Skeletal and cranio-facial signs in Gorlin syndrome from ancient Egypt to the modern age: sphenoid asymmetry in a patient with a novel PTCH1 mutation

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Skeletal and cranio-facial signs in Gorlin syndrome from ancient Egypt to modern age: report of sphenoid asymmetry in a patient with a novel *PTCH1* mutation.

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Short running head: Skeletal signs in Gorlin Syndrome

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Abstract

Gorlin-Goltz syndrome is an autosomal dominant disorder linked to *PTCH1* mutation, identified by a collection of clinical and radiologic signs. NBCCS clinical behavior is basically benign, since the pathognomonic *PTCH1* mutation has been preserved during the centuries as it's witnessed from the presence of criteria for Gorlin syndrome in Egyptian mummies. We describe here the peculiar case of a family in which father and son fulfilled clear cut diagnostic criteria for Gorlin-Goltz syndrome including multiple basal cell carcinomas, keratocystic odontogenic tumours, segregation of the clinical phenotype in multiple family members, atypical skeletal anomalies and a novel *PTCH1* germline mutation (c.1041delAA). Craniofacial and other skeletal anomalies displayed at 3D and helical CT scan were: macrocephaly, positional plagiocephaly, skull base asymmetry, mandibular prognathism, mandibular condylar deformation with hyperplasia of the coronoid process, bifidity of multiple ribs and giant multilocular odontogenic jaw cysts. Extensive multilamellar calcifications were found in *falx cerebri, tentorium, falx cerebelli* and in the apical segment of the atlanto-occipital ligament. Thoracic anomalies included bifid ribs and *sacrum acutum*. Interestingly, volume-CT scan with multiplanar and 3D reconstruction identified a significant asymmetry of sphenoid wings with dysmorphic features. Abnormalities of the sphenoid bone are not very common, and consist of differently aggressive entities: some of them are typical of the pediatric age in few hereditary and congenital disorders. The application of new criteria (i.e. peculiar calcifications of ligaments and sphenoid asymmetry) to a wider case series can lead to the early diagnosis of Gorlin syndrome, especially in pediatric patients, when the full phenotype is not yet expressed. The inclusion of bifid ribs as a novel major criteria and the recognition of peculiar cranial anomalies such as sphenoid asymmetry, well detected at volume CT reconstruction, might be useful for the recognition and characterization of misdiagnosed cases.

Key words: Gorlin-Goltz syndrome, Nevoid basal cell carcinoma syndrome, bifid ribs, sphenoid anomalies, *falx cerebri* calcifications, volume CT scan, *PTCH1*.

Introduction

Gorlin-Goltz or Nevoid Basal Cell Carcinoma (NBCCS) syndrome is an autosomic dominantly inherited disorder associated to *PTCH1* germline mutations, which is involved in the proliferative *SHH* pathway [1, 2]. The phenotypic expression of the disease includes a wide spectrum of skeletal anomalies, congenital malformations and the predisposition to the development of various neoplasms such as multiple basal cell carcinomas (BCCs), keratocystic odontogenic tumors (KCOTs), ameloblastomas, ovaric and cardiac fibromas and medulloblastomas [3, 4]. Skeletal anomalies are extremely various in patients with NBCCS and affect both axil and appendicular components. Bifid ribs, macrocephaly, frontal bossing, skull base asymmetry, syndactyly or polydactyly, *pectus excavatum* and *carinatum*, vertebral anomalies are among the most represented [5].

PTCH1 mutation carriers can also be affected by hypogonadotrophic hypogonadism (5–10%), cryptorchidism or gynecomastia, but most individuals are able to reproduce. This is well demonstrated by the survival of the genetic mutation throughout the centuries, since peculiar skeletal anomalies characteristic of NBCCS (i.e. jaw KCOTs, bifid ribs, frontal bossing) were also found in ancient Egyptian mummified individuals belonging to archaeological collections that we have personally documented and further characterized [6].

NBCCS is a complex entity and its evaluation is based on different criteria [4] (Table 1). Since *Kimonis* et al. described major and minor criteria, other diagnostic criteria have been proposed and vary by source, but few studies have tried to define the sensitivity and specificity of which phenotypic combination is most accurate for diagnosis. Diagnostic criteria should therefore be considered as dynamic entities and should be widened for the earlier and most accurate diagnosis of syndromic settings, especially after the widespread of novel and extremely accurate diagnostic techniques such as volume and 3D CT scan. We describe here a family displaying a clear cut full phenotype of NBCCS, highlighting the potential diagnostic value of a peculiar sphenoid dimorphism among cranio-facial anomalies, detected at a deepened volume CT scan study. Those

can be useful for early diagnosis, diagnosis at pediatric age before the full phenotype is expressed and distinction from other hereditary settings.

