Genetics Corner: Cat-Eye-Syndrome and Genetic Syndromes Associated with Ear Anomalies

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Clinical Summary:

A 5-week-old female infant was referred for an initial evaluation in the Craniofacial Team clinic for bilateral microtia and external auditory canal atresia.

The prenatal history was non-contributory. Fetal movements were normal. Second-trimester fetal ultrasound detected polyhydramnios and a 2-vessel umbilical cord. Maternal serum screening tests were negative; the mother declined an amniocentesis for advanced maternal age.

A 36-week gestation was delivered by repeat C-section to a 36-year old G4P3 mother. Birth weight was 4 lb 11oz (2521 g). She was admitted to the NICU of an outside hospital for respiratory distress and transient tachypnea of the newborn and discharged at two weeks of age.

The family history was non-contributory for ear anomalies, hearing loss, or other congenital anomalies. Parental consanguinity was denied. The patient has three healthy siblings. A maternal aunt had recurrent miscarriages and infertility. Parents are of Hispanic ancestry from Mexico.

On exam, the infant had dysplastic ears, a skin tag on the right cheek, an inferior coloboma of the right iris, and an asymmetric crying face. She had failure to thrive, and all growth parameters were significantly below the 3rd %ile: weight Z-score = -4.17, length Z-score = -3.63, and head circumference Z-score = -3.63.

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Assessment:

Cat-Eye syndrome (1) is characterized by the presence of ocular colobomas, including those of the iris and retina in about 50% of affected individuals, anal atresia with fistula, renal and heart malformations, as well as ear anomalies with preauricular pits and tags (Figures 1 a, b,c, d). The clinical symptoms can be highly variable. There is an increased risk for growth problems, developmental delay, and intellectual disability. The chromosome abnormality is an accessory small supernumerary chromosome resulting from an inverted duplication of proximal 22q11: inv dup dup(22)(q11). The derivative chromosome is small (smaller than chromosome 21), and it frequently has two centromeres and is bisatellited.

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The principal reason for her referral to the Craniofacial Team Clinic was bilateral microtia. Microtia is a broad term that encompasses

a spectrum of ear anomalies. Although the name microtia implies a small ear, the term usually describes a dysplastic auricle or pinna of the ear. Ectopic structures such as preauricular or even cheek tags are frequently seen. Microtia is usually associated with conductive hearing loss. Sometimes the unique shape of the pina is enough to suggest the diagnosis, but more often, it is the associated pattern of anomalies that points to the underlying diagnosis in a child with microtia.

Microtia is an etiologically and pathogenically heterogeneous anomaly (2), and it provides a clue to an underlying diagnosis that can be appreciated in the newborn period. To help you in your efforts to care for your newborn patients, we have compiled a summary of syndromes that feature microtia. You can test your knowledge by taking the quiz at the end. Good luck and see you in the New Year.

"Microtia, especially unilateral and isolated, is often a sporadic abnormality. Oculoauriculovertebral syndrome (OAVS) is a relatively common cause of microtia caused by abnormal morphogenesis of the first and second branchial arches. It is usually a sporadic, nongenetic condition, more often seen in infants of poorly controlled diabetic mothers. Facial asymmetry and cervical vertebral anomalies are common in OAVS, including cerebral, renal, and ocular anomalies."

Syndromes Associated with Microtia

Microtia, especially unilateral and isolated, is often a sporadic abnormality. Oculoauriculovertebral syndrome (OAVS) is a relatively common cause of microtia caused by abnormal morphogenesis of the first and second branchial arches. It is usually a sporadic, nongenetic condition, more often seen in infants of poorly controlled diabetic mothers. Facial asymmetry and cervical vertebral anomalies are common in OAVS, including cerebral, renal, and ocular anomalies. When an epibulbar dermoid is present, which can be deep in a far corner of the eye, the condition is often referred to as Goldenhar syndrome, but many use OAVS and Goldenhar interchangeably.

About a third of patients with microtia have a genetic syndrome. This is especially true when the ear anomalies are bilateral, and other anomalies are present. Table 1 provides causative genes for some common syndromes that include microtia.

Syndrome	Causative gene(s)
Auriculo-condylar syndrome	*PLCB4,GNAI3*
Branchio-oculo-facial (BOF)	*TFAP2A*
Branchio-oto-renal/Branchiootic (BOR/BO)	*EYA1,SIX1,SIX5*
CHARGE	*CHD7,(SEMA3E)*
Fraser	*FRAS1,FREM2,GRIP1*
Kabuki	*MLL2, KDM6A*
Klippel-Feil	*GDF6*
Labyrinthine aplasia, microtia and microdontia (LAMM)	*FGF3*
Lacrimo-auriculo-dento-digital (LADD)	*FGFR2,FGFR3,FGF10*
Mandibulofacial dysostosis	*HOXD*
Mandibulofacial dysostosis with microcephaly	*EFTUD2*
MeiereGorlin (Ear-patella-short stature)	*ORC1,ORC4,ORC6,CDT1,CDC6*
Microtia, hearing impairment, and cleft palate	*HOXA2*
Miller	*DHODH*
Nager	*SF3B4*
Oculo-auricular (OA)	*HMX1*
Townes-Brocks	*SALL1*
Treacher-Collins	*TCOF1,POL1RC,POL1RDT*

Table1: Modified from T.C. Cox et al. European Journal of Medical Genetics 57 (2014) 394e401397

Practical applications:

1. When an ear anomaly is present, examine the infant for other anomalies
2. Pay special attention when the ear anomaly is bilateral and when other anomalies are present. Consider a chromosome microarray or genetic consultation.
3. Learn to recognize a few characteristic auricular anomalies that are distinctive and help point to a genetic diagnosis.

