



# USC University of Southern California



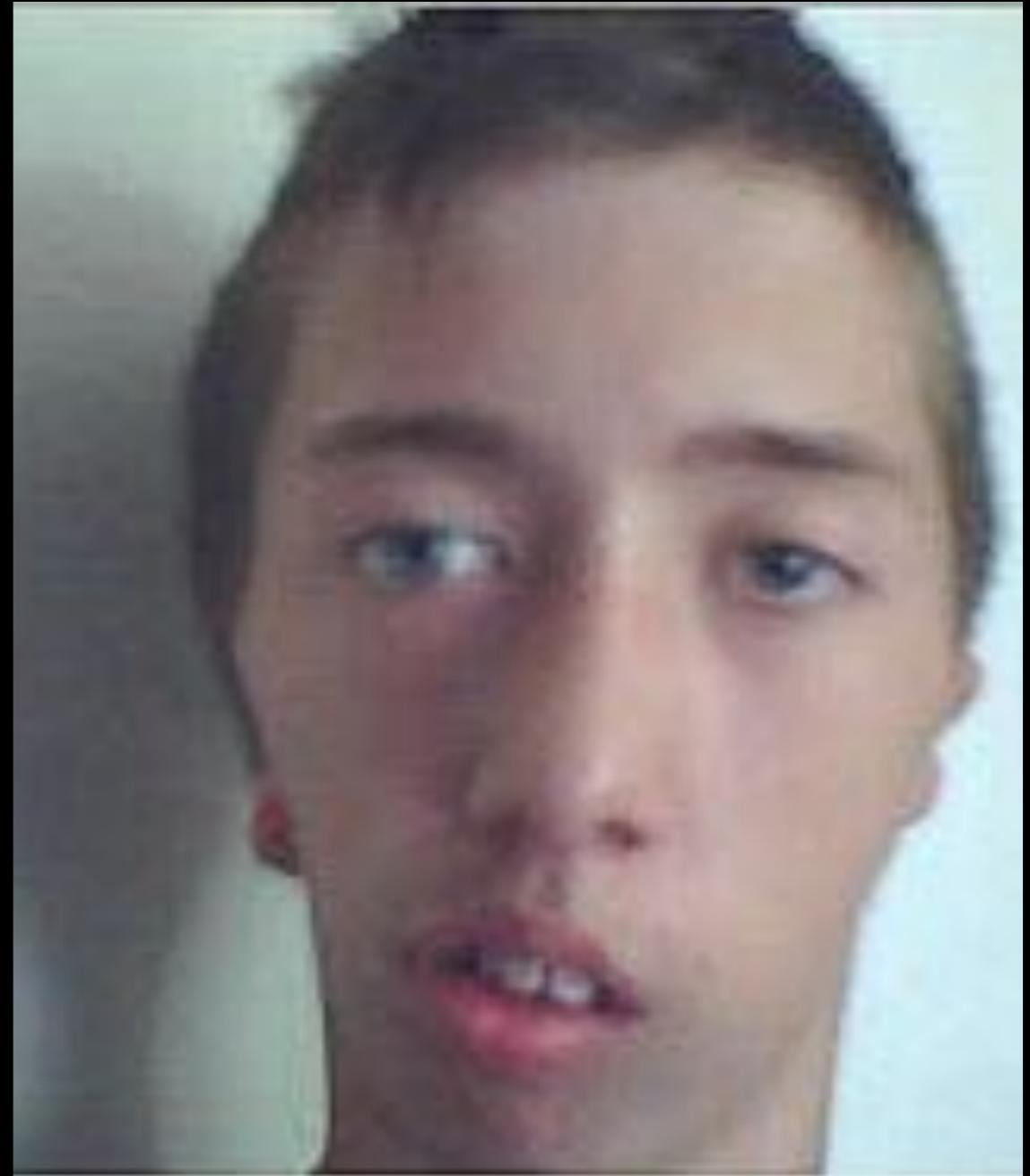
Hemifacial Microsomía

Diana Sedler DDS  
Class of 2019

# Introduction

Condition in which the lower half of one side of the face is underdeveloped and does not grow normally

Also referred to as first and second brachial arch syndrome, oral-mandibular-auricular syndrome, lateral facial dysplasia, or otomandibular dysostosis



# Characteristics and Incidence

Usually occurs on one side of the face, but both sides are sometimes affected

May result in difficulties in breathing due to obstruction of the trachea—sometimes even requiring a tracheotomy

Incidence in the range of 1:3,500 to 1:4,500

Second most common birth defect of the face, after cleft lip and cleft palate

Boys are affected more than girls 3:2

# Etiology

Develops in the fetus at approximately 4 weeks gestational age

As a result of some form of vascular problem such as blood clotting or hypoxia, which leads to insufficient blood supply to the face

Could result from medications that cause vasoconstriction as well as smoking

This condition results from problems in the development of structures in the embryo called the first and second pharyngeal arches

# OMENS Classification

One of the ways clinicians describe and assess the severity of hemifacial microsomia is the OMENS classification

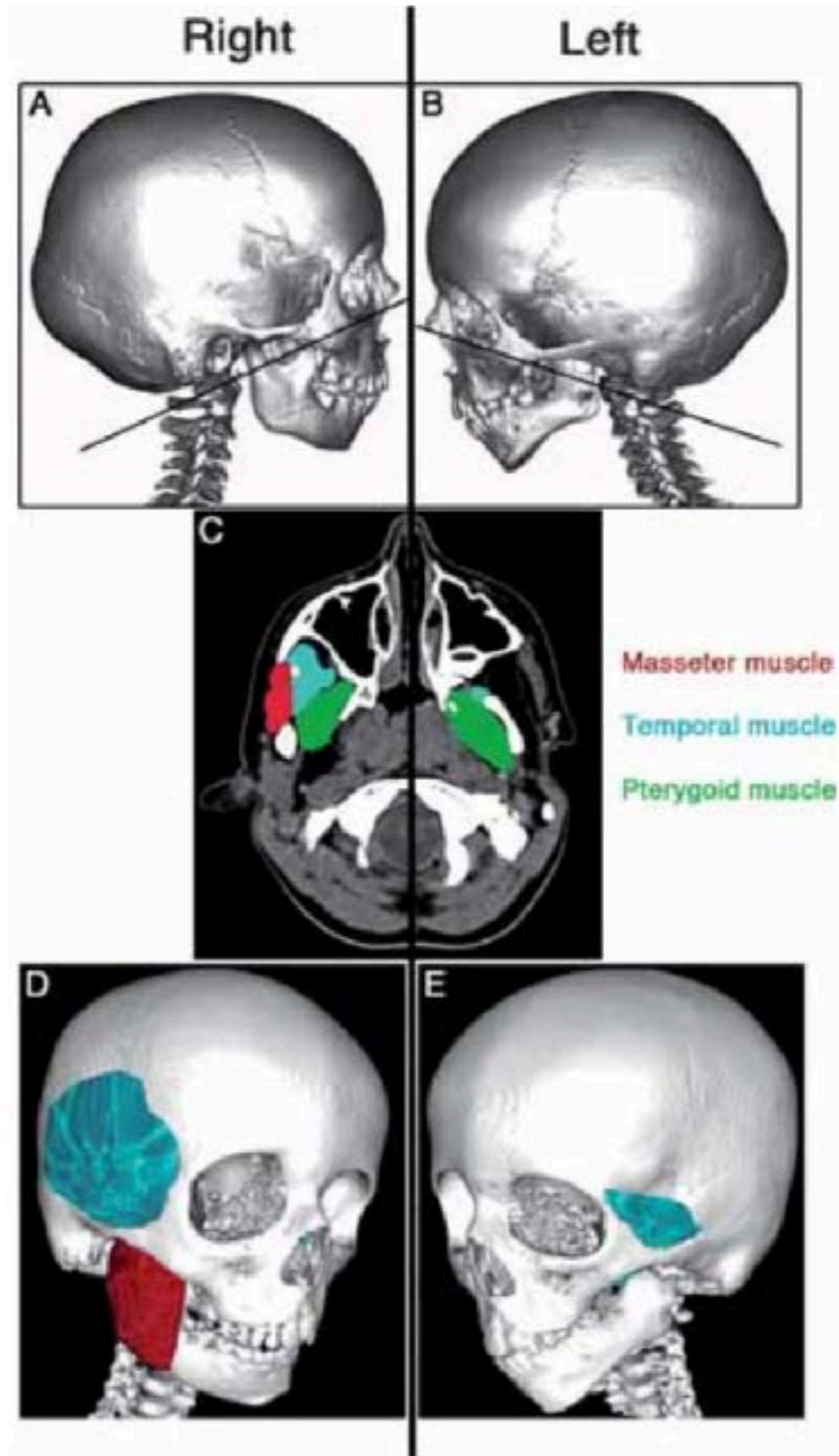
- Orbit (eye socket): small and underdeveloped eyes with impaired vision; absent or unformed eye; growths on the eye; one eye appearing smaller than the other, but with normal vision
- Mandible (the jaw bones): underdeveloped upper and lower jaw on one side; crooked jaw; missing, misaligned or overcrowded teeth; cleft lip and/or cleft palate; limited opening or closing of the mouth
- Ear: small skin tags; misshapen or missing external ear; absent or abnormal development of the ear canal resulting in partial or total hearing loss
- Nerves: ranging from mild weakness to partial or full facial paralysis
- Soft tissues (skin, muscle, fat, tendons and ligaments): flattened forehead or cheekbone, unequal cheek fullness, asymmetrical mouth with lateral cleft

# Radiographic Appearance



# Dental Anomalies





# Treatment

- Depends on presenting features and severity
- Some need
  - feeding support due to jaw deformities
  - breathing support and/or a tracheostomy
- Surgeries
  - Eye due to incomplete closure
  - Ear reconstruction and/or hearing aids
  - Soft tissue grafts for soft tissue deficiencies

THANK YOU!!!





# COHEN SYNDROME

BY JAMES SPENCER BISBAS, DDS

# INTRODUCTION

## AKA Pepper Syndrome

**Clinical Characteristics Summary:** failure to thrive in infancy and childhood; truncal obesity in the teen years; early-onset hypotonia and developmental delays; microcephaly developing during the first year of life; moderate to profound psychomotor retardation; progressive retinochoroidal dystrophy and high myopia; neutropenia in many with recurrent infections and aphthous ulcers in some; cheerful disposition; joint hypermobility; and characteristic facial features\*

**Genetic disorder that affects**

**MOTOR SKILLS**

**MENTAL DEVELOPMENT**

**BEHAVIOR**

**Exhibits:**

**HYPOTONIA-diminished muscle tone, abnormalities of the head, face, hands  
feet, eye abnormalities**

**Non-progressive intellectual disability**

**JOINT HYPERMOBILITY**

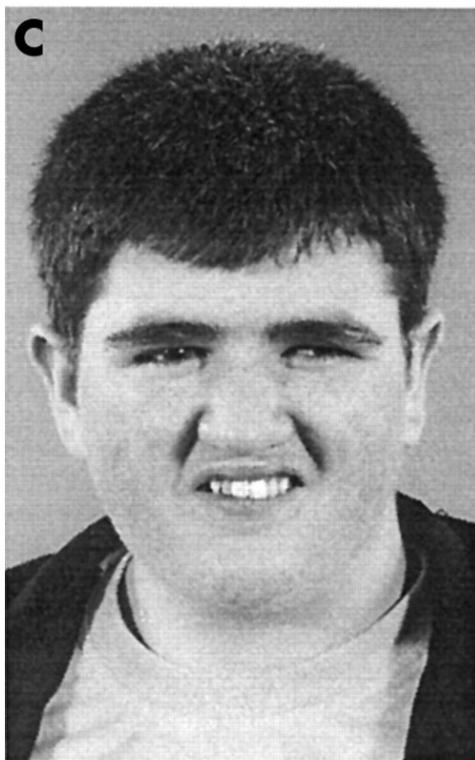
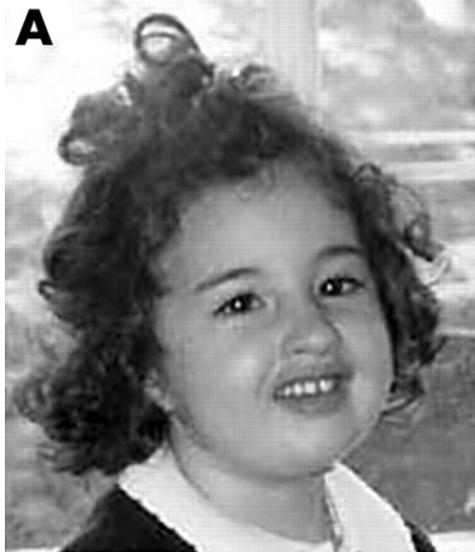
**MICROCEPHALY**