Materials and methods

Patients

The NBCCS family was examined in the department of Dermatology of the University of Modena and Reggio Emilia. Family and personal history was accurately collected through interviews and clinical charts. The NBCCS diagnostic criteria that we used were those updated by *Kimonis* et al. in 1997 [4] and detailed by *Evans and Farndon* in 2002 [7]. Diagnosis of NBCCS was established when 2 major or 1 major and 2 minor criteria were present. Blood samples were acquired after specific informed consent. This study was approved by the Ethics Committee of the University Hospital of Modena.

PCR amplification and RNA isolation

Genetic analysis was performed according to what was previously described by our group [8].

Case report

Grandfather, father and son were brought to our attention because of the presence of multiple BCCs and further investigated for other signs of cancer hereditary setting (Figure 1). The first family member to be examined was E.B., born 1984, who referred to our clinic at the age of 10 because of multiple skin lesions of the back and abdomen. At the age of 13, orthopantomography showed well defined multiple multilocular radiolucencies with sclerotic borders, 1-5 cm in diameter, in the left and right emi-mandibular body. Maxillar bone presented one lesion in the right part (2.3 cm) and one in the left (2 cm) part. All of them were histologically examined and resulted KCOTs. KCOTs were associated to unerupted lower second and third molars and upper right third molar and central incisor. Roots of lower left first and second molars were also dislocated by KCOTs. The father, D.B., born 1948, presented with frontal bossing and multiple BCCs of the back, chest and front. In

1999, resection of the left mandible branch and reconstruction with a free vascularized fibular graft was performed because of a giant multilocular histologically proven KCOTs (Figure 2).

Both patients developed further superficial and nodular BCCs over the years (Figure 1). E.B. was also diagnosed of a Fibroepithelioma of Pinkus, while D.B. had multiple recurrent epidermoid cysts of the back and face.

X-rays and CT scan showed dimorphism of the posterior arches of the left 3rd, 4th, 5th and 6th rib and of the body of the 3rd thoracic vertebra, scoliosis of dorsolumbar spine, diffuse spondylosis of the lumbar spine, *sacrum acutum*, osteoporosis. Calcifications of the *falx cerebri* and cranial asymmetry were also found.

E.B. presented with scoliosis of the nasal septum, deviation of the anterior wall of the sella turcica and calcification of the *falx cerebri.* Total body CT scan highlighted pectus excavatum, bifidity of 3rd, 4th, 6th and 7th right rib and 2nd, 4th and 5th left rib, scoliosis of dorsolumbar spine, deformation of 7th cervical, 1st and 2nd thoracic vertebrae (butterfly-like), schisis of the posterior arch of the 7th cervical vertebra and of the 1st sacral vertebra (Figure 3). Other characteristic findings of NBCCS were true gynecomastia, renal cysts, accessory spleen and a mild cognitive impairment. He's now awaiting for the surgical removal of recurrent KCOTs of the maxillary bone.

Skull radiographs, helical and volume CT scan showed macrocephaly and skull base asymmetry (positional plagiocephaly), mandibular prognathism (skeletal Class III malocclusion), mandibular condylar deformation and hyperplasia of the coronoid process. Giant multilocular cysts, likely corresponding to KCOTs, were located in the maxilla, left mandibular body and ramus (Figure 2). Extensive multilamellar calcifications were found in falx cerebri and tentorium cerebelli, moreover we found small calcifications of in the apical ligament and atlanto-occipital membrane (Figure 2). Helical CT scan showed asymmetry of both sphenoid wings with thickening of the left wing, together with irregularity of trabecular bone architecture with alternating osteolytic and sclerotic areas (Figure 4).

Also the proband's grandfather had undergone surgery for excision of multiple BCCs. Genetic analysis of peripheral blood samples revealed the presence of a novel *PTCH1* germline mutation (c.1041delAA), that has not been described so far in other families.

Discussion

A deepened radiological examination using 3D and volume CT scan allowed us to characterize in details the peculiar cranio-facial anomalies that can be found in the NBCCS hereditary syndromes which can support the diagnosis of complex or misdiagnosed cases of NBCCS. In particular, we highlighted the potential diagnostic role of sphenoid anomalies among the other craniofacial and skeletal aberrations.

Abnormalities of the sphenoid bone are not very common, and consist of differently aggressive entities: some of them are typical of the pediatric age. Critical skull base structures can be affected, due to the central location of the sphenoid bone: the dura mater, the cavernous sinus, the internal carotid artery, the oculomotor nerve, the optic nerve and chiasm, the hypophysis, the trochlear nerve, the ophthalmic nerve, the abducens nerve, the maxillary division of the trigeminal nerve, the sphenopalatine ganglion and artery, and the pterygoid canal and nerve. An adequate preoperative imaging is mandatory for a correct diagnosis and proper surgical planning in these patients. Possible findings are mucocele, aneurysmal bone cyst, giant cell lesions, meningioma, fibrous dysplasia, chordoma, craniopharyngioma, rhabdomyosarcoma, sinonasal carcinoma, and neuroblastoma. Some of these lesions can be associated to hereditary syndromes (cystic fibrosis, neurofibromatosis type 1 and 2, fibrous dysplasia, Mc-Cune Albright syndrome, Keipert syndrome, Li-Fraumeni syndrome).

