and quality. *Disabil Health J* 12: 269-277, 2019. PMID: 30442576. DOI: 10.1016/j.dhjo.2018.11.004
- 31 Paulson H: Repeat expansion diseases. *Handb Clin Neurol* 147: 105-123, 2018. PMID: 29325606. DOI: 10.1016/B978-0-444-63233-3.00009-9
- 32 Sauna-Aho O, Bjelogrić-Laakso N, Siren A and Arvio M: Signs indicating dementia in Down, Williams and fragile X syndromes. *Mol Genet Genomic Med* 6: 855-860, 2018. PMID: 29971948. DOI: 10.1002/mgg3.430
- 33 Heulens I, Suttie M, Postnov A, De Clerck N, Perrotta CS, Mattina T, Faravelli F, Forzano F, Kooy RF and Hammond P: Craniofacial characteristics of fragile X syndrome in mouse and man. *Eur J Hum Genet* 21: 816-823, 2013. PMID: 23211703. DOI: 10.1038/ejhg.2012.265
- 34 Oberlé I, Rousseau F, Heitz D, Kretz C, Devys D, Hanauer A, Boué J, Bertheas MF and Mandel JL: Instability of a 550-base pair DNA segment and abnormal methylation in fragile X syndrome. *Science* 252(5009): 1097-1102, 1991. PMID: 2031184. DOI: 10.1126/science.252.5009.1097
- 35 Kremer EJ, Pritchard M, Lynch M, Yu S, Holman K, Baker E, Warren ST, Schlessinger D, Sutherland GR and Richards RI: Mapping of DNA instability at the fragile X to a trinucleotide repeat sequence p(CCG)_n. *Science* 252(5013): 1711-1714, 1991. PMID: 1675488. DOI: 10.1126/science.1675488

- 36 Verkerk AJ, Pieretti M, Sutcliffe JS, Fu YH, Kuhl DP, Pizzuti A, Reiner O, Richards S, Victoria MF, Zhang FP, Eussen BE, van Ommen GJB, Blonden LAJ, Riggins GJ, Chastain JL, Kunst CB, Galjaard H, Caskey CT, Nelson DL, Oostra BA and Warren ST: Identification of a gene (*FMR-1*) containing a CGG repeat coincident with a breakpoint cluster region exhibiting length variation in fragile X syndrome. *Cell* 65: 905-914, 1991. PMID: 1710175. DOI: 10.1016/0092-8674(91)90397-h
- 37 Meijer H, de Graaff E, Merckx DM, Jongbloed RJ, de Die-Smulders CE, Engelen JJ, Fryns JP, Curfs PM and Oostra BA: A deletion of 1.6 kb proximal to the CGG repeat of the *FMR1* gene causes the clinical phenotype of the fragile X syndrome. *Hum Mol Genet* 3: 615-620, 1994. PMID: 8069307. DOI: 10.1093/hmg/3.4.615
- 38 Chiurazzi P, Kozak L and Neri G: Unstable triplets and their mutational mechanism: size reduction of the CGG repeat vs. germline mosaicism in the fragile X syndrome. *Am J Med Genet* 51: 517-521, 1994. PMID: 7943033. DOI: 10.1002/ajmg.1320510446
- 39 Gedeon AK, Baker E, Robinson H, Partington MW, Gross B, Manca A, Korn B, Poustka A, Yu S, Sutherland GR and Mully JC: Fragile X syndrome without CCG amplification has an *FMR1* deletion. *Nat Genet* 1: 341-344, 1992. PMID: 1302032. DOI: 10.1038/ng0892-341
- 40 Hagerman RJ, Van Housen K, Smith AC and McGavran L: Consideration of connective tissue dysfunction in the fragile X syndrome. *Am J Med Genet* 17: 111-121, 1984. PMID: 6711590. DOI: 10.1002/ajmg.1320170106
- 41 Schultz-Pedersen S, Hasle H, Olsen JH and Friedrich U: Evidence of decreased risk of cancer in individuals with fragile X. *Am J Med Genet* 103: 226-230, 2001. PMID: 11745995.