**OBESITY AROUND THE TORSO**

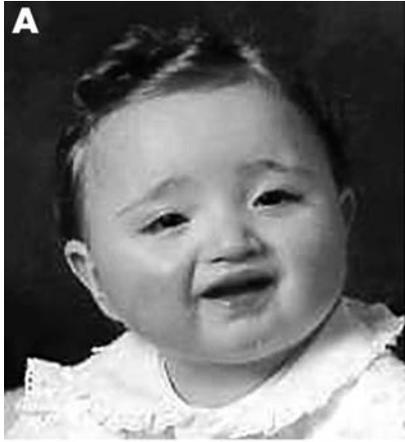
**VISUAL DISABILITY**

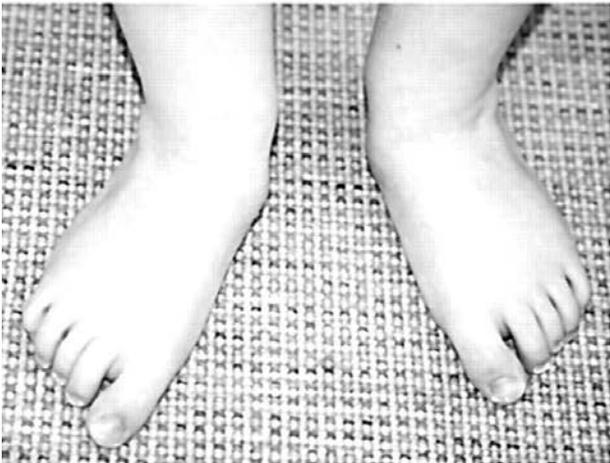
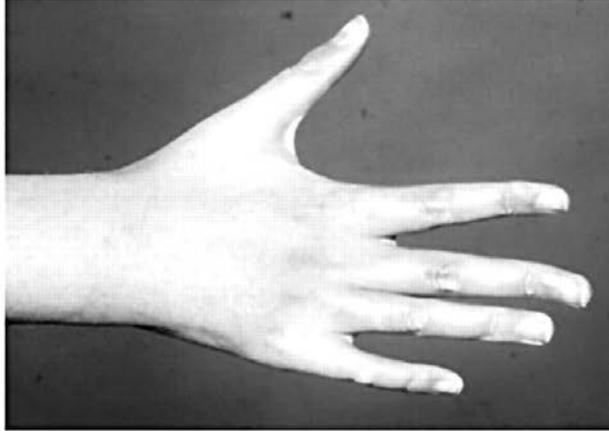
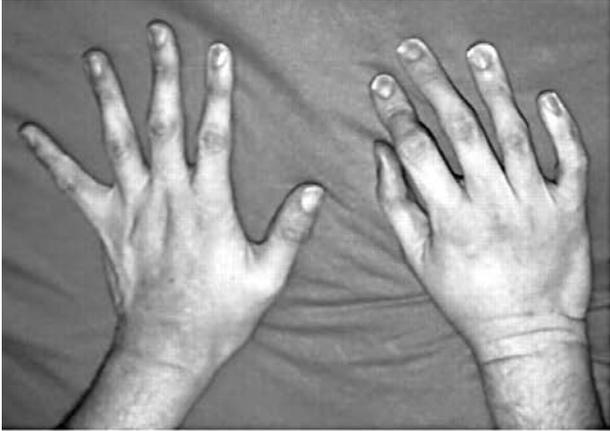
**Lowered level of certain white blood cells (neutropenia)**

**Autosomal recessive altered gene located on chromosome 8**









# CAUSES

**Alterations in the COH1 gene aka VPS13B**

**Located on the long arm (q) of chromosome 8 (8q22-q23)**

**Inheritance: autosomal recessive**

**Protein product of the COH1 gene is involved with glycosylation**

# DIAGNOSIS AND TESTING

**Clinical Findings, but no consensus diagnostic criteria exists.**

**Identification of Biallic pathogenic variants in VPS13B (COH1) on molecular genetic testing if clinical features are inconclusive**

**COH1 gene, which contains 62 exons, is the only gene known to be associated with Cohen Syndrome**

# COHEN SYNDROME DIAGNOSIS USING WHOLE GENOME ARRAYS

**Article by Nuria Rivera-Brugués in the Journal of Medical Genetics**

**Diagnosis of Cohen Syndrome can be reached in patients with unexplained mental retardation by applying high resolution oligonucleotide arrays**

**“The phenotype of Cohen Syndrome defined by COH1 mutations is fairly unspecific, particularly in very young patients but in older children too. In addition, deletions in the neighboring genes may affect the phenotype of Cohen Syndrome in the context of a contiguous gene syndrome. Nevertheless, young patients with a hypotonic facial expression, almond shaped eyes, short philtrum, mental retardation, and motor and speech delay are suspicious for Cohen Syndrome. Microarrays have the potential to diagnose Cohen syndrome in very young patients and in patients with an atypical phenotype”.**

**FIRST REPORT ON PATIENTS WITH COHEN SYNDROME DIAGNOSED BY MOLECULAR WHOLE GENEOME ANALYSES BUT NOT BY CLINICAL EXAMINATION**

# SIGNS AND SYMPTOMS

Variable-often missed diagnosis leaving total number to around 500

-much is still not understood

-need for more clinical studies

## **“Core” symptoms include:**

Newborns: low birth weight and hypotonia (leading to feeding and breathing difficulties); **delays in developmental milestones**

Weak or high pitched cry

Infants have an inability to gain weight and grow

Joints are described as ‘loose’ abnormally large range of motion (joint hypermobility)

Mild to moderate microcephaly

Speech delays are common

Non-progressive intellectual disability

Most are sociable and have a cheerful disposition

# CHILDHOOD

**~5 years old may exhibit**

- Large ears**
- Low hairline**
- Highly arched or wave-shaped eyelids**
- Long thick eyelashes**
- Thick eyebrows**
- High, narrow roof of the mouth\***
- Abnormally short groove in the middle of the upper lip**
- Prominent central incisors\***
- Small rounded ulcers in the mouth\***
- Inflammation/infection of the gums\***

# EYES

**Decreased visual acuity**

**Nearsightedness (Myopia)**- Myopia usually becomes progressively worse

**Crossed Eyes (Strabismus)**

**Chorioretinal dystrophy**-abnormalities affecting the choroid (middle layer of the eye that converts light to specific nerve signals) and retina including degeneration of the retina

->eventual night blindness (nyctalopia) and constriction of the peripheral field (tunnel vision)

**Abnormal curvature of the cornea (astigmatism)**

**Reduced size of the cornea (microcornea)**

**Abnormally small eyeballs (microphthalmia)**

**Clouding (opacity) of the lenses**

**Degeneration of the optic nerve**

# TORSO

**Develop obesity in the trunk or the torso**

**Arms and legs remain slender or thin**

**Below average height**

**Delayed puberty/undescended testicles (cryptorchidism)**

**Abnormal curvature of the spine**

# NEUTROPENIA

**Abnormally low level of neutrophils**

**Mild or moderate episodes**

**Repeated infections**

**-respiratory and skin are common**

**Middle ear infections (otitis media)**

**Chronic aphthous ulcers and gingivitis**

**Increased risk of AI disorders (diabetes)**

# OCCURRENCE

**M:F ratio is about 1:1**

**More common in Finnish, Amish, Greek and Irish**

**Affects 1/500 in small Amish community in Ohio**

# MANAGEMENT

**VISION**-Spectacle correction, Low-vision training, Psychosocial support

**Early intervention and physical, occupational, and speech therapy help address developmental delay, hypotonia, joint hyperextensibility and motor clumsiness**

# THERAPIES

**Due to the wide variety of symptoms, treatment is directed toward the specific symptoms that are apparent in each individual**

**Early developmental intervention is important**

**Pediatricians, Pediatric Neurologists, Orthopedists, Ophthalmologists, Psychiatrists, Speech Pathologists**

**Glasses + Antibiotics very common**

**G-CSF-Granulocyte-colony stimulating factors**

# MAINTENANCE

**Annual ophthalmologic and hematologic evaluations; monitor growth and weight gain**

**Caution should be used regarding medications with the potential to decrease the neutrophil count**

## **Genetic Counseling**

**Many diagnosed live into their 50's (although variable), not necessarily affecting the life expectancy**

# G-CSF

**Manufactured version of the natural hormones that stimulate the bone marrow to produce neutrophils**

**Increases the number of neutrophils generated by the bone marrow and improved the efficacy of their bacteria-killing ability**

**Glycoprotein**

**There are different types of G-CSF including:**

**Lenograstim (Granocyte)**

**Filgrastim (Neupogen, Zarzio, Nivestim, Ratiograstim)**

**Long Acting (pegylated) Filgrastim (pegfilgrastim, Neulasta) and lipegfilgrastim (Longquex)**

**Pegylated G-CSF stays in the body for longer so you have treatment less often than with the other types of G-CSF**

# RESOURCES

**NORD-National Organization for Rare Disorders**

**Cohen Syndrome by Helen Wang, MD in Gene Reviews**

**Cohen Syndrome Association**

**[Cohensyndrome.org](http://Cohensyndrome.org)**



Presented by: Katie Marsh, DDS

# Gorlin-Goltz Syndrome



# Introduction

- Other names: See next slide
  - Nevoid Basal Cell Carcinoma Syndrome (NBCS)
  - Basal cell nevus syndrome
- Autosomal dominant inheritance
  - 70-80% inherited from parent
  - 20-30% have de novo mutation
  - Mutation in PTCH1 tumor suppressor gene
- Classic triad: multiple BCCs, KCOT, bifid ribs
- Major diagnostic indicator: Numerous basal cell carcinomas
  - BCCs of the temporal, pre-auricular, zygomatic and orbital areas
  - Aggressive BCCs invading facial bones are rare
  - Treatment of temporal/orbital region requires coordination among numerous medical specialties with excision of the BCC and reconstruction

# Other names for Gorlin-Goltz

Synonyms of Gorlin-Goltz syndrome.