In particular, mucoceles are cystic masses filled with mucus and arise as a consequence of the chronic obstruction of sinus ostia. Mucoceles are a well-known complication of sinusitis in adults but they are very rare in the pediatric age; although benign, they can enlarge by accumulation of secretions, and may displace erode the surrounding bone with complications and infections. A child

with mucoceles should therefore be investigated for the presence of cystic fibrosis (*CFTR*, autosomal recessive). Meningiomas are benign slow-growing tumors that can cause hyperostosis of the sphenoid bone and enlargement of the sinus cavity, usually rare in pediatric age, where they can be found in association to Neurofibromatosis type 2 (*NF2*, autosomal dominant). An association of Neurofibromatosis type 1 (*NF1*, autosomal dominant) has been reported with pilocytic astrocytoma, that can extend along the floor of the sella and planum sphenoidale and cause bone remodelling. A very aggressive tumor, rhabdomyosarcoma, can also extend in the sphenoid area; although mainly sporadic, a genetic predisposition can be linked to Li-Fraumeni syndrome (*TP53*, autosomal dominant). Sphenoid bone and in general skull base is often affected by fibrous dysplasia, an idiopathic skeletal developmental anomaly occurring in children, where normal bone is replaced with fibrous bone tissue. When the diseases is polyostotic and associated to *café-au-lait* spots and endocrine diseases, such as precocious puberty, a diagnosis of McCune-Albright syndrome has to be suspected (mosaicism of *GNAS1*). Fibrous dysplasia of the sphenoid bone has been seen in other genetic syndromes such as Keipert or Nasodigitoacoustic syndrome (X-linked recessive) [9], Neurofibromatosis type 1 associated with plexiform neurofibroma. Fibrous dysplasia of the extremity was also misdiagnosed in a patient successively diagnosed with NBCCS [10], while the coexistence of fibrous dysplasia of maxilla, temporal bone and sphenoid sinus and unicystic ameloblastoma in a patient with no other signs for GS has been reported [11, 12]. To our knowledge, no peculiar sphenoid anomalies in Gorlin-Goltz patients have been described so far, except for bridging of the sella turcica and hyperpneumatization of sphenoid sinus [5, 13].

It is thanks to volume CT scan that we could accurately investigate the intracranial anomalies highlighting the marked asymmetry of the sphenoid wings (Figure 2, 4). In our opinion, the synchronous diagnosis of these anomalies together with other characteristic cranio-facial signs of early onset might allow the early diagnosis of NBCCS even in selected pediatric patients before the full phenotype is expressed. Nevertheless, the presence of concomitant asymmetric macrocephaly and other radiologic findings. Sphenoid asymmetry and intracranial and soft-tissue calcifications

should be a critical diagnostic aid for this hereditary disorder. At this regard, the calcification of the atlanto-occipital ligament has been recently described by Lo Muzio et al., as one suitable criteria for the diagnosis of Gorlin syndrome [10]. However we cannot consider the peculiar finding of calcification of the apical ligament detected in our patient as specific for this syndromic setting because the above mentioned study evaluated only radiograms, which do not allow an accurate study of the anatomic relationships. 3D-scan can allow a better characterization and can be used in future studies on wider case series that can provide a more accurate description of pathognomonic calcifications in GS.

In this patient, volume CT scan showed asymmetry both sphenoid wings with thickening of the left wing, irregularity of the architecture of trabecular bone with alternated osteolytic and fibrous areas. Lacking the histopathologic examination, we cannot infer that the above mentioned alterations are congenital and linked to true bone dysplasia; the altered architecture might be considered the consequence of dimorphisms due to a defect in the regeneration of trabecular bone. These findings cannot be attributable to Paget disease, Fibrous Dysplasia or other bone dysplastic syndromes, but might be peculiar for skeletal anomalies in GS, linked to the altered pathways in the development of mesenchymal structures.

Falx cerebri calcification can be an incidental radiologic finding and physiological variant, but is often associated to hereditary syndromes. In particular, it is found in 65% of patients with Gorlin syndrome [5], but also Papillon-Lefèvre (palmoplantar keratoderma with periodontitis) and Hallermann-Streiff syndrome (oculo-mandibulo-dyscephaly syndrome), craniofacial dystostosis with diaphyseal hyperplasia. Moreover, infectious (i.e. neurocysticercosis), metabolic diseases (hypervitaminosis D) and tumors (chondromas) can be suspected. In details, in the context of GS calcifications of the *falx cerebri* are usually multilamellar, disposed in multiple parallel strands at a respective distance of 0,5-2 mm; this particular subtype has been described has type IV group of *falx calcifications*, and considered as specific for GS in a retrospective study on 4787 radiograms.