- 42 Rosales-Reynoso MA, Ochoa-Hernández AB, Aguilar-Lemarrooy A, Jave-Suárez LF, Troyo-Sanromán R and Barros-Núñez P: Gene expression profiling identifies *WNT7A* as a possible candidate gene for decreased cancer risk in fragile X syndrome patients. *Arch Med Res* 41: 110-118.e2, 2010. PMID: 20470940. DOI: 10.1016/j.arcmed.2010.03.001
- 43 Sund R, Pukkala E and Patja K: Cancer incidence among persons with fragile X syndrome in Finland: A population-based study. *J Intellect Disabil Res* 53: 85-90, 2009. PMID: 18705633. DOI: 10.1111/j.1365-2788.2008.01116.x
- 44 Lucá R, Averna M, Zalfa F, Vecchi M, Bianchi F, La Fata G, Del Nonno F, Nardacci R, Bianchi M, Nuciforo P, Munck S, Parrella P, Moura R, Signori E, Alston R, Kuchnio A, Farace MG, Fazio VM, Piacentini M, De Strooper B, Achsel T, Neri G, Neven P, Evans DG, Carmeliet P, Mazzone M and Bagni C: The fragile X protein binds mRNAs involved in cancer progression and modulates metastasis formation. *EMBO Mol Med* 5: 1523-1536, 2013. PMID: 24092663. DOI: 10.1002/emmm.201302847
- 45 Au WY, Man C, Pang A and Kwong YL: Acute lymphoblastic leukemia in a patient with fragile X syndrome: Cytogenetic and molecular features. *Haematologica* 88: ECR13, 2003. PMID: 12681986.
- 46 Collins DT, Mannina EM and Mendonca M: Total body irradiation in a patient with fragile X syndrome for acute lymphoblastic leukemia in preparation for stem cell transplantation: A case report and literature review. *Am J Med Genet A* 167A: 2444-2446, 2015. PMID: 26097012. DOI: 10.1002/ajmg.a.37204
- 47 Phelan MC, Stevenson RE, Collins JL and Trent HE 3rd: Fragile X syndrome and neoplasia. *Am J Med Genet* 30: 77-82, 1988. PMID: 2845782.
- 48 Rodewald L, Miller DC, Sciorra L, Barabas G, Lee ML, Opitz, JM and Reynolds JF: Central nervous system neoplasm in a young man with Martin-Bell syndrome – fra(X)-XLMR. *Am J Med Genet* 26: 7-12, 1987. PMID: 3812581. DOI: 10.1002/ajmg.1320260103
- 49 Cunningham M and Dickerman JD: Fragile X syndrome and acute lymphoblastic leukemia. *Cancer* 62: 2383-2386, 1988. PMID: 3179954. DOI: 10.1002/1097-0142(19881201)62:11<2383::aid-cncr2820621122>3.0.co;2-r
- 50 Ferrari A, Meazza C and Casanova M: Nasopharyngeal carcinoma in a boy with fragile X syndrome. *Pediatr Hematol Oncol* 17: 597-600, 2000. PMID: 11033736.
- 51 Wirojanan J, Kraff J, Hawkins DS, Laird C, Gane LW, Angkustsiri K, Tassone F, Hagerman RJ: Two boys with fragile X syndrome and hepatic tumors. *J Pediatr Hematol Oncol* 30: 239-241, 2008. PMID: 18376289. DOI: 10.1097/MPH.0b013e31815f88c9
- 52 Alexiou GA, Siozos G, Stefanaki K, Vlachakis E, Sfakianos G, Prodromou N and Moschovi M: Medulloblastoma in a child with fragile X syndrome. *Neuropediatrics* 43: 155-158, 2012. PMID: 22605614. DOI: 10.1055/s-0032-1315430
- 53 Nielsen KB: Sex chromosome aneuploidy in fragile X carriers. *Am J Med Genet* 23: 537-544, 1986. PMID: 3953664.