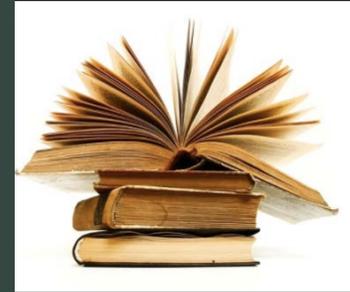
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## Designations of the Gorlin-Goltz syndrome used in the scientific papers

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Basal cell naevus (carcinoma) syndrome	Multiple hereditary cutaneomandibular polyoncosis
Epithelioma naevique multiple	Multiple naevoid basal-cell carcinoma syndrome
Fifth phakomatosis	Naevous epitheliomatodes multiplex
Gorlin syndrome <sup>12</sup>	Nevoid basal cell carcinoma syndrome
Hereditary cutaneo-mandibular polyoncosis	Nevoid basal cell carcinoma epithelioma – jaw cysts
Hermans-Grosfeld-Spaas-Valk syndrome	Multiple bifid rib syndrome
Multiple basal-cell carcinoma syndrome	Ward syndrome II
Multiple basal-cell naevi syndrome	

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# History

- First report made in 1894 by Jarisch and White in a patient with multiple BCCs, scoliosis and learning disability
- 1939- Straith described case with multiple basocellular carcinomas and cysts
- 1951- Binkley and Johnson observed relationship between basal cell epitheliomas and developmental malformations
- \*\*1960- **Robert James Gorlin and William Goltz** discovered classical triad (multiple basocellular epitheliomas, KCOT, and bifid ribs) that established diagnosis of this syndrome
- Rayner et al- established that cysts had to appear simultaneously either with calcifications of the falx cerebi or with palmar and plantar pits



# Etiology

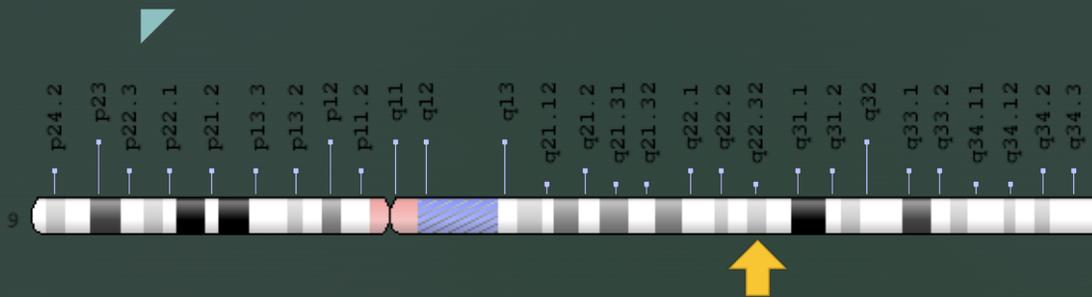
- Mutations in the patched (PTCH) gene
  - Encodes a 12-pass transmembrane receptor protein which recognizes sonic hedgehog signaling proteins and suppresses the HH signaling cascade
  - This gene plays major role in tumor suppression, embryonic structuring, and cellular cycle
  - Mutations in this gene results in loss of control of several genes known to play role in organogenesis, carcinogenesis, and odontogenesis
  - Complete penetrance with variable expressivity
  - 20-30% de novo mutations (maybe more)



# Epidemiology

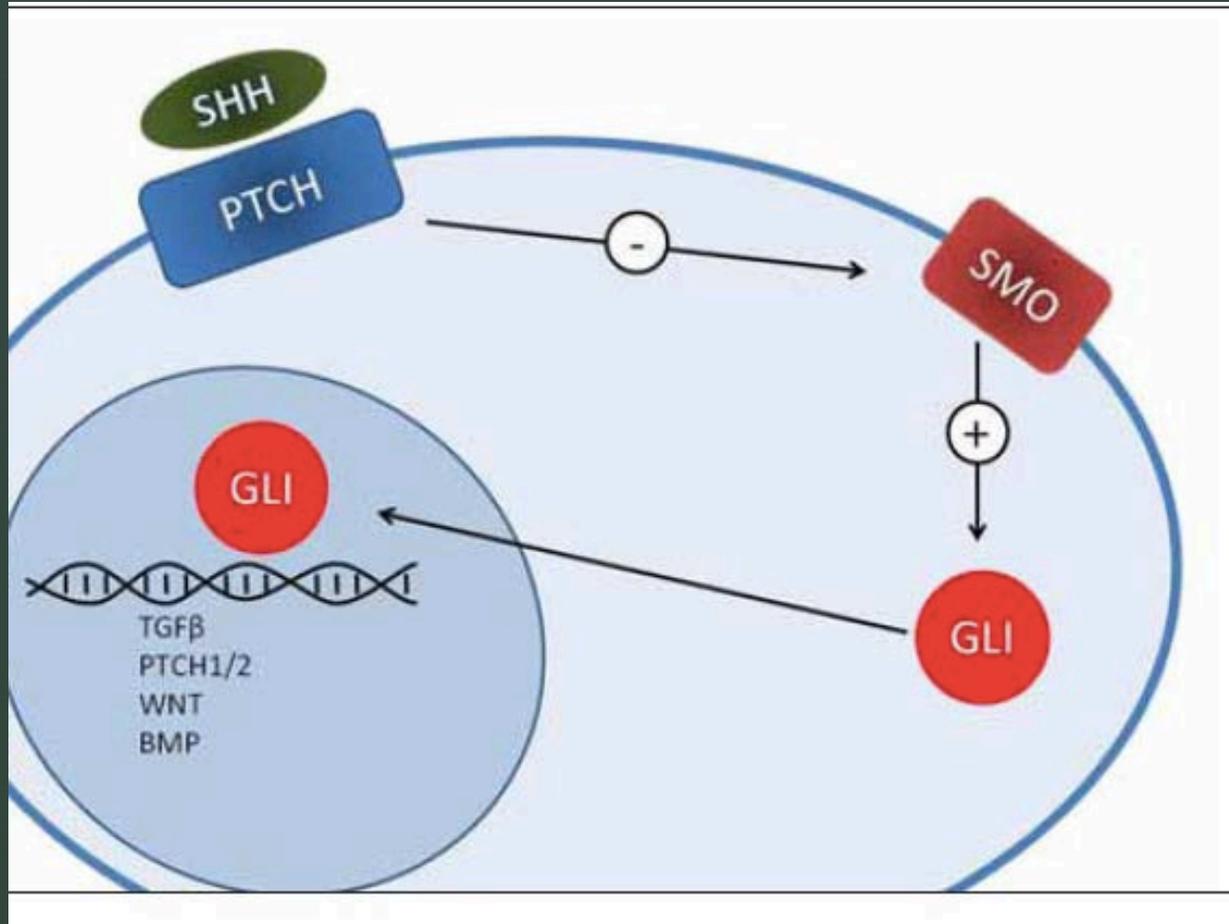
- Prevalence
  - 1/40,000-60,000 depending on population studied
  - Affects men and women equally
  - Affects all races but most cases reported in Caucasians
  - Sporadic and familial incidence
  - Diagnosed in young patients but mostly between 17-35 years old
  - Difficult to diagnose in childhood because symptoms appear gradually
  - Nine variants of mutations have been reported

# Pathophysiology



- Mutation in patched 1 (PTCH1), tumor suppressor gene located on chromosome 9q22.3-q31 (frameshift, nonsense, missense)
  - Mutations of other genes: Patched2 (PTCH2), smoothed (SMO), and sonic hedgehog (SHH)
- PTCH encodes transmembrane receptor protein that acts as antagonist for sonic hedgehog ligand in sonic hedgehog and SMO signaling pathways, which regulate cells growth
- Homozygous inactivation of PTCH gene → tumorigenesis (multiple BCCs and other neoplasms)
- Patients inherit one defective copy of tumor suppressor gene and acquire a second hit mutation e.g. from UV light or ionizing radiation

# Sonic Hedgehog pathway



**FIGURE 1:** Representation of the hedgehog pathway  
SHH: *sonic hedgehog protein*, PTCH: *Protein Patched hedgehog receptor*, SMO, *Smoothened receptor*, GLI: *GLI Factor-1*, TGF $\beta$ : *Transforming growth factor type*, WNT: *wingless signaling pathway*, BMP: *bone morphogenetic protein*

# Clinical Presentation- 9 Categories

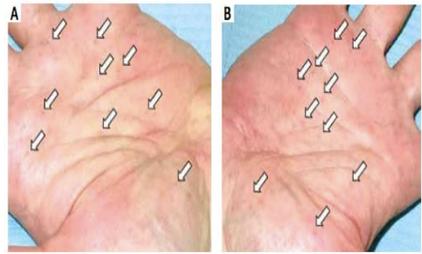


Figure 4. Multiple palmar pits on both hands



Fig. 15-25  
Nevoid Basal Cell Carcinoma Syndrome.  
Plantar pits.



Fig. 15-28  
Nevoid Basal Cell Carcinoma Syndrome.  
Large cysts are present in the right and left mandibular molar regions, together with a smaller cyst involving the right maxillary canine in the same patient shown in Fig. 15-23 .

- 1. Cutaneous anomalies
  - BCC, other benign dermal cysts and tumors, palmar/plantar pitting, palmar/plantar keratosis and dermal calcinosis
  
- 2. Dental anomalies
  - **KCOT (most common)**, maxillary hypoplasia, mandibular prognathism, high arched palate, cleft lip/palate, impacted teeth and/or agenesis, ectopic teeth and malocclusion
  
- 3. Craniofacial abnormalities
  - Calcification of falx, bridged sella turcica, macrocephaly, brachycephaly, frontal bossing, parietal and temporal bossing, coarse face

# Clinical Presentation- 9 Categories

- 4. Skeletal Anomalies
  - Polydactyly, syndactyly, scoliosis, hemivertebrae, spina bifida, osteoporosis
- 5. Cardiac
  - Cardiac fibroma
- 6. Ophthalmic anomalies
  - Hypertelorism, congenital blindness, internal strabismus, glaucoma
- 7. Neurological anomalies
  - Mental retardation (6%), bridging of sella, medulloblastoma (3-5%)- Second most common malignancy
- 8. Sexual anomalies
  - hypogonadism (3%), uterine and ovarian fibromas (15%) ovarian cysts
- 9. Laboratory findings
  - Increased serum uric acid level and alkaline phosphatase and cyclic adenosine monophosphate



Fig. 15-23  
Nevroid Basal Cell Carcinoma Syndrome.  
This 11-year-old girl shows hypertelorism and mandibular swelling.  
(Courtesy of Dr. Richard DeChamplain.)

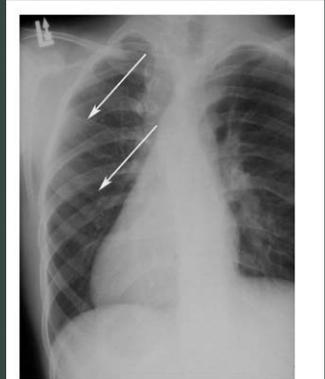


Fig. 15-26  
Nevroid Basal Cell Carcinoma Syndrome.  
Chest film showing presence of bifid ribs (arrows).



Fig. 15-27  
Nevroid Basal Cell Carcinoma Syndrome.  
Anteroposterior skull film showing calcification of the fatx cerebri.

# Basal Cell Carcinomas

- Multiple basal cell carcinomas hallmark feature of the syndrome
- Usually between ages of puberty to 35
- Range in several to thousands
- 1mm-10mm in diameter
- Location: face, back and chest or anywhere exposed to sun
- Rare aggressive forms infiltrate facial bones and require medical intervention by maxillofacial surgeons, plastic surgeons, laryngologists, oncologist, radiation oncologist, dentists, psychologists
- Prevention of new BCC lesions: reduce excessive sun exposure, use protective sunglasses and sunscreen!!



Fig. 15-24  
Nevoid Basal Cell Carcinoma Syndrome.  
An ulcerating basal cell carcinoma is present on the upper face.

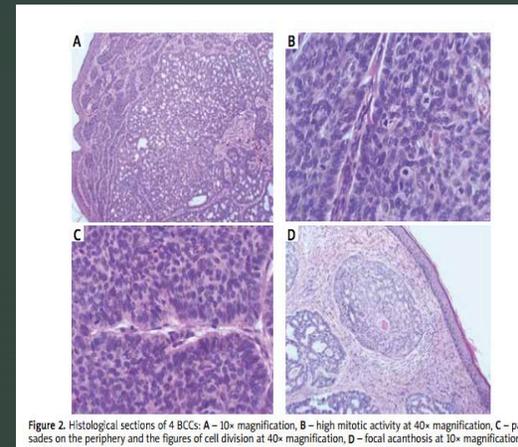


Figure 2. Histological sections of 4 BCCs: A - 10x magnification, B - high mitotic activity at 40x magnification, C - palisades on the periphery and the figures of cell division at 40x magnification, D - focal acanthosis at 10x magnification

# Keratocystic Odontogenic Tumor (KCOT)

- **Most important manifestation within the oral cavity** are recurrent multiple jaw tumors called keratocysts. Usually initial reason for presentation
- 90% of patients above age 40. First sign in 78% of cases
- Usually in mandible- 44% mandibular angle, 18% adjacent to incisor and canines. In maxilla, more aggressive
- Parakeratotic, orthokeratotic and mixed lesions differentiated based on histological lining of cells
- KCOTs associated with this syndrome have overexpression of p53 and cyclin D1 oncoproteins compared to nonsyndromic KCOT
- **\*\*Usually diagnosed accidentally during routine x-ray at dentist\*\*** – shows spherical oval unilocular lytic bone lesion often involving wisdom teeth. Well-circumscribed and well defined osteosclerotic rim. Causes bony expansion and may result in asymmetry
- Treatment: depends on age, size, extent, and location of lesion
  - Conservative: regular enucleation of tumor – high recurrence rate
  - Aggressive: enucleation + liquid nitrogen or Carnoy's solution applied to bone
  - Radical- partial resection of tumor-invaded bone together with 5mm margin of healthy bone (not good for children with teeth still erupting)