The remaining three described groups were characterized by calcifications that differed significantly in form and extent from this particular subtype, appearing as line-shaped shading (type 1), divergent shading (type 2), patchy and diffuse shading (type 3) [14]. *Falx* calcifications are part of the major criteria for the diagnosis of the syndrome.

The main malformative rib lesions are bifid ribs, rib spurs, and widened ribs. Bifid ribs occur when the sternal end of a rib is cleaved into upper and lower divisions. Each part has its own costal cartilage, that may fuse before articulating with the sternum. Their prevalence in the general population is reported around 1,4 %, and is higher in males. Bifidity usually involves the anterior fourth and third rib, followed by the fifth, sixth, and second ribs and can be an isolated finding as well as part of genetic syndromes or associations of malformations. Hereditary settings include NBCCS (*PTCH1*), Robinow syndrome (*ROR2*), Seckel syndrome (*ATR*), Jarcho–Levin syndrome (*DLL3*), cerebro-costo-mandibular syndrome, spondylocostal and spondylothoracic dysostoses. Non-random associations of birth defects that comprise bifid ribs are VACTERL (vertebral anomalies, anal atresia, cardiovascular anomalies, tracheoesophageal fistula, renal and/or radial anomalies, limb defects), MURCS (Müllerian duct aplasia, renal aplasia, and cervico-thoracic somite dysplasia) [15]. A single bifid rib is most commonly a normal incidental finding and may be detected as a palpable chest wall mass; it is usually considered a normal anatomic variant and it's often asymptomatic. However, bifid ribs especially when bilateral may cause musculoskeletal pain or intercostal nerve entrapment. A bifid 1st rib may be an uncommon cause of thoracic outlet syndrome. Differential diagnosis of bifid ribs are infections (osteomyelitis), tumors (Ewing sarcoma, chondroma) and trauma. Bifid ribs are found in about 26% of patients with NBCCS [5, 16]. The occurrence of bifid ribs is quite rare in the general population, with an estimated prevalence of 0.15% to 3.4%, until increasing to 26% in patients with NBCCS [5]. The association of rib and other skeletal anomalies with other tumors, especially KCOTs, is even less frequent, so that the combination of these findings has become part of the diagnostic criteria for NBCCS. This rare association was noted in 1967 by Wells and Satinoff in two mummified skeletons of the

Egyptian osteological collection of the Turin Antropology Institute; the former, in fact, suggested to "*look for bifid ribs*" of the same body where dentigerous cysts were found, because "*it would be a splendid find if he discovered the dual anomaly!*". In this way, the two archeologists diagnosed NBCCS (named dentigerous cyst-bifid ribs syndrome) in two skeletons excavated at Assiut about four thousands year old (Figure 5) [6]. The finding of the peculiar phenotype of Gorlin syndrome in mummies of Egyptian dynasties demonstrates the relative benignity of NBCCS that allows, in most cases, the survival of the affected individual to the fertile age, so that the germline *PTCH1* mutation has been preserved throughout millenniums of evolution.

Bifid ribs and other skeletal abnormalities represent a peculiar hallmark of NBCCS, together with a wide spectrum of signs and symptoms [17]. The reason why rib defects are easily found in association with other malformations has to be identified in the embryologic development: ribs develop from the costal process of the primordial thoracic vertebrae through endochondral ossification; those structures share the same mesodermal origin as cardiac muscle, kidney and skin and can therefore be affected by multiple malformations.

Conclusion:

The collection of anamnestic data and the clinical screening for BCCs and KCOTs represent a basic stage in the NBCCS diagnosis and for the clinical differentiation from other syndromes that can share similar skeletal anomalies. Although the finding of a single bifid rib, sphenoid anomalies or intracranial calcifications can be recognized as a normal anatomic variant, the synchronous presence of these aberrations in the general population is so low that it deserves a deepened clinical examination at least through a complete and accurate familial and personal history.

The NBCCS diagnostic criteria, reviewed by Kimonis, found their confirmations in the successive genetic, biomolecular and epidemiologic studies. However, they shoud be considered dynamic entities that can be improved and better characterized. Thus, the introduction and application of new criteria (bifid ribs as major criteria, skull and mandibular anomalies, peculiar calcifications of ligaments and sphenoid abnormalities) to a wider NBCCS patients population can lead to the early

diagnosis of this syndrome, especially in pediatric patients, when the full phenotype is not yet expressed. At this regard, 3D and volume CT scan can be an efficacious tool in the diagnosis and characterization of early onset cranio-facial and other skeletal anomalies, since it allows the detection of details that wouldn't be visible with traditional radiograms and it enables a deepened anatomical study together with a pre-operative assessment.