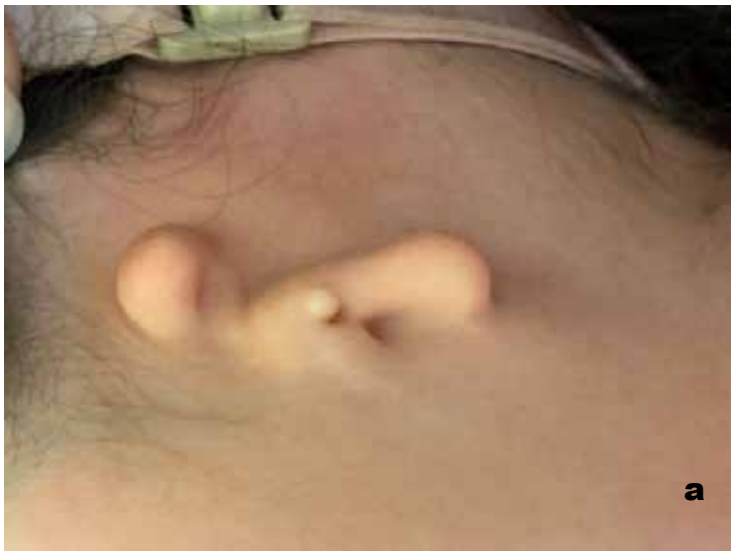
Syndrome	Ear manifestations		Other
	External ear	Additional anomalies	
Auriculo-condylar dysplasia	**Question-mark ear (interruption between the helix and antihelix and the lobule)**, posteriorly rotated cup-shaped ears	Middle ear malformations, CHL	Micrognathia, temporomandibular joint dysfunction, prominent cheeks, microstomia, facial asymmetry, cleft palate
Beckwith Weidemann	**Linear creases, indentations, or pits in anterior or posterior helix or lobule**		Macroglossia, large size at birth, lateralized overgrowth hypoglycemia (hemihypertrophy), umbilical hernia or omphalocele, visceromegaly
Branchio-oto-renal/ Branchio-otic (BOR/ BO)	Minor anomalies to severe microtia with external auditory canal atresia, uni- or bilateral. (prominent, cup, flap, lop, flattened, underdeveloped), preauricular pits. tags	Ossicle malformations, inner ear malformations (bulbous IAC, hypoplastic cochlea, Mondini, widened vestibular aqueduct and sac); HL-variable	Usually **bilateral branchial fistulas or cysts (50–60%), renal abnormalities** ranging from mild hypoplasia to complete absence/no renal malformations; risk for end-stage renal disease
CHARGE (coloboma, heart defects, choanal atresia, retarded growth and development, genital abnormalities, ear anomalies)	**The lower part of the ear is more severely affected, the lobule and lower helix absent, as if clipped-off**. Antihelix and antitragus are discontinuous, hypoplastic/absent lobe, **triangular concha,** protruding, usually asymmetric	Ossicular fixations/ malformations, **Mondini defect of the cochlea**, absent/**hypoplastic semicircular canals** (>90%), hypoplasia of auditory nerve; mild to profound SNHL	Unilateral/bilateral **coloboma of the iris, retina, choroid, and/or disc with/ without microphthalmos** (80–90%), unilateral/bilateral **choanal atresia/ stenosis (50–60%), cranial nerve dysfunction** (hyposmia/anosmia, unilateral/bilateral facial palsy (40%), swallowing problems (70–90%), **small genitalia in males,** hypogonadotropic hypogonadism in both males/ females, developmental delay, cardiovascular malformations (75–85%), growth deficiency (70–80%), orofacial clefts (15–20%), tracheoesophageal fistula (15–20%)
Kabuki	**Large, protruding, cup ear**, prominent lobules, hypoplastic anthelix; preauricular pits	Malformed ossicles; recurrent otitis media, CHL; Mondini defect of the cochlea, rarely an absence of cochlea/ malformed vestibule, sensorineural hearing loss	**Long palpebral fissures, eversion of the lower lateral eyelid, broad arched eyebrows with lateral sparseness,** depressed nasal tip; cleft lip/palate, skeletal anomalies (brachydactyly V, spine deformity); dermatoglyphics (including fetal fingertip pads); intellectual disability/ short stature. Dental/heart anomalies
Townes-Brocks	Overfolded superior helices (“satyr form” of cup ear: 25–35%), small ears, preauricular tags/ pits	Progressive SNHL; middle ear malformations (ossicle defects); mixed HL	**Imperforate anus, thumb malformations** (triphalangeal thumbs, preaxial polydactyly, rarely hypoplasia), renal dysfunction (+/- structural abnormalities), cardiac anomalies, **genitourinary malformations**
Treacher-Collins	Any degree of microtia, ear tags/fistulas; **preauricular hair displacement: a tongue-like extension of hair extends toward the cheek**	Any degree of middle ear malformations; in some cases inner ear malformation (malformed cochlea/vestibular apparatus); CHL (at least 55%)	**Downward-slanting palpebral fissures, hypoplasia of zygomatic complex/mandible, lower eyelid coloboma, micrognathia, macrostomia, cleft palate**