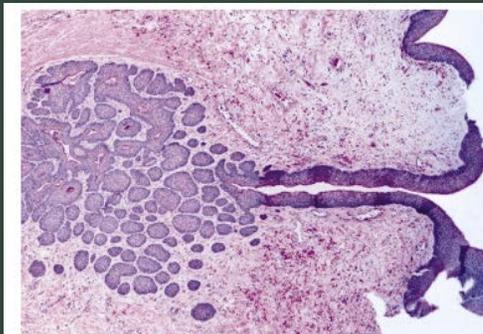
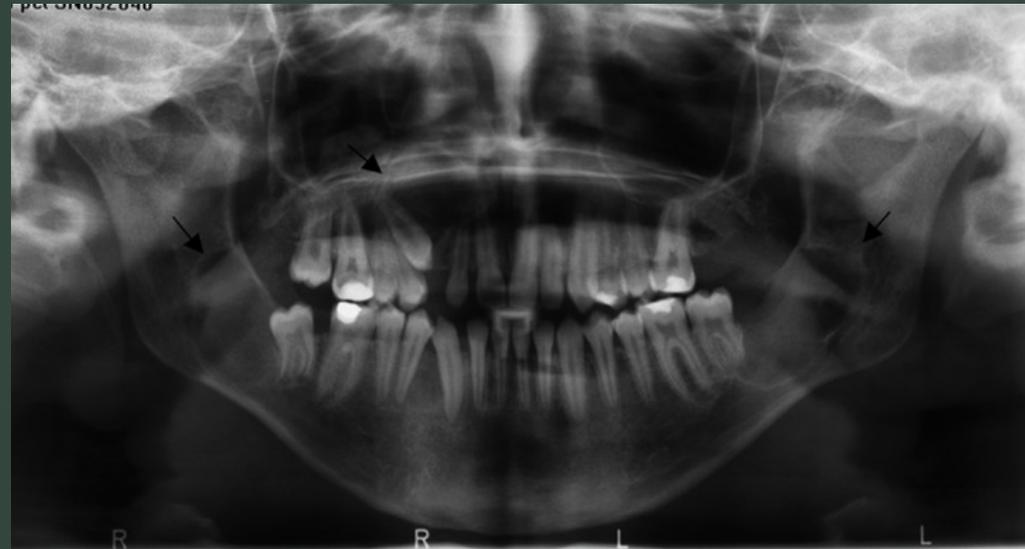


Fig. 15-29  
Nevoid Basal Cell Carcinoma Syndrome.  
Odontogenic keratocyst (OKC) showing numerous odontogenic epithelial rests in the cyst wall.

# Diagnosis

- Physical exam and imaging studies
- ~ **Presence of two major or one major and two minor clinical criteria** ~
- Diagnosis can be confirmed through detection of mutation in PTCH gene

## Major Criteria:

- Multiple (>2) BCCs or 1 BCC by <20 years
- Odontogenic keratocyst of the jaw (KCOT) proven by histology
- Palmar or plantar pitting
- Bilamellar calcification of falx cerebri
- Bifid/fused/splayed ribs
- First-degree relative with BCNS

## Minor Criteria:

- Medulloblastoma
- Increased circumference of the head
- Congenital malformations (frontal bossing, coarse facies, cleft lip/palate, hypertelorism)
- Other skeletal abnormalities (Sprengel deformity, marked pectus deformity, syndactyly of the digits)
- Radiographic anomalies (bridging of sella turcica, hemivertebrae, fusion of vertebral bodies, modeling defects of hands and feet)

## Table 2

Diagnostic criteria by Kimonis *et al.* in 1997

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### Major criteria

- More than 2 BCCs or one BCC in patients younger than 20 years of age
- Odontogenic keratocysts of the jaw (proven by histologic analysis)
- Three or more palmar or plantar pits
- Bilamellar calcification of the falx cerebri
- Bifid, fused or markedly splayed ribs
- A first degree relative with NBCCS

### Minor criteria

- Macrocephaly
- Congenital malformations (e.g., cleft lip or palate, frontal bossing, coarse faces and moderate or severe hypertelorism)
- Other skeletal abnormalities (e.g., Sprengel deformity, marked pectus deformity and marked syndactyly of the digits)
- Radiological abnormalities (e.g., bridging of the sella turcica, vertebral anomalies, modeling defects of the hands and feet, or flame-shaped lucencies of the hands and the feet)
- Ovarian fibroma or medulloblastoma

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BCCs: Basal cell carcinomas, NBCCs: Nevoid basal cell carcinomas



# Treatment/Management

- Multidisciplinary approach
  - Dermatologist: diagnose and treat BCCs → rare metastasis can happen. Skin checks every 4-6 months
  - Pediatrician: baseline MRI scan for pediatric patients yearly until 8 years old due to risk of medulloblastoma. Also cardiac ultrasounds to evaluate for cardiac fibromas
  - Jaw x rays repeated annually until first jaw cyst → then every 6 months
  - Annual speech, vision, hearing screening
- Treatment of BCCs
  - Electrodesiccation and curettage, cryosurgery, surgical excision, Mohs micrographic surgery (MMS) and CO2 laser treatment
  - Topical treatment with 5% 5-fluorouracil, 5% imiquimod, photodynamic therapy
  - Vismodegib- antagonist of smoothed receptor and hedgehog pathway inhibitor

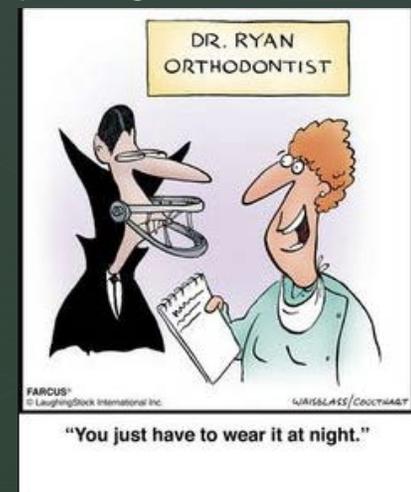


# Treatment/Prognosis

- Future treatment options: PTCH1 or SMO specific targeted drugs which prevent the expression of the tumor mediating genes within the hedgehog pathway
  - Vismodegib and sonidegib are hedgehog pathway inhibitors approved for BCC treatment
- Prognosis
  - Very good prognosis with normal life expectancy, except for rare cases of very aggressive multiple BCCs or medulloblastoma

# Conclusions

- Gorlin-Goltz syndrome is a relatively rare generalized disorder and its diagnosis in childhood is usually through oral abnormalities → We are dentists and may be the ones who catch it! Study on a few cases where orthodontist caught it because of panorex.
- Patients with Gorlin-Goltz syndrome need particular multidisciplinary medical care. The consequences of the disease pose a threat to the health and life of the patients. Early diagnosis key
- Avoid the sun due to harmful UV rays
- Prevention is better than cure



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# Saethre-Chotzen Syndrome

— Katherine Schwartz DDS —  
CBY579L Molecular Genetics

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# Craniosynostosis

- Saethre-Chotzen syndrome associated with craniosynostosis
- **Craniosynostosis:** premature fusion or growth arrest at one or more of the cranial sutures
- **Syndromic Craniosynostosis:** multiple sutures involved - part of a larger group of associated anomalies
- **Syndromes associated with craniosynostosis:** Apert Syndrome, Crouzon Syndrome, Pfeiffer Syndrome, Carpenter Syndrome and Saethre-Chotzen Syndrome
- Syndromic craniosynostoses are usually sporadic and are the result of de novo autosomal dominant mutations involving fibroblast growth factor receptors (**FGFRs**) and **TWIST** genes
- Features of these syndromes: abnormal skull-base, midface hypoplasia, limb anomalies

(Hollier, 2017)

# Saethre-Chatzen Syndrome

- Also known as **Acrocephalosyndactyly type III**
- Named for two physicians who independently discovered it in 1930s: Haakon Saethre, a Norwegian psychiatrist and F. Chatzen, a German psychiatrist
- Autosomal dominant disorder
- Craniosynostosis: 1/2000-2500 live births
- Saethre-Chatzen Syndrome: 1/25000 - 50,000 live births
- At least 20% caused by genetic mutations: of those 86% single gene mutations and 14% chromosome abnormalities
- Mutations in the **TWIST** gene, located on chromosome 7 - key role in development of skull, face, limbs
  - Defects in TWIST gene have been linked to mutations in FGFR2 (interaction during development) → leading to premature cranial ossification
- Mutations in FGFR2 alone have also been reported in patients with S-C syndrome

# Genetic Mutations of Saethre-Chotzen Syndrome

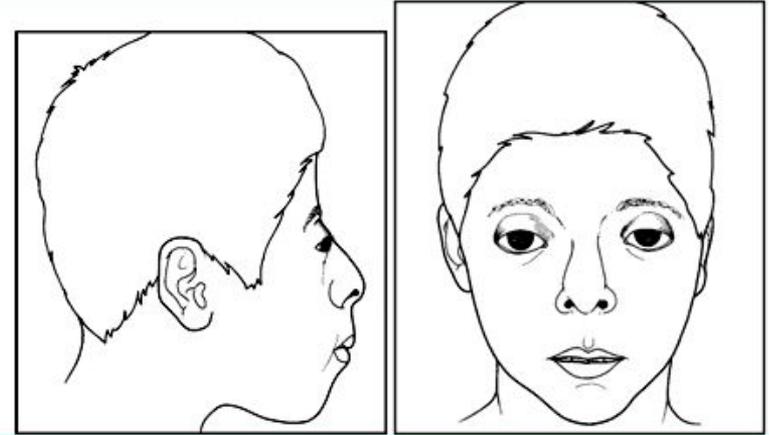
- **TWIST1**: part of small family of helix-loop-helix transcription factors that play a role in calvarial osteoblast proliferation and differentiation
- TWIST mutation → decreased osteocalcin gene expression; increased bone formation; potent inhibitor of osteoblast differentiation (Chu, 2013)
- Saethre-Chotzen Syndrome: loss-of-function mutations in TWIST
  - Missense, nonsense, deletions, insertions and duplications
- TWIST mutation → craniosynostosis in humans and mice; also plays key role in mediating cell patterning during limb morphogenesis and development through effects on sonic hedgehog and FGF signaling; TWIST mutation is autosomal dominant
- S-C Syndrome: associated mutations in **FGFR2**
- S-C Syndrome: Reduction in the amount of **RUNX2** (transcription factor essential for osteoblast differentiation and bone formation)
- Possible role of Twist1 in etiology of osteoarthritis (Abd-El-Barr, 2017)

# Clinical Features of Saethre-Chotzen Syndrome

- Craniosynostosis of coronal, lambdoid and/or metopic sutures
  - Unilateral or bilateral coronal synostosis
- Characteristic facial appearance:
  - Towering forehead
  - Low-set hairline
  - Facial asymmetry with septal deviation/flat face
  - Beaked nose
  - Ptosis of upper eyelids
  - Hypertelorism (widely spaced eyes)
  - Small and dysmorphic ears
  - Midfacial hypoplasia leads to small maxilla and relative mandibular prognathia, as well as high arched palate
  - Cleft palate may occur
  - Supernumerary teeth
  - Enamel hypoplasia

(Sharma, 2017)

## Saethre-Chotzen syndrome



Craniosynostosis (mild). Ptosis with facial asymmetry and septal deviation. Low-set hairline and simple syndactyly of index and middle finger.