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Tables

Table 1. Major and minor criteria for the diagnosis of NBCCS (Kimonis et al.)

Figure legends

Figure 1. Family tree and clinical features of the patients with NBCCS gene-carrier of the *PTCH1* mutation c.1041delAA.

Figure 2. Radiologic study of cranio-facial anomalies in the 65 year old proband with NBCCS.

A. Frontal view of the skull 3D-CT scan; B. Lateral view of the skull 3D-CT scan of skull base shows asymmetry and frontal bossing (minor diagnostic criteria); C. Frontal view of the skull 3D-CT scan, detail: Keratocystic odontogenic tumor of the left mandibular body and ramus and left maxilla, a stigmata of GS (major diagnostic criterion). The patient had undergone surgery and bone craft reconstruction of the right mandibular body and ramus for keratocystic odontogenis tumor; D. Detail of the skull: mild asymmetry of the right parietal-occipital calvarial vault (positional plagiocephaly); E. CT scan highlights extensive multilamellar calcifications of falx cerebri, tentorium cerebelli and apical segment of the atlanto-occipital ligament; F. Axial CT scan, detail: multilamellar calcifications of falx cerebri (major diagnostic criterion); G. Axial CT scan shows significant asymmetry of sphenoid wings with dysplastic hyperplasia.

Figure 3. 65-year-old man with Gorlin-Goltz syndrome: Radiologic findings (X-rays, 3D-CT scan) of the proband with highlighted bifid ribs (arrows).

Figure 4. Sphenoid anomalies in the same patient: multiplanar CT-scan reconstruction confirms left sphenoid wings thickening and irregularity of the trabecular bone's pattern, with alternating osteolytic and osteosclerotic areas.

Figure 5: Skeletal anomalies characteristic of NBCCS found in two Egyptian skeletons, belonging to the anthropological museum of the University of Turin. In details: frontal bossing, odontogenic keratocystic tumors, bifid ribs (arrows). Courtesy of Prof. Emma Rabino-Massa.

Figure
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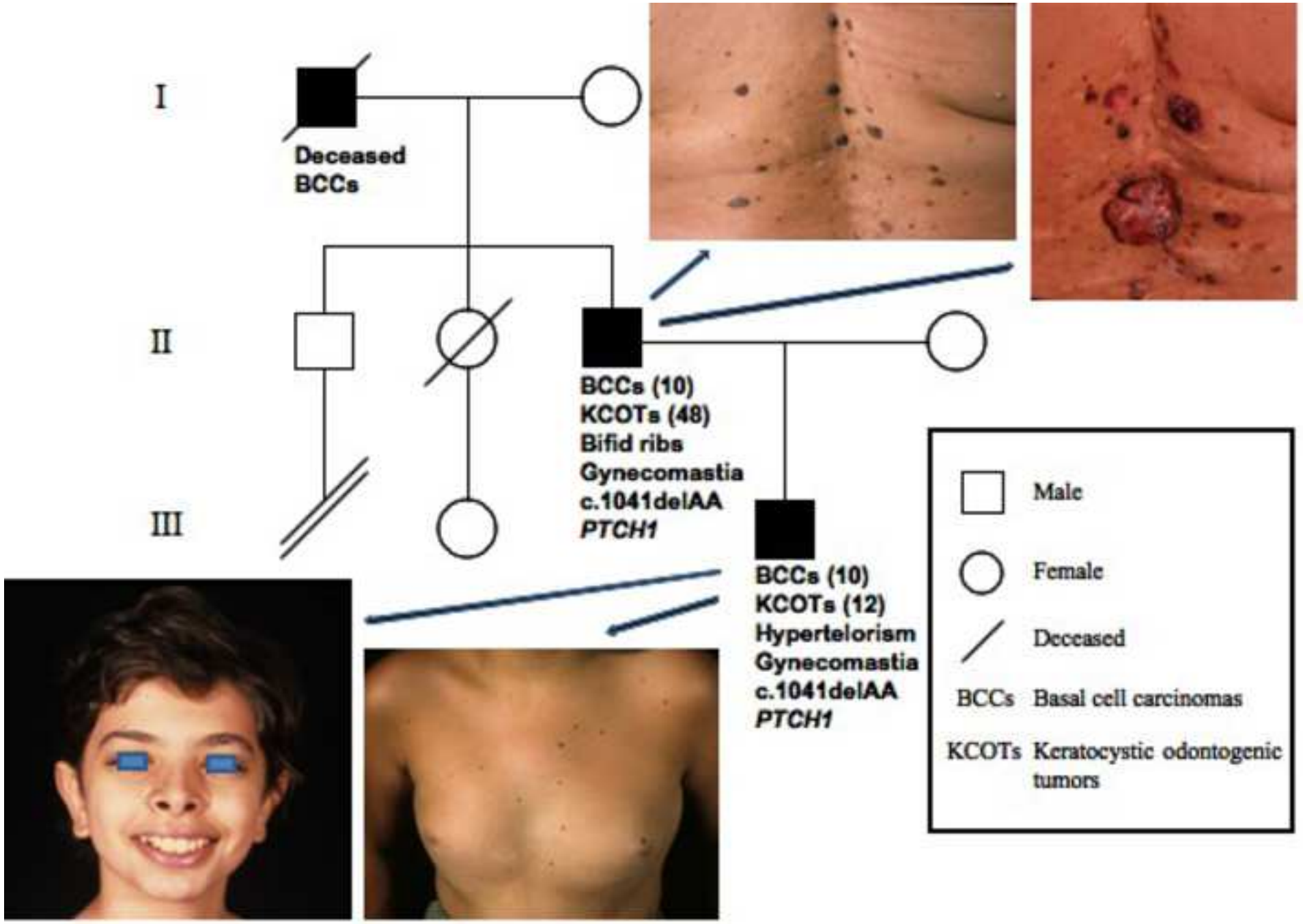