- 54 Fuster C, Templado C, Miró R, Barrios L and Egozcue J: Concurrence of the triple-X syndrome and expression of the fragile site Xq27.3. *Hum Genet* 78: 293, 1988. PMID: 3346020. DOI: 10.1007/bf00291682
- 55 Watson MS, Breg WR, Pauls D, Brown WT, Carroll AJ, Howard-Peebles PN, Meryash D and Shapiro LR: Aneuploidy and the fragile X syndrome. *Am J Med Genet* 30: 115-121, 1988. PMID: 2972203.
- 56 Hoyos LR and Thakur M: Fragile X premutation in women: recognizing the health challenges beyond primary ovarian insufficiency. *Assist Reprod Genet* 34: 315-323, 2017. PMID: 27995424. DOI: 10.1007/s10815-016-0854-6
- 57 Stagi S, Iurato C, Lapi E, Cavalli L, Brandi ML and de Martino M: Bone status in genetic syndromes: a review. *Hormones* 14: 19-31, 2015. PMID: 25885101. DOI: 10.1007/BF03401378
- 58 Hang JF and Chen PC: Parosteal osteosarcoma. *Arch Pathol Lab Med* 138: 694-699, 2014. PMID: 24786129. DOI: 10.5858/arpa.2013-0030-RS
- 59 Giam M and Rancati G: Aneuploidy and chromosomal instability in cancer: a jackpot to chaos. *Cell Div* 10: 3, 2015. PMID: 26015801. DOI: 10.1186/s13008-015-0009-7
- 60 Ganmore I, Smootha G and Izraeli S: Constitutional aneuploidy and cancer predisposition. *Hum Mol Genet* 2009 18(R1): R84-R93, 2009. PMID: 19297405. DOI: 10.1093/hmg/ddp084
- 61 Lichtenstein L: Polyostotic fibrous dysplasia. *Arch Surg* 36: 874-898, 1938. DOI: 10.1001/archsurg.1938.01190230153012
- 62 Lichtenstein L and Jaffe HL: Fibrous dysplasia of bone. A condition affecting one, several or many bones, the graver cases of which may present abnormal pigmentation of skin, premature sexual development, hyperthyroidism or still other extraskeletal abnormalities. *Arch Pathol* 33: 777-816, 1942.
- 63 Rao VV, Schnittger S and Hansmann I: G protein Gs alpha (*GNAS1*), the probable candidate gene for Albright hereditary osteodystrophy, is assigned to human chromosome 20q12-

- q13.2. *Genomics* 10: 257-261, 1991. PMID: 1904395. DOI: 10.1016/0888-7543(91)90508-c
- 64 Weinstein LS, Chen M and Liu J: Gs(alpha) mutations and imprinting defects in human disease. *Ann N Y Acad Sci* 968: 173-197, 2002. PMID: 12119276. DOI: 10.1111/j.1749-6632.2002.tb04335.x
- 65 Szuhai K, Cleton-Jansen AM, Hogendoorn PC and Bovée JV: Molecular pathology and its diagnostic use in bone tumors. *Cancer Genet* 205:193-204, 2012. PMID: 22682618. DOI: 10.1016/j.cancergen.2012.04.001
- 66 McCune DJ: Osteitis fibrosa cystica: the case of a nine year old girl who also exhibits precocious puberty, multiple pigmentation of the skin and hyperthyroidism. *Am J Dis Child* 52: 743-747, 1936.