(Hollier, 2017)

# Clinical Features of Saethre-Chotzen Syndrome (cont.)

- Many patients with S-C syndrome will have normal intelligence
- Severe cases: patients may also have mental retardation or learning disabilities
- Personality disorders
- Cutaneous syndactyly of second and third fingers and/or third and fourth toes (webbing)
- Congenital heart defects (ASD, VSD, pulm stenosis, PDA, TOF)
- Renal anomalies
- Cryptorchidism (absence of one or both testes in males)
- Brachydactyly (short fingers and toes)
- Short stature
- Vertebral fusions
- Speech problems

(Sharma, 2017)

# Clinical Presentation

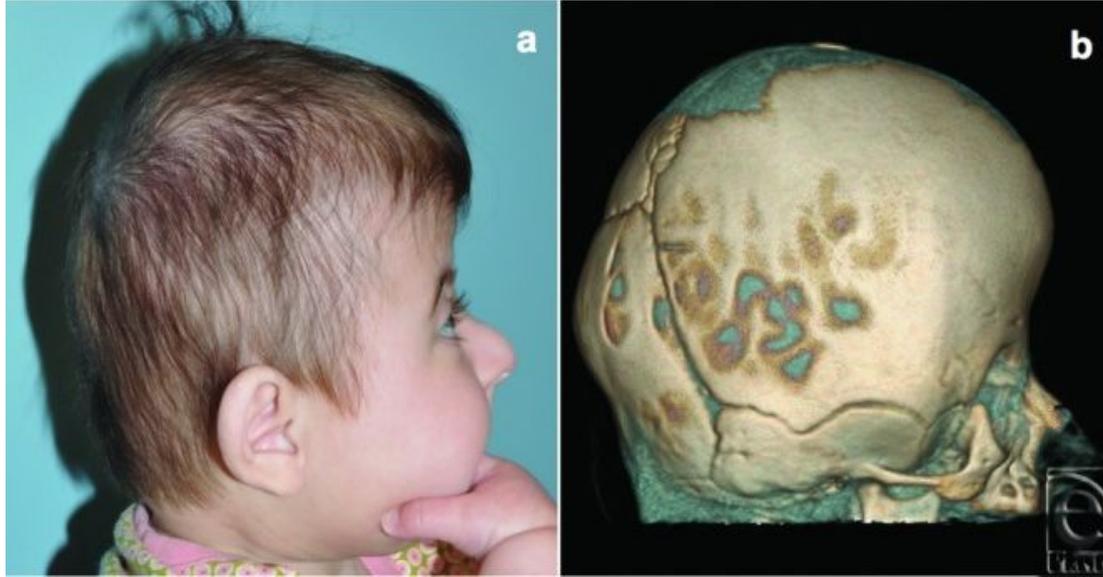


Ptosis and left unicoronal synostosis in Saethre-Chotzen Syndrome (Johnson, 2011)



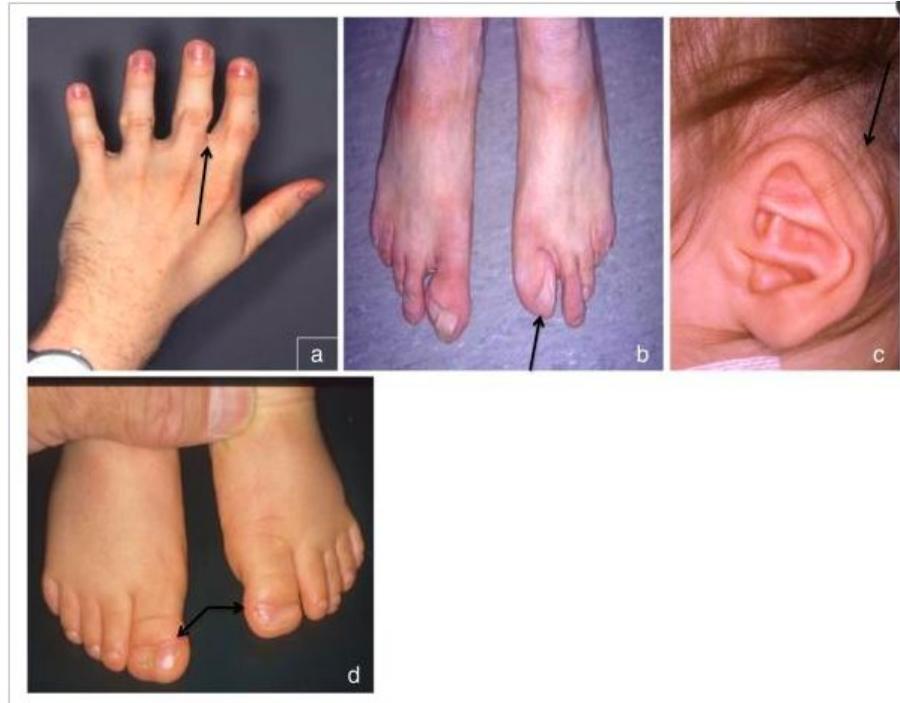
8-month-old girl with asymmetric bicoronal synostosis in Saethre-Chotzen syndrome; she has brachycephaly, right eyelid ptosis, mild facial asymmetry, indented nasal bridge and dysmorphic external ear (Woods, 2009)

# Clinical Presentation

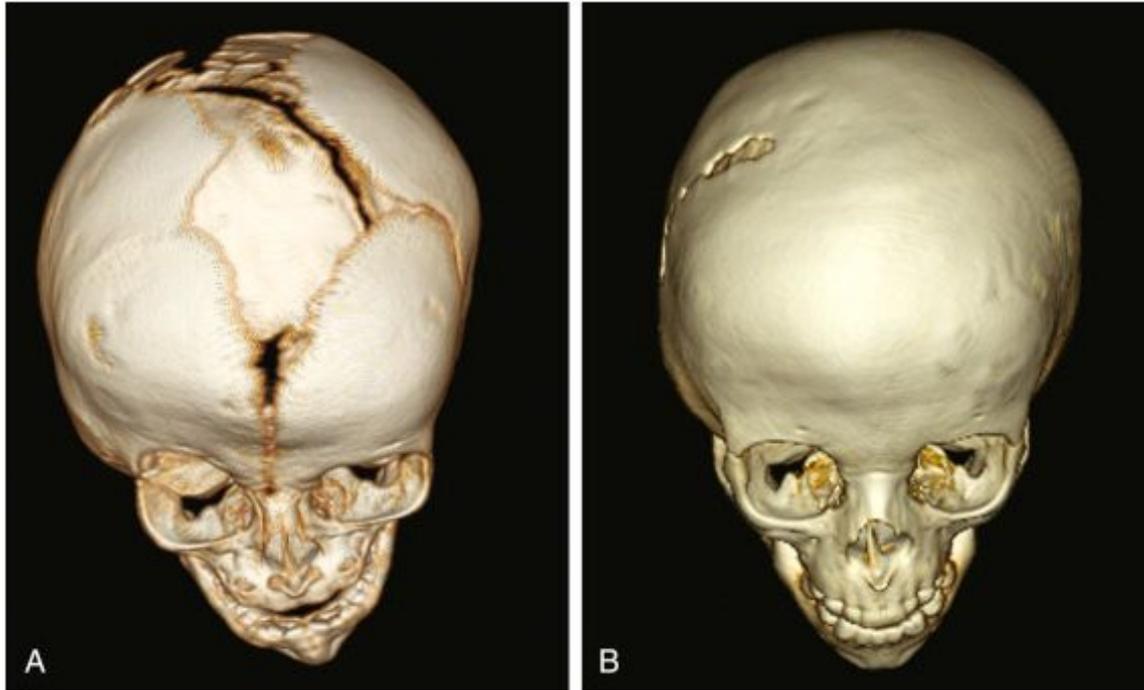


Three-month-old female patient with Saethre-Chatzen syndrome and bicornal synostosis. The sagittal, lambdoid, and squamosal sutures were patent with a large fontanelle, characteristic of Saethre-Chatzen syndrome (Chu, 2013).

# Clinical Presentation



**a** Cutaneous syndactyly (webbing) in a patient with Saethre–Chotzen syndrome. **b** Lateral deviation of the large toes in a patient with Saethre–Chotzen syndrome. **c** Ear anomalies in a patient with Saethre–Chotzen syndrome. **d** Duplication of the distal phalanx of the hallux (large toe) in a patient with Saethre–Chotzen syndrome (Agochukwu, 2012)



- A. 3D construction of CT revealed right coronal craniosynostosis. This was corrected with an endoscopic-assisted release of right coronal suture
- B. 3.5 years later patient had a drop in head circumference; 3D of CT revealed fusion of right coronal suture, sagittal suture and metopic suture; patient underwent fronto-orbital advancement

# Radiographic Examination:

- Computed Tomography (CT) and 3D reconstruction using bone and soft tissue windows is ideal for evaluation of most craniofacial defects - this will reveal patency or closure of each suture
- Absence of normal sutural lucency may indicate synostosis
- Skull radiographs are limited in their sensitivity for detecting sutural patency
- MRI good to visualize brain but not great for visualizing cranial sutures

**Anteroposterior radiograph in a patient with Saethre-Chotzen syndrome**



Anterior plagiocephaly demonstrated in a patient with Saethre-Chotzen syndrome. Note the closure of the metopic suture (arrow) although both coronal sutures (arrowheads) remain present.

(Sharma, 2017)

# Treatment of Saethre-Chotzen Syndrome

- Team of doctors treat these patients: craniofacial surgeon, pediatrician, neurosurgeon, ophthalmologist, dentist, orthodontist, oral surgeon, prosthodontist, geneticist, nurse, speech pathologist, audiologist, anthropologist, psychologist and nutritionist
- Head evaluated by palpation of sutures and fontanelles to detect patency; signs of ICP such as ridging and bulging fontanelles (Demke, 2017)
- Acute Care: Airway, feeding, eye protection and treatment of raised ICP is critical with infants
  - Synostosis patients should undergo cranioplasty within first year of life to decrease ICP and prevent further facial asymmetry
  - Hydrocephalus needs a shunt
  - Obstructive sleep apnea requires improving airway
  - Craniocerebral disproportion requires calvarial expansion

(Johnson, 2011)

# Treatment of Saethre-Chotzen Syndrome (cont.)

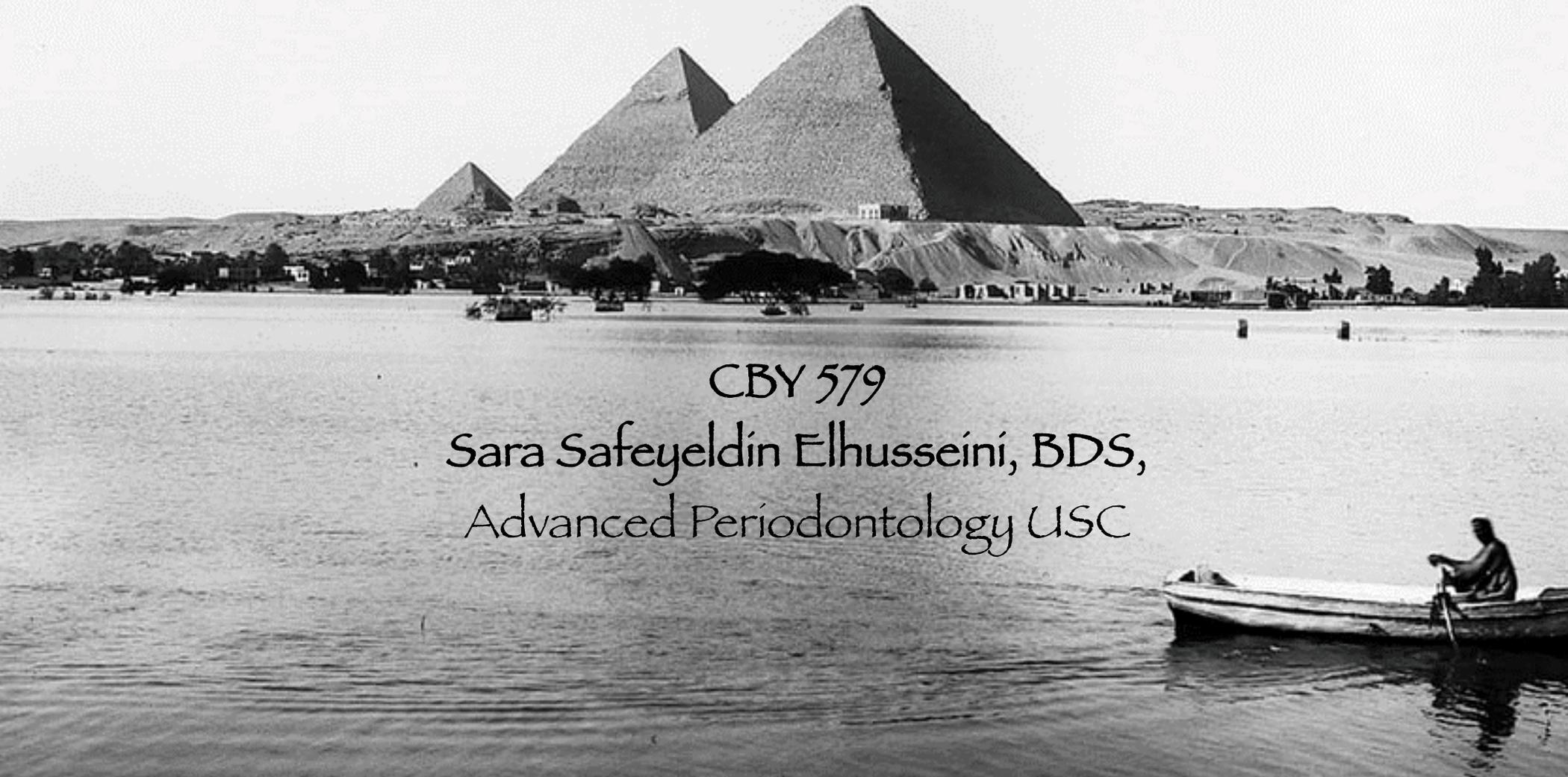
- Majority of primary surgical procedures performed between ages 6 mo - 2 yrs: goals to correct skull deformity/prevent progression and reduce risk of ICP
- More severely affected patients require cranial remodeling and cranio-orbital reshaping
- Childhood follow-up care advisable to monitor symptoms of raised ICP, such as headaches, behavior change, declined school performance
- Patients with TWIST1 mutations are at highest risk for secondary development of ICP and learning disability.