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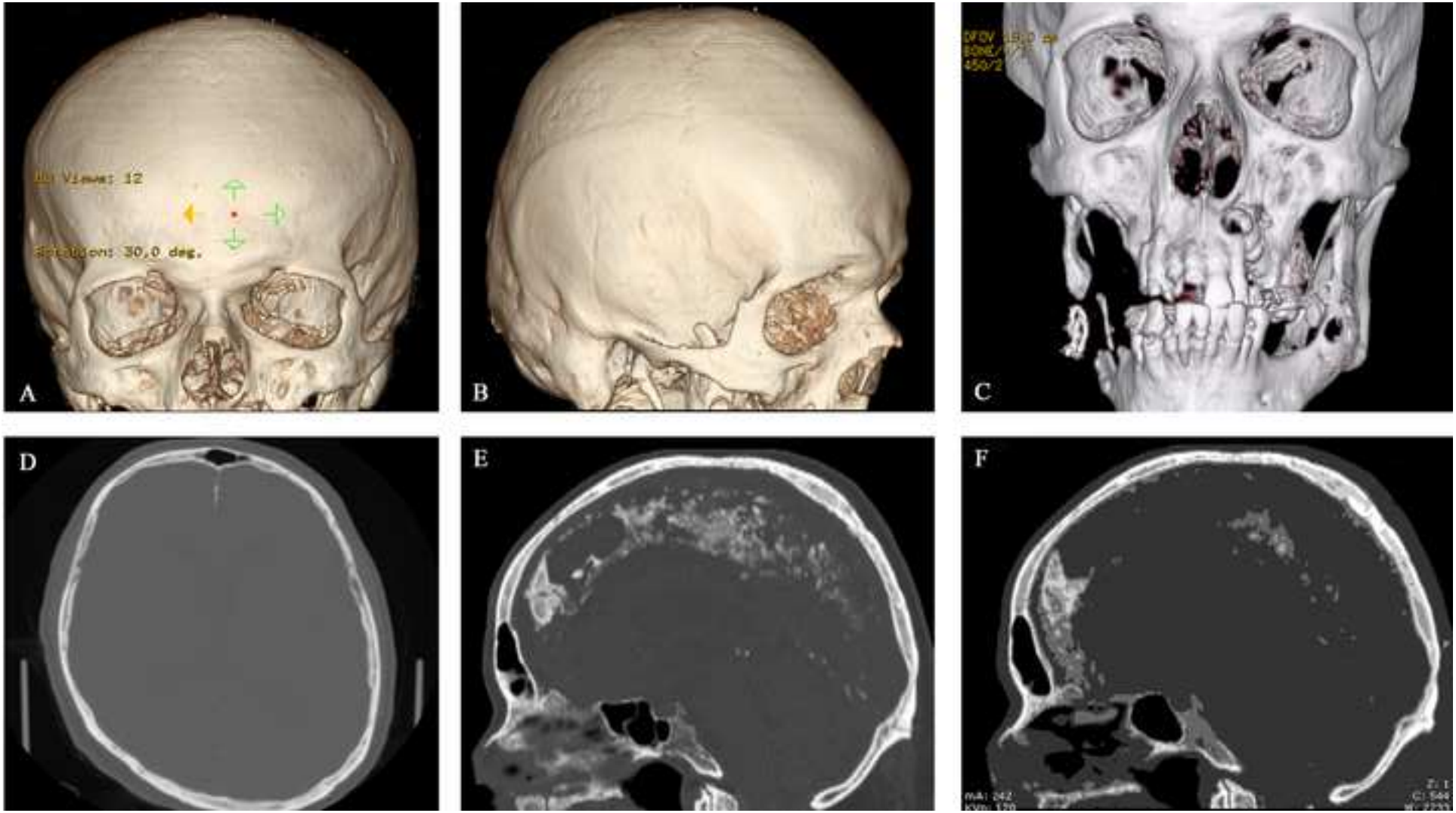