- 67 Albright F, Butler AM, Hampton AO and Smith P: Syndrome characterized by osteitis fibrosa disseminata, areas of pigmentation and endocrine dysfunction, with precocious puberty in females. Report of five cases. *N Engl J Med* 216: 727- 746, 1937. DOI: 10.1056/NEJM193704292161701
- 68 Javaid MK, Boyce A, Appelman-Dijkstra N, Ong J, Defabianis P, Offiah A, Arunde P, Shaw N, Pos VD, Underhill A, Portero D, Heral L, Heegaard AM, Masi L, Monsell F, Stanton R, Dijkstra PDS, Brandi ML, Chapurlat R, Hamdy NAT and Collins MT: Best practice management guidelines for fibrous dysplasia/McCune-Albright syndrome: a consensus statement from the FD/MAS international consortium. *Orphanet J Rare Dis* 14:139, 2019. PMID: 31196103. DOI: 10.1186/s13023-019-1102-9
- 69 Lecumberri B, Pozo-Kreiling JJ, Esteban I, Gomes M, Royo A, Gómez de la Riva Á and Pérez de Nanclares G: Head and neck manifestations of an undiagnosed McCune-Albright syndrome: clinicopathological description and literature review. *Virchows Arch* 473: 645-648, 2018. PMID: 29984378. DOI: 10.1007/s00428-018-2396-z
- 70 Riminucci M, Liu B, Corsi A, Shenker A, Spiegel AM, Robey PG and Bianco P: The histopathology of fibrous dysplasia of bone in patients with activating mutations of the Gs alpha gene: site-specific patterns and recurrent histological hallmarks. *J Pathol* 187: 249-258, 1999. PMID:10365102. DOI: 10.1002/(SICI)1096-9896(199901)187:2<249::AID-PATH222>3.0.CO;2-J
- 71 Marie PJ: Cellular and molecular basis of fibrous dysplasia. *Histol Histopathol* 16: 981-988, 2001. PMID: 11510989. DOI: 10.14670/HH-16.981
- 72 Pereira TDSF, Gomes CC, Brennan PA, Fonseca FP and Gomez RS: Fibrous dysplasia of the jaws: Integrating molecular pathogenesis with clinical, radiological, and histopathological features. *J Oral Pathol Med* 48: 3-9, 2019. PMID: 30376190. DOI:10.1111/jop.12797
- 73 Macdonald-Jankowski DS and Li TK: Fibrous dysplasia in a Hong Kong community: The clinical and radiological features and outcomes of treatment. *Dentomaxillofac Radiol* 38: 63-72, 2009. PMID: 19176647. DOI: 10.1259/dmfr/56740531
- 74 Papadakis GZ, Millo C, Sadowski SM, Karantanis AH, Bagci U and Patronas NJ: Fibrous dysplasia mimicking malignancy on ⁶⁸Ga-DOTATATE PET/CT. *Clin Nucl Med* 42: 209-210, 2017. PMID: 28072620. DOI: 10.1097/RLU.0000000000001527
- 75 De Coster L, Sciôt R, Everaerts W, Gheysens O, Verscuren R, Deroose CM, Pans S, Van Laere K and Goffin KE: Fibrous dysplasia mimicking bone metastasis on ⁶⁸Ga-PSMA PET/MRI. *Eur J Nucl Med Mol Imaging* 44: 1607-1608, 2017. PMID: 28488027. DOI: 10.1007/s00259-017-3712-6
- 76 Lee H, Lee KS and Lee WW: ¹⁸F-NaF PET/CT findings in fibrous dysplasia. *Clin Nucl Med* 40: 912-914, 2015. PMID: 26444650. DOI: 10.1097/RLU.0000000000000948
- 78 Hennessy G, Shetty D, Loh H, Bui C, Le K and Mansberg R: Polyostotic fibrous dysplasia in McCune-Albright syndrome demonstrated on ⁶⁸Ga-DOTATATE PET/CT. *Clin Nucl Med* 41: 982-985, 2016. PMID: 27740949. DOI: 10.1097/RLU.0000000000001372
- 79 Martini M, Klausning A, Heim N, Fischer HP, Sommer A and Reich RH: Fibrous dysplasia imitating malignancy. *J Craniomaxillofac Surg* 46: 1313-1319, 2018. PMID: 29859820. DOI: 10.1016/j.jcms.2018.05.019
- 80 Ogul H and Keskin E: Locally aggressive fibrous dysplasia mimicking malign calvarial lesion. *J Craniofac Surg* 29: e318-e319, 2018. PMID: 29485574. DOI: 10.1097/SCS.00000000000004453
- 81 Tao L, Sun J, Jain A, Ouyang J and Tambunan D: Polyostotic fibrous dysplasia mimicking osseous metastases. *Cureus* 11: e3884, 2019. PMID: 30899635. DOI: 10.7759/cureus.3884
- 82 Worth HM and Stoneman DW: Osteomyelitis, malignant disease, and fibrous dysplasia. Some radiologic similarities and differences. *Dent Radiogr Photogr* 50: 1-8 and 12-15, 1977. PMID: 264832.