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*CBY 579*

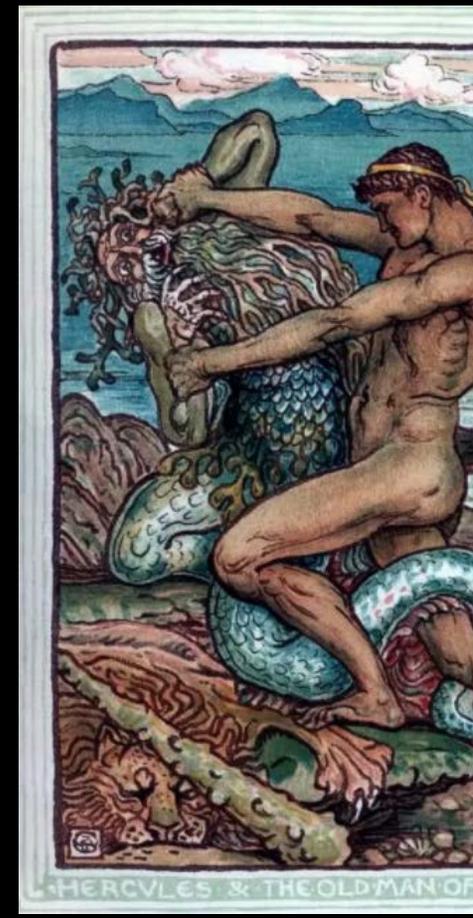
*Sara Safeyeldin Elhousseini, BDS,  
Advanced Periodontology USC*

# Proteus Syndrome

Where does the name come from ??

# Named after Proteus : the God of the seas in greek Mythology

The ability to assume different forms



# Joseph Merrik , 19<sup>th</sup> century “Elephant Man “

First described by Drs. Samia Temtamy and John Rogers in 1976



# Prevalence

- Is a **rare** condition incidence of less than **1 in 1 million** people worldwide, is characterized by **overgrowth of the bones, skin, and other tissues**. Organs and tissues affected by the disease grow out of proportion to the rest of the body. The overgrowth is usually asymmetric, which means it affects the right and left sides of the body differently.



# Onset and Symptoms

- Newborns with Proteus syndrome have few or no signs of the condition.
- Overgrowth becomes apparent between the ages of 6 and 18 months and gets more severe with age.
  - The gene mutation occurs at or before birth
- Patients are usually normal at birth but during the child's first year some parts of the body begin to grow progressively
  - Can affect any part of the body but usually affects the skull, arms legs and the skin
- Other Areas could be vascular (DVT) or adipose tissue or even nerve tissue which then causes neurological disorders
  - Pulmonary embolism is also a common cause of death of people with the disease
  - Afflicted individuals are at increased risk for developing certain tumors including unilateral Ovarian cystadenomas, testicular tumors, meningiomas, and monomorphic adenomas of the parotid gland

### General Criteria

Mosaic Distribution  
Progressive Course  
Sporadic Occurrence

### Specific Criteria

#### Category A

Cerebriform connective tissue nevus

#### Category B

Linear epidermal nevus

Asymmetric, disproportionate overgrowth of two of:

Limbs, skull, external auditory canal, vertebrae, or viscera

Specific tumors in the first decade of life:

Bilateral ovarian cystadenomas

Monomorphic parotid adenomas

#### Category C

Dysregulated adipose tissue

Vascular Malformations

Capillary, venous, and/or lymphatic

Lung bullae

Facial phenotype:

Long face, dolichocephaly, down-slanted palpebral fissures, low nasal bridge, wide or anteverted nares, open mouth at rest

The diagnosis of Proteus syndrome requires all three general criteria, plus one criterion from category A, or two criteria from category B, or three criteria from category C.  
(Adapted from Biesecker, 2006)

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# Cribriform Connective tissue lesion



# Linear epidermal lesion



# Etiology

A mutation in the AKT1 gene.

The *AKT1* gene belongs to a class of genes known as oncogenes. When mutated, **oncogenes** have the potential to cause normal cells to become cancerous.

The *AKT1* gene **provides instructions** for making a protein called **AKT1 kinase**. This protein is found in various cell types throughout the body, where it plays a **critical role in many signaling pathways**.

For example, **AKT1 kinase helps regulate cell growth and division (proliferation)**, the process by which cells mature to carry out specific functions (differentiation), and cell survival.

AKT1 kinase also **helps control apoptosis**, which is the self-destruction of cells when they become damaged or are no longer needed.

Signaling involving AKT1 kinase appears to be essential for the normal development and function of the nervous system. Studies have suggested a role for **AKT1 kinase in cell-to-cell communication among nerve cells (neurons)**, neuronal survival, and the formation of memories.

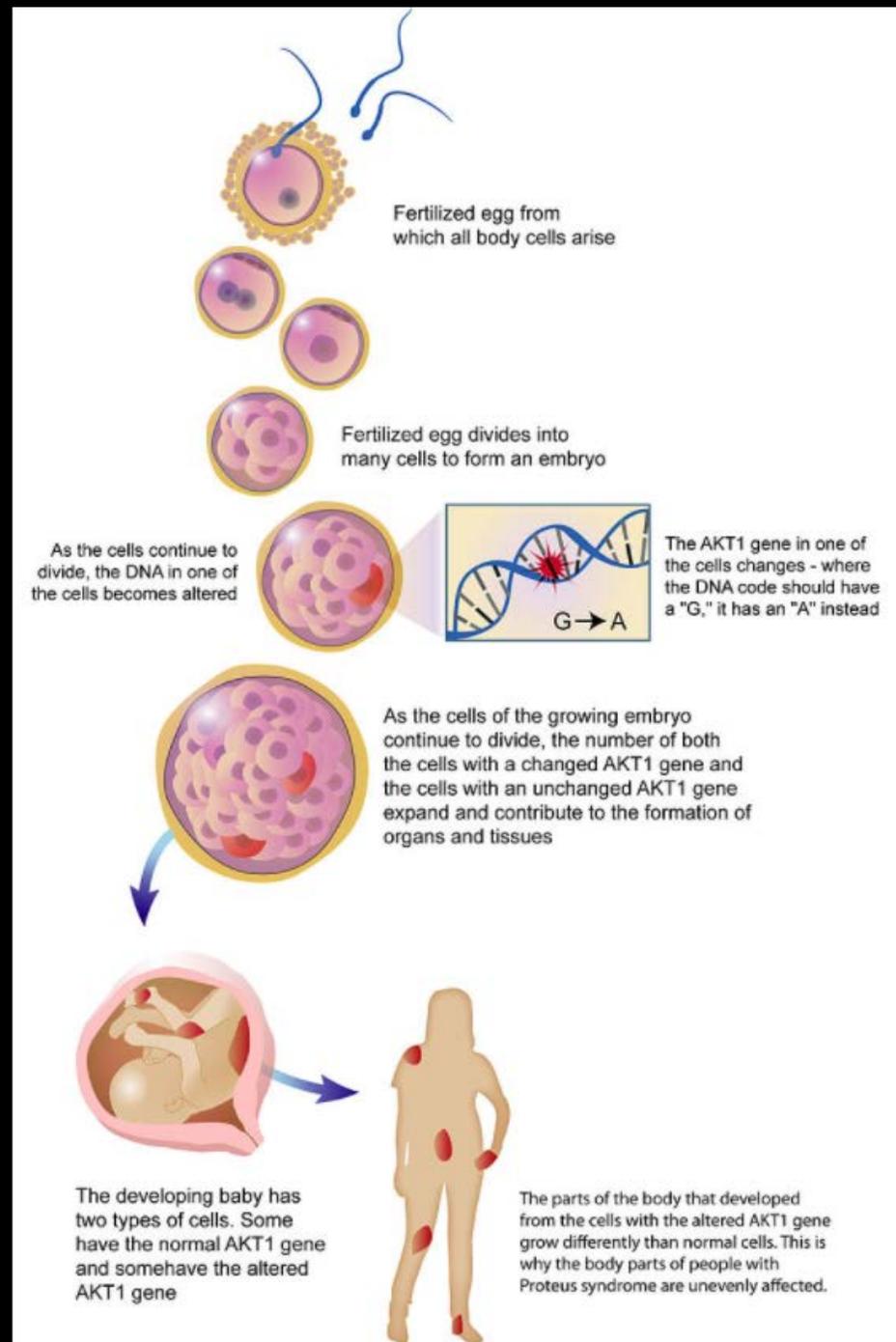
# Etiology

This mutation changes a single protein building block (amino acid) in AKT1 kinase. Specifically, it replaces the amino acid glutamic acid with the amino acid lysine at protein position 17.

The mutation arises randomly in one cell during the early stages of development before birth. As cells continue to grow and divide, some cells will have the mutation and other cells will not. This mixture of cells with and without a genetic mutation is known as mosaicism.

The Glu17Lys mutation leads to the production of an overactive AKT1 kinase that is turned on when it should not be. The abnormally active protein disrupts a cell's ability to regulate its own growth, allowing the cell to grow and divide abnormally.

# biology



# Interesting fact !

- ATK1 creates an oncogene a kind of mutation that can drive uncontrolled cell division , this is normally also associated with cancer spread and migration.
- Research is currently undergoing to see if medication used in treating cancer could be used to treat proteus syndrome as well, since some cancer forms share the same gene mutation as this syndrome.

# Treatment

National Human Genome Research Institute at the United States National Institutes of Health finding trial with the **AKT1 inhibitor ARQ 092**, which is being developed by the Arqule Corporation. In earlier tests on tissue and cell samples obtained from patients, ARQ 092 reduced phosphorylation of AKT and downstream targets of AKT in as little as two hours.

Usually treatment involves surgical procedures to reduce the over growth if possible and palliative treatment if there is any pain associated.