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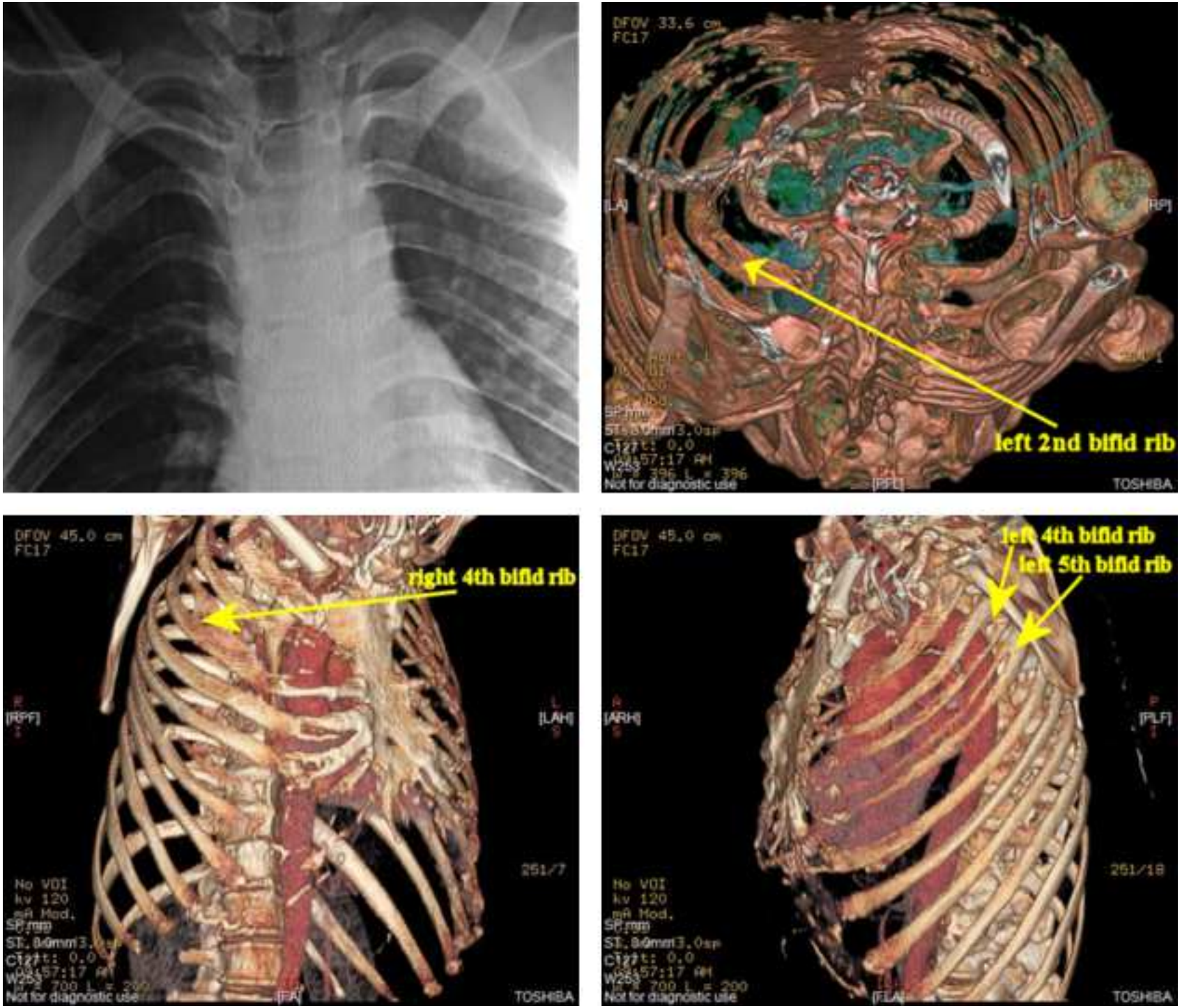