- 83 Collins MT, Singer FR and Eugster E: McCune-Albright syndrome and the extraskeletal manifestations of fibrous dysplasia. *Orphanet J Rare Dis* 7 Suppl 1: S4, 2012. PMID: 22640971. DOI: 10.1186/1750-1172-7-S1-S4
- 84 Pilheu F and Del Soldato G: Fibro-osteosarcoma of the jaw in a case of polyostotic fibrous dysplasia. *Oral Surg Oral Med Oral Pathol* 21: 778-781, 1966. PMID: 5219668. DOI: 10.1016/0030-4220(66)90101-0
- 85 Gross CW and Montgomery WW: Fibrous dysplasia and malignant degeneration. *Arch Otolaryngol* 85: 653-657, 1967. PMID: 6024495.
- 86 Slow IN and Friedman EW: Osteogenic sarcoma arising in a preexisting fibrous dysplasia: report of case. *J Oral Surg* 29: 126-129, 1971. PMID: 5279098.
- 87 Immenkamp M: Malignant change in fibrous dysplasia (author's transl). *Z Orthop Ihre Grenzgeb* 113: 331-343, 1975 (Article in German). PMID: 1058566.
- 88 Pack SE, Al Share AA, Queresby FA and Baur DA: Osteosarcoma of the mandible arising in fibrous dysplasia - A case report. *J Oral Maxillofac Surg* 74: 2229.e1-2229.e4, 2016. PMID: 27425882. DOI: 10.1016/j.joms.2016.06.174
- 89 Sugiura Y, Kanda H, Motoi N, Nomura K, Inamura K, Okada E, Matsumoto H, Shimoji T, Matsumoto S, Nakayama J, Takazawa Y, Ishikawa Y and Machinami R: Osteosarcoma arising in fibrous dysplasia, confirmed by mutational analysis of GNAS gene. *Pathol Res Pract* 214: 318-324, 2018. PMID: 29268950. DOI: 10.1016/j.prp.2017.10.018
- 90 Sasikumar A, Joy A, Pillai MRA, Alex TM and Narayanan G: ⁶⁸Ga-PSMA PET/CT in osteosarcoma in fibrous dysplasia. *Clin Nucl Med* 42: 446-447, 2017. PMID: 28346248. DOI: 10.1097/RLU.0000000000001646
- 91 Oh SH, Kang JH, Seo YK, Kim JH, Choi YS and Hwang EH: Malignant transformation of fibrous dysplasia into angiosarcoma. *Oral Radiol*, 2019. PMID: 31368093. DOI: 10.1007/s11282-019-00404-2

- 92 Majoor BC, Boyce AM, Bovée JV, Smit VT, Collins MT, Cleton-Jansen AM, Dekkers OM, Hamdy NA, Dijkstra PS and Appelman-Dijkstra NM: Increased risk of breast cancer at a young age in women with fibrous dysplasia. *J Bone Miner Res* 33: 84-90, 2018. PMID: 28856726. DOI: 10.1002/jbmr.3286
- 93 Burke AB, Collins MT and Boyce AM: Fibrous dysplasia of bone: Craniofacial and dental implications. *Oral Dis* 23: 697-708, 2017. PMID: 27493082. DOI: 10.1111/odi.12563
- 94 Akintoye SO, Boyce AM and Collins MT: Dental perspectives in fibrous dysplasia and McCune-Albright syndrome. *Oral Surg Oral Med Oral Pathol Oral Radiol* 116: e149-e155, 2013. PMID: 23953425. DOI: 10.1016/j.oooo.2013.05.023