# Why is it important to learn about this rare disease ?

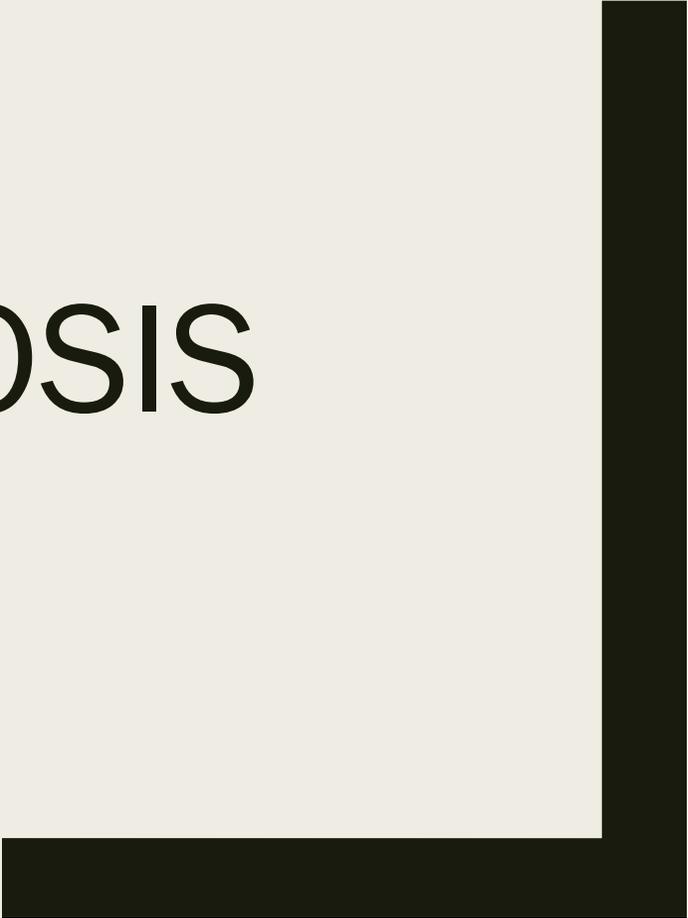
The same gene mutation is found in some cancer forms, studying the genetics of rare diseases and finding ways to treat them could lead us to cure for a more common disease as cancer.

Thank you !



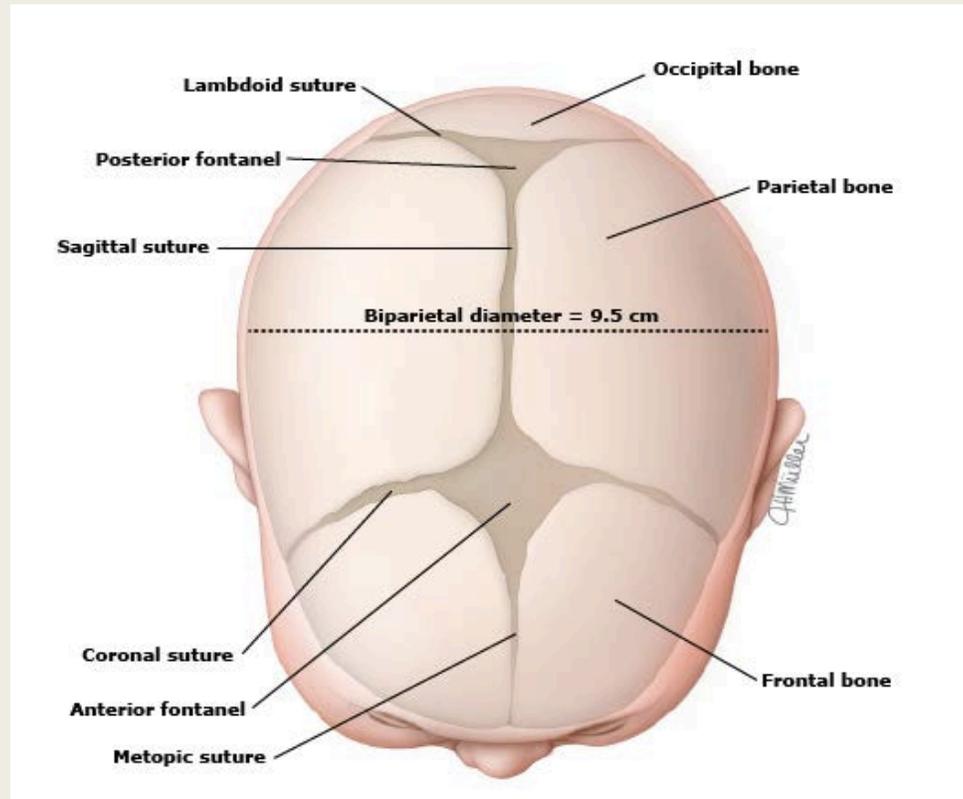
# CRANIOSYNOSTOSIS

By: Zoey Gutierrez, DDS



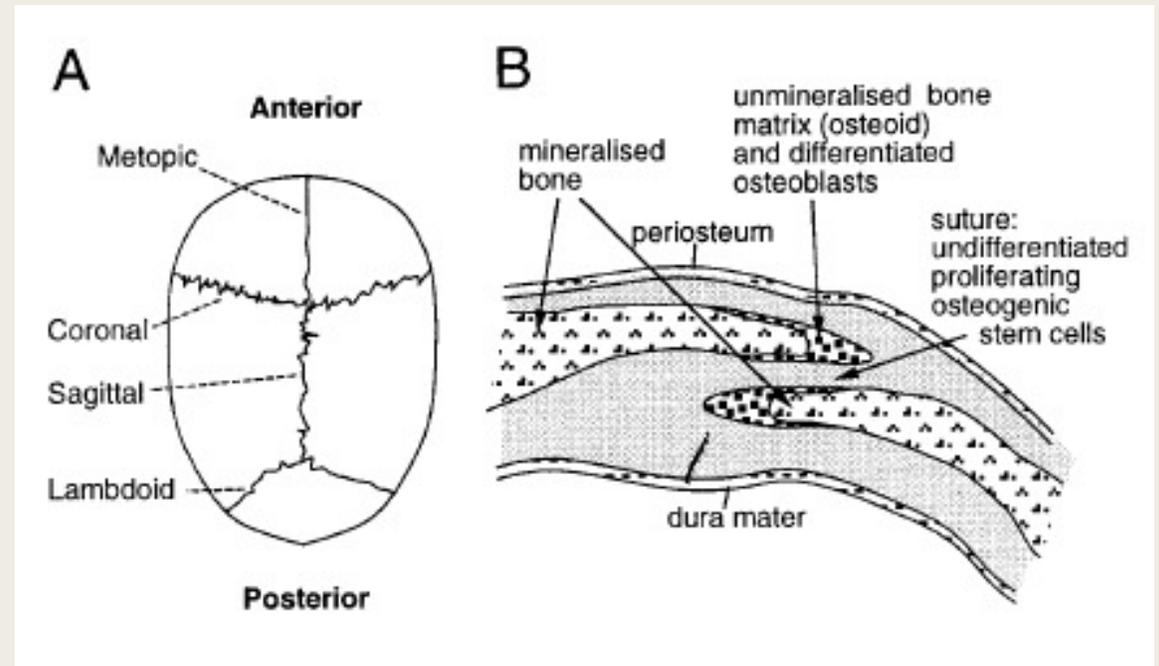
# CRANIAL ANATOMY

- Newborn infant's skull is composed of bony plates separated by sutures
  - *Permits the future growth of the brain, which quadruples during the first 2 years of life*
  - *Allows distortion during birth*
- 4 major sutures
  - *Metopic*
  - *Coronal*
  - *sagittal*
  - *lambdoid*



# CRANIAL ANATOMY

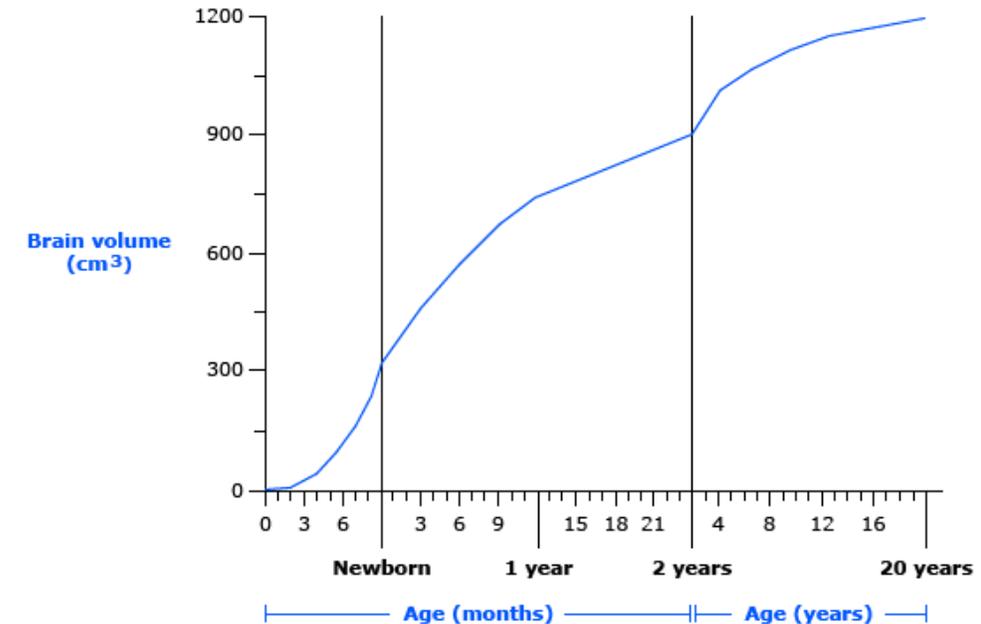
- The osseous cranial base is endochondral bone that undergoes a proliferative growth pattern
- Cranial sutures are articulations along the margins of adjacent bones.
- The calvarium grows by depositing new bone along the suture lines in response to the distending forces of the rapidly growing brain
- Fontanelles are formed at the junctional boundaries of the cranial sutures where larger areas of connective tissue occur without underlying the bone.
- Fontanelles are closed by 3 (posterior) to 20 (anterior) months



# CRANIAL ANATOMY

- The skull enlarges by appositional growth at the suture with deposition of premineralized bone matrix (osteoid) along suture margins
- Normally, the skull grows in planes perpendicular to the suture, but premature fusion forces growth in the plane parallel to the closed suture
- Two years after birth, the brain increases in size to 75% of its adult volume
  - *Remaining 25% grows over the next 18 years*

**Skull growth**



# PATHOGENESIS

- Premature fusion of one or more cranial sutures
- Affects 1/2500 births worldwide.
- Premature fusion restricts the growth of the skull perpendicular to the affected suture.
- Sagittal suture is affected most often
  - *Review of 519 subjects: Sagittal Suture 56%, Coronal Suture 25%, Metopic Suture 4%, Lambdoid Suture 2%*

**Age of suture closure**

Suture	Begins closure, months
Metopic	2
Sagittal	22
Coronal	24
Lambdoid	26
Palatal	30 to 35
Frontonasal	68
Frontozygomatic	72

(Shillito, 1968)

# PATHOGENESIS

## ■ ISOLATED DEFECT

- *In general, craniosynostosis involving a single suture occurs sporadically*
- *Increased incidence of craniosynostosis involving multiple pregnancies and in the presence of uterine abnormalities, such as bicornuate uterus, implying that compression of the fetal skull during pregnancy can contribute to craniosynostosis*

## ■ SYNDROMIC

- *Craniosynostosis involving multiple sutures is often part of a genetic syndrome with additional anomalies*
- *Dysmorphisms involving the face, skeleton, nervous system, and is usually accompanied by developmental delay*

(Vlad, 2009)

# SYNDROMIC CRANIOSYNOSTOSIS

- Apert
    - Often sporadic and are the result of de novo autosomal dominant mutations involving fibroblast growth factor receptors (FGFRs) and TWIST genes
  - Crouzon
  - Pfeiffer
  - Carpenter
  - Saethre-Chotzen
- Common features:
- skull-based abnormalities
  - Midface hypoplasia, and limb anomalies.
  - More than 180 different syndromes involve craniosynostosis

# NONSYNDROMIC CRANIOSYNOSTOSIS HYPOTHESES

- Moss' dural hypothesis:
  - *Abnormal dural attachments exert restrictive tensile forces → arrest bone growth → premature suture closure*
- Endocrine abnormalities
  - *Hyperthyroidism*
  - *Warfarin*
  - *Valproate (use during pregnancies)*
- Intrinsic abnormality:
  - *Osteoblasts are inhibited by exposure to osteoblast growth factor*

# INTRINSIC ABNORMALITY

- Fragale A- cell proliferation & differentiation in osteoblasts from patients with 3 genetically and clinically distinct craniosynostoses compared with control osteoblasts
- Found: osteoblasts from craniosynostotic patients exhibited a lower proliferation rate than control osteoblasts

(Fragale, 1999)