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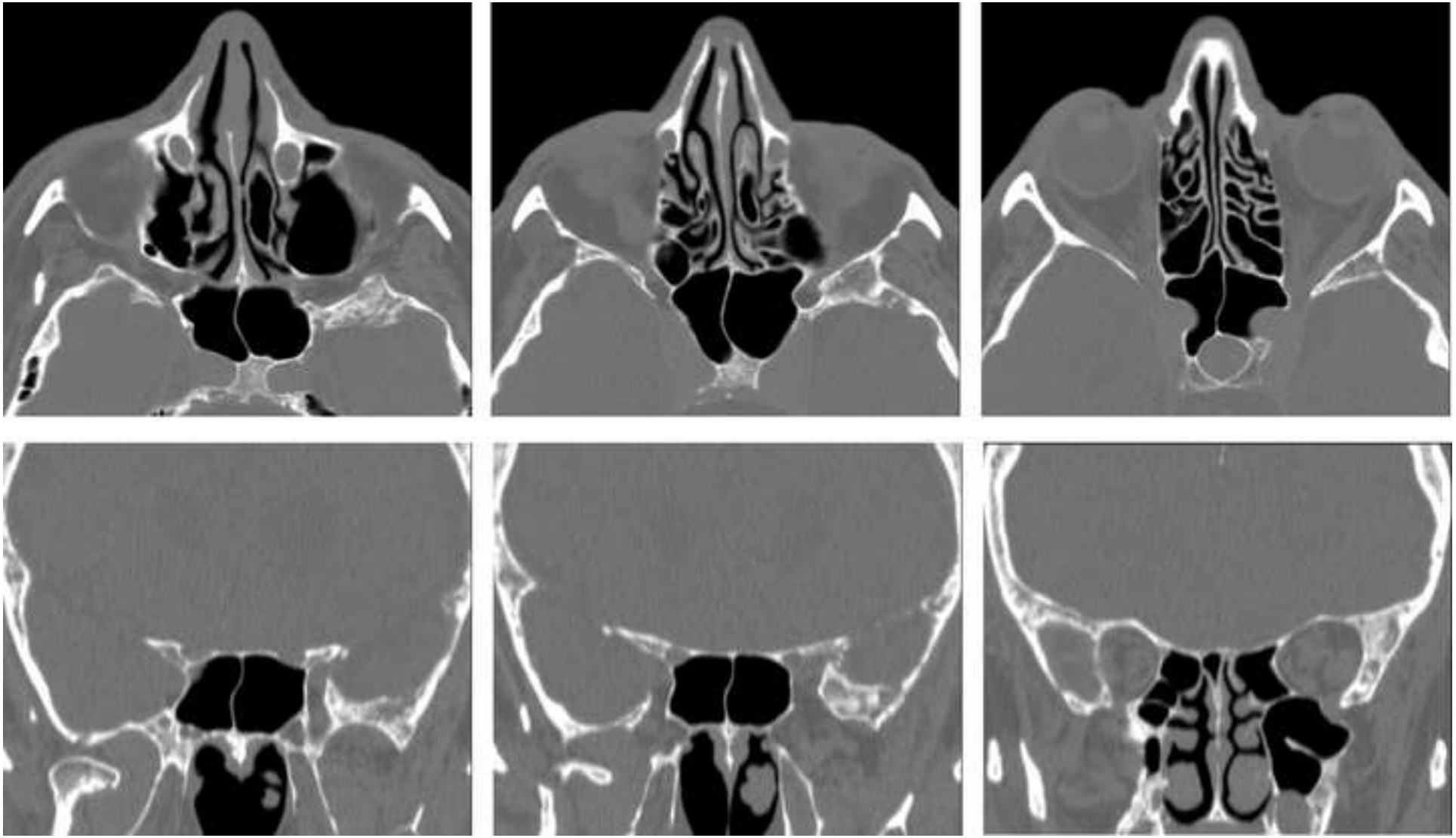

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Table
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Table 1. Major and minor criteria for the diagnosis of NBCCS

Major Criteria
▪ Multiple (>2) basal cell carcinomas at any age or one basal cell carcinoma less than 30 years or >10 basal cell naevi
▪ Histologically proven odontogenic keratocyst or a polyostotic bone cyst
▪ Palmar or plantar pits (3 or more)
▪ Ectopic calcification: lamellar or early (<20 years) calcification of the falx cerebri
▪ Family history of Gorlin's syndrome
Minor Criteria
▪ Congenital skeletal defects: bifid, fused, splayed, or missing rib, or bifid, wedged, or fused vertebra
▪ Large head with occipitofrontal circumference >97th percentile, with frontal bossing
▪ Cardiac or ovarian fibroma (benign tumour in heart or ovary)
▪ Medulloblastoma (a malignant brain tumour that usually arises in young children)
▪ Lymphomesenteric cysts (abdominal cysts full of lymph fluid)
▪ Congenital malformation: cleft lip and/or palate, polydactyly (extra fingers or toes), congenital eye defect such as cataract, microphthalmos (small eye) or coloboma (iris tumour)