- 95 Tan YC, Yu CC, Chang CN, Ma L and Chen YR: Optic nerve compression in craniofacial fibrous dysplasia: the role and indications for decompression. *Plast Reconstr Surg* 120: 1957-1962, 2007. PMID: 18090759. DOI: 10.1097/01.prs.0000287338.28018.c7
- 96 Amit M, Collins MT, FitzGibbon EJ, Butman JA, Fliss DM and Gil Z: Surgery *versus* watchful waiting in patients with craniofacial fibrous dysplasia – a meta-analysis. *PLoS One* 6: e25179, 2011. PMID: 21966448. DOI: 10.1371/journal.pone.0025179
- 97 Bessho K, Tagawa T, Murata M and Komaki M: Monostotic fibrous dysplasia with involvement of the mandibular canal. *Oral Surg Oral Med Oral Pathol* 68: 396-400, 1989. PMID: 2797736. DOI: 10.1016/0030-4220(89)90135-7
- 98 Colella G, Giudice A, Siniscalchi G, Falcone U and Guastafierro S: Chin numbness: a symptom that should not be underestimated: A review of 12 cases. *Am J Med Sci* 337: 407-410, 2009. PMID: 19359984. DOI: 10.1097/MAJ.0b013e31819299fa
- 99 Friedrich RE: Mental neuropathy (numb chin syndrome) leading to diagnosis of metastatic mediastinal cancer. *Anticancer Res* 30: 1819-1821, 2010. PMID: 20592385.
- 100 Assaf AT, Jürgens TP, Benecke AW, Riecke B, Blessmann M, Zrnc TA, Much CC, Heiland M and Friedrich RE: Numb chin syndrome: A rare and often overlooked symptom. *J Oral Facial Pain Headache* 28: 80-90, 2014. PMID: 24482791. DOI: 10.11607/jop.994
- 101 Friedrich RE, Heiland M, Assaf AT and Riecke B: Cone beam computed tomography in the differential diagnosis of mental neuropathy (numb chin syndrome) in metastatic colon cancer. *Anticancer Res* 33: 1757-1760, 2013. PMID: 23564829.
- 102 Grün P, Bandura P, Grün A, Sutter W, Meller O and Turhani D: Sensory disturbance along the inferior alveolar nerve as a first clinical sign of multiple florid cemento-osseous dysplasia of the mandible – A case report. *Int J Surg Case Rep* 53: 452-457, 2018. PMID: 30567067. DOI: 10.1016/j.ijscr.2018.11.036
- 103 Chen M, Yang C, Fang B, Zhang S and Xu K: Treatment of hemimandibular fibrous dysplasia with radical excision and immediate reconstruction with free double costochondral graft. *J Oral Maxillofac Surg* 68: 2000-2004, 2010. PMID: 20493608. DOI: 10.1016/j.joms.2009.09.035
- 104 Villa VG: Fibrous dysplasia in the upper jaw undergoing myxomatous degeneration. *Oral Surg Oral Med Oral Pathol* 8: 400-404, 1955. PMID: 14370766.
- 105 Hara H, Ohishi M and Higuchi Y: Fibrous dysplasia of the mandible associated with large solitary bone cyst. *J Oral Maxillofac Surg* 48: 88-91, 1990. PMID: 2294217. DOI: 10.1016/0278-2391(90)90189-9
- 106 Lagundoye SB, Obisesan AA, Daramola JO and Oluwasanmi JO: Radiology of multiloculated fibrous dysplasia of the jaws. *J Natl Med Assoc* 69: 779-781, 1977. PMID: 752729.