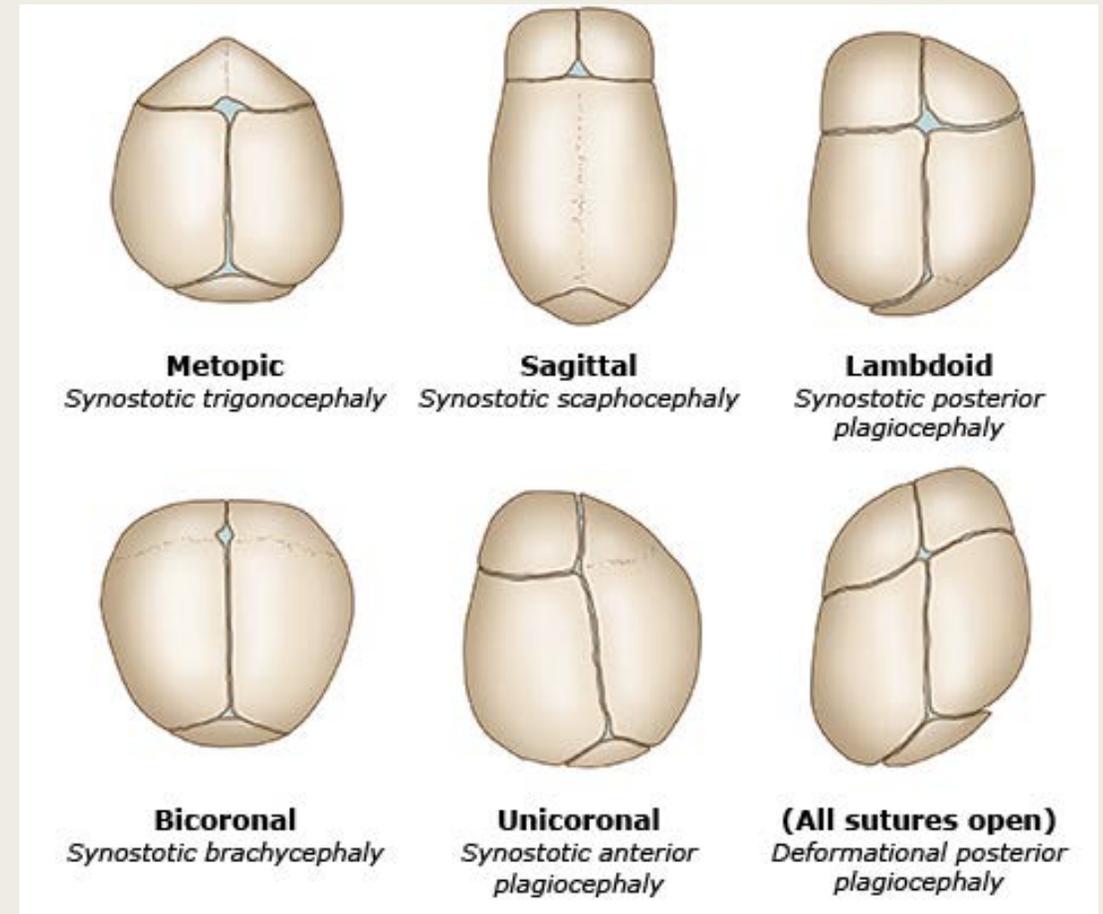
# PATHOGENESIS

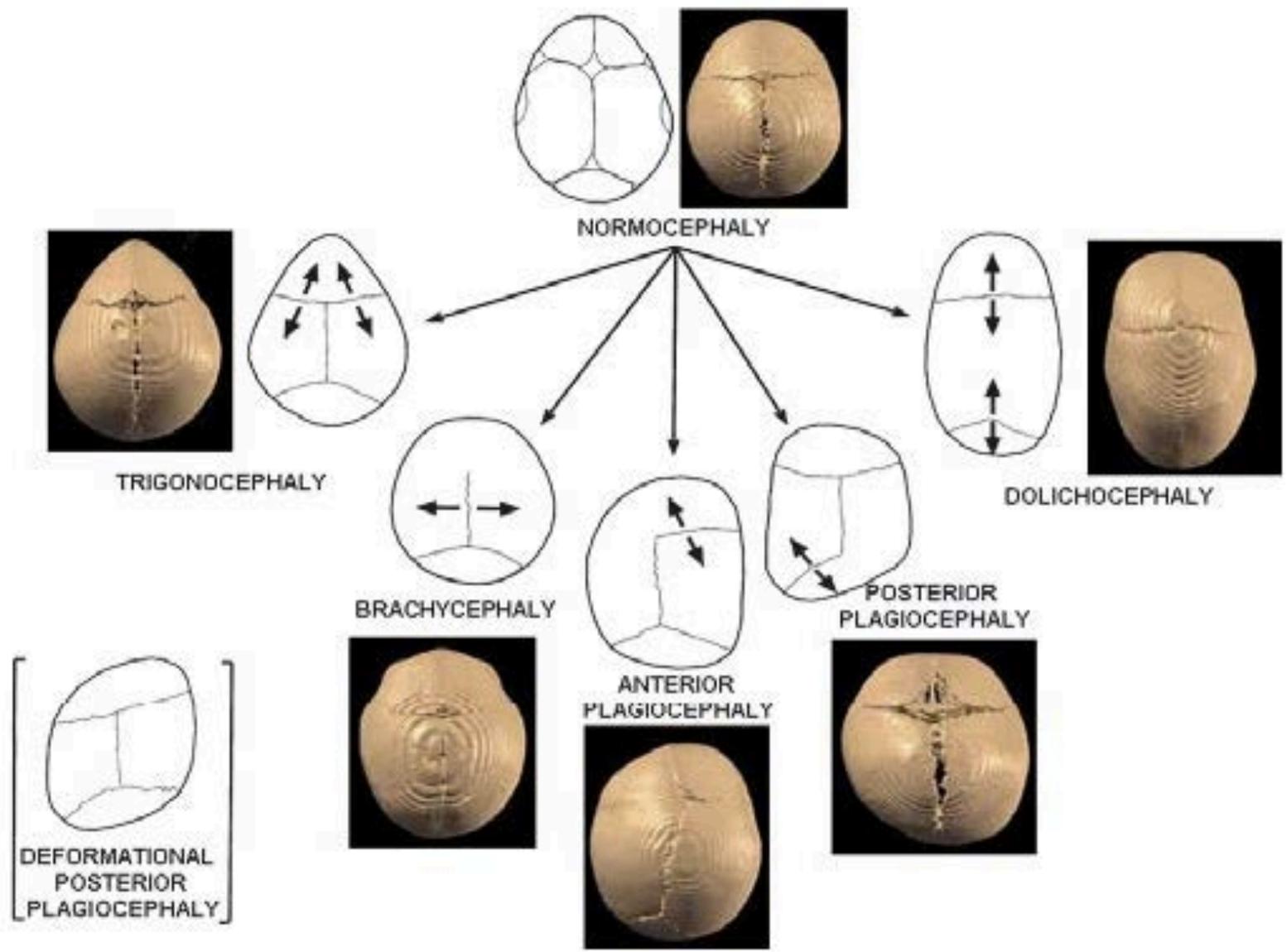
- Mutations in specific genes have been identified in most of the common autosomal dominant craniosynostosis syndromes
  - *Most mutations affect genes that code for fibroblast growth factor receptor (FGFR)*
  - *Mutations in these genes are also found in patients with nonsyndromic craniosynostosis*
  - *Ex: 57 pts with bilateral coronal synostosis, mutations in **FGFR2/FBFR3** were identified in ALL pts with phenotypic diagnosis (Apert, Crouzon, or Pfeiffer syndrome)*
  - *In another Ex., the most commonly mutated genes were **FGFR2, FGFR3, and TWIST1, and EFNB1***
- Single gene defects accounted for 86% of the molecular defects identified in this study, whereas chromosome abnormalities accounted for only 14%

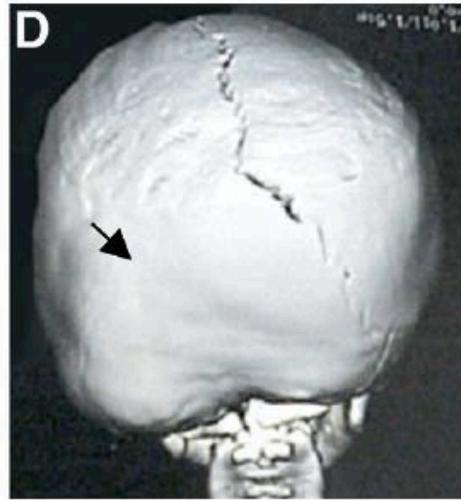
(Mulliken, 1999)

# CATAGORIES OF CRANIAL DEFORMITIES

- **Scaphocephaly**
  - *Premature fusion of sagittal suture*
  - *50% of cases*
- **Plagiocephaly**
  - *Premature closure of a unilateral coronal or lambdoidal suture (twisted skull)*
  - *1/10,000 births*
- **Trigonocephaly**
  - *Premature closure of metopic suture*
  - *10% of cases*
- **Kleeblattschadel**
  - *Multiple sutures fuse prematurely*
  - *Cloverleaf deformity, most severe form*
  - *Very rare*







- Lambdoid synostosis
- Secondary facial asymmetry
  - Does not occur in positional plagiocephaly\*
- Lambdoid craniosynostosis and positional plagiocephaly pose a significant diagnostic dilemma that requires careful clinical and radiologic differentiation and different therapeutic approaches

(Kimonis, 2007)

# DIAGNOSING DEFORMITIES

## ■ COMPUTED TOMOGRAPHY

- *Identify sutures most accurately*
- *Assess extent of fusion and its effect on adjacent bones*
- *Brain can be examined for hydrocephalus*
- *3D surface reconstruction from CT data can be used to plan craniofacial operations (Altobelli, 1993)*
- *Ultrasound (lower cost alternative to CT) → less diagnostic than CT.*
- *CT allows for eval. of more than just the affected suture*
- *Minor cranial sutures, brain anatomy, and any concerning vascular structures are also assessed*

# DIAGNOSING DEFORMATIES

- CEPHALOMETRICS
- GENETICS \*all subclassifications of craniosynostosis can be genetic\*
  - *Early screening for genetic mutations can be performed in affected newborns with suspected syndromic forms of craniosynostosis*
  - *FGFR family, and TWIST*
  - *Causative mutations are more commonly identified in children with unicoronal or bicoronal, rather than sagittal or metopic nonsyndromic craniosynostosis* (Wilkie, 2010)

**Molecular Testing of recurrent mutations** (Adapted with permission from [5]).

Disorder	Gene (% responsible)	Gene (% responsible) Mutations	Mutation Detection Rate
Pfeiffer	FGFR2 (>95%) FGFR1 (<5%)	Several	67%
Apert	FGFR2 (100%)	Ser252Trp, Pro253Arg	>98%
Crouzon	FGFR2 (100%)	Several	>50%
Crouzon with acanthosis	FGFR3 (100%)	Ala391Glu	100%
Muenke	FGFR3 (100%)	Pro250Arg	100%
Saerthre Chotzen	TWIST1	Several mutations & deletions	46% to 80%

(Kimonis, 2007)

# GENETIC COUNSELING

- Majority of craniosynostosis are autosomal dominant
- The identification of a mutation in an affected individual should be followed by parental testing
- In AD types of craniosynostosis, mutation carriers have a 50% risk of passing the affected gene to their offspring
- prenatal testing strategies:
  - *Chorionic villus sampling (10-14 weeks gestation)*
  - *Amniocentesis (16-18 weeks gestation)*

# COMPLICATIONS

- Increased intracranial pressure and inhibition of brain growth
  - *Compression of the brain is more likely when multiple sutures are affected*
- Impairments in cognitive and neurodevelopment function
  - *Global development delay, poor feeding, weight gain*
- Defects in vision, hearing, and speech
  - *Cranial nerve impairment*
- Poor self-esteem/ social isolation
  - *Abnormal appearance*

# TREATMENT

- Time for surgical intervention depends on type of craniosynostosis being treated and surgical technique used
- Open approach (commonly coronal)
  - *Large incision*
  - *Open technique delayed until 9-12 months old so that bones are strong enough*
  - *Post-op regression less likely when surgery is performed at 9-12 months*
- Endoscopic approach (commonly sagittal and metopic)
  - *Smaller incision, performed at a younger age*
  - *Wide craniectomy of the involved cranial suture with limited shaping maneuvers to allow for directed cranial growth postoperatively*
  - *This growth is usually guided by post-op cranial orthotics*

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