- 107 Laurian N and Zohar Y: Polyostotic fibrous dysplasia of upper and lower jaws. *Laryngoscope* 80: 440-447, 1970. PMID: 5436963.
- 108 Assaf AT, Benecke AW, Riecke B, Zustin J, Fuhrmann AW, Heiland M and Friedrich RE: Craniofacial fibrous dysplasia (CFD) of the maxilla in an 11-year old boy: a case report. *J Craniomaxillofac Surg* 40: 788-792, 2012. PMID: 22436487. DOI: 10.1016/j.jcms.2012.02.016
- 109 Kos M, Luczak K, Godzinski J and Klempous J: Treatment of monostotic fibrous dysplasia with pamidronate. *J Craniomaxillofac Surg* 32: 10-15, 2004. PMID: 14729043.
- 110 Eversole LR, Sabes WR and Rovin S: Fibrous dysplasia: a nosologic problem in the diagnosis of fibro-osseous lesions of the jaws. *J Oral Pathol* 1: 189-220, 1972. PMID: 4199101.
- 111 Pollandt K, Engels C, Kaiser E, Werner M and Delling G: Gs alpha gene mutations in monostotic fibrous dysplasia of bone and fibrous dysplasia-like low-grade central osteosarcoma. *Virchows Arch* 439: 170-175, 2001. PMID: 11561757. DOI: 10.1007/s004280100453
- 112 Krusinskiene V, Alvesalo L and Sidlauskas A: The craniofacial complex in 47, XXX females. *Eur J Orthod* 27: 396-401, 2005. PMID: 16043476. DOI: 10.1093/ejo/cji016
- 113 Miura M, Kato N, Kojima H and Oguchi H: Triple-X syndrome accompanied by single maxillary central incisor: Case report. *Pediatr Dent* 15: 214-217, 1993. PMID: 8378162.
- 114 Hillebrand U, Mohr C and Plewa G: [Taurodontism in patients with sex chromosome anomalies]. *Dtsch Z Mund Kiefer Gesichtschir* 14: 187-189, 1990. (Article in German). PMID: 2102428.
- 115 Farach A, Farach LS and Paulino AC: Therapeutic challenges in treating patients with fragile X syndrome and neoplasia. *Pediatr Blood Cancer* 60: E153-E156, 2013. PMID: 23873828. DOI: 10.1002/pbc.24688
- 116 Loesch DZ, Lafranchi M and Scott D: Anthropometry in Martin-Bell syndrome. *Am J Med Genet* 30: 149-164, 1988. PMID: 3177440. DOI: 10.1002/ajmg.1320300113
- 117 Butler MG, Pratesi R, Watson MS, Breg WR and Singh DN: Anthropometric and craniofacial patterns in mentally retarded males with emphasis on the fragile X syndrome. *Clin Genet* 44: 129-138, 1993. PMID: 8275570.
- 118 Loesch DZ, Hay DA, and Sheffield LJ: Fragile X family with unusual digital and facial abnormalities, cleft lip and palate, and epilepsy. *Am J Med Genet* 44: 543-550, 1992. PMID: 1481805. DOI: 10.1002/ajmg.1320440502
- 119 Doray B, Badila-Timbolschi D, Schaefer E, Fattori D, Monga B, Dott B, Favre R, Kohler M, Nisand I, Viville B, Kauffmann I, Bruant-Rodier C, Grollemund B, Rinkenbach R, Astruc D, Gasser B, Lindner V, Marcellin L, Flori E, Girard-Lemaire F and Dollfus H: Epidemiology of orofacial clefts (1995-2006) in France (Congenital Malformations of Alsace Registry). *Arch Pediatr* 19: 1021-1029, 2012. (Article in French). PMID: 22925539. DOI: 10.1016/j.arcped.2012.07.002
- 120 Hjalgrim H, Fisher Hansen B, Brondum-Nielsen K, Nolting D and Kjaer I: Aspects of skeletal development in fragile X syndrome fetuses. *Am J Med Genet* 95: 123-129, 2000. PMID: 11078561. DOI: 10.1002/1096-8628(20001113)95:2<123::aid-ajmg6>3.0.co;2-u

- 121 Kjaer I, Hjalgrim H and Russell BG: Cranial and hand skeleton in fragile X syndrome. *Am J Med Genet* 100: 156-161, 2001. PMID: 11298378. DOI: 10.1002/ajmg.1226
- 122 Sabbagh-Haddad A, Haddad DS, Michel-Crosato E and Arita ES: Fragile X syndrome: panoramic radiographic evaluation of dental anomalies, dental mineralization stage, and mandibular angle. *J Appl Oral Sci* 24: 518-523, 2016. PMID: 27812623. DOI: 10.1590/1678-775720160170
- 123 Shellhart WC, Casamassimo PS, Hagerman RJ and Belanger GK: Oral findings in fragile X syndrome. *Am J Med Genet* 23: 179-187, 1986. PMID: 3953646. DOI: 10.1002/ajmg.1320230112
- 124 Nunn JH and Durning P: Fragile X (Martin Bell) syndrome and dental care. *Br Dent J* 168: 160-162, 1990. PMID: 2138025. DOI: 10.1038/sj.bdj.4807112
- 125 Quan F, Grompe M, Jakobs P and Popovich BW: Spontaneous deletion in the FMR1 gene in a patient with fragile X syndrome and cherubism. *Hum Mol Genet* 4: 1681-1684, 1995. PMID: 8541863. DOI: 10.1093/hmg/4.9.1681
- 126 Friedrich RE, Scheuer HA, Zustin J and Grob T: Cherubism: A case report with surgical intervention. *Anticancer Res* 36: 3109-3115, 2016. PMID: 27272835.
- 127 Topazian RG and Costich ER: Familial fibrous dysplasia of the jaws: report of a case. *J Oral Surg* 23: 559-568, 1965. PMID: 14329537.
- 128 van Capelle CI, Hogeman PH, van der Sijs-Bos CJ, Heggelman BG, Idowu B, Slootweg PJ, Wittkamp AR and Flanagan AM: Neurofibromatosis presenting with a cherubism phenotype. *Eur J Pediatr* 166: 905-909, 2007. PMID: 17120035. DOI: 10.1007/s00431-006-0334-6
- 129 Mitchell JA, Wray J and Michalski K: Neurofibromatosis and fragile-X syndrome in the same patient. *Am J Med Genet* 22: 571-575, 1985. PMID: 3933345.
- 130 Watano K, Okamoto H, Takagi C, Matsuo H, Hirao N and Kitabatake A: Neurofibromatosis complicated with XXX syndrome and renovascular hypertension. *J Intern Med* 239: 531-535, 1996. PMID: 8656147. DOI: 10.1046/j.1365-2796.1996.422778000.x
- 131 Sujatha S and Jatti D: Neurofibromatosis and fibrous dysplasia manifesting in the same patient: a rare case report. *J Investig Clin Dent* 6: 77-80, 2015. PMID: 24000123. DOI: 10.1111/jicd.12059
- 132 Arinami T, Kondo I, Hamaguchi H, Tamura K and Hirano T: A fragile X female with Down syndrome. *Hum Genet* 77: 92-94, 1987. PMID: 2957304. DOI: 10.1007/bf00284722
- 133 Utine GE, Aktas D, Boduroğlu K, Alikasifoğlu M and Tunçbilek E: Coexistent mosaic monosomy 21 and fragile X syndrome in a mentally retarded male patient. *Genet Couns* 18: 171-177, 2007. PMID: 17710869.
- 134 Lachiewicz AM, Hoegerman SF, Holmgren G, Holmberg E and Arinbjarnarson K: Association of the Robin sequence with the fragile X syndrome. *Am J Med Genet* 41: 275-278, 1991. PMID: 1789278. DOI: 10.1002/ajmg.1320410302

Received November 1, 2019

Revised November 13, 2019

Accepted November 14, 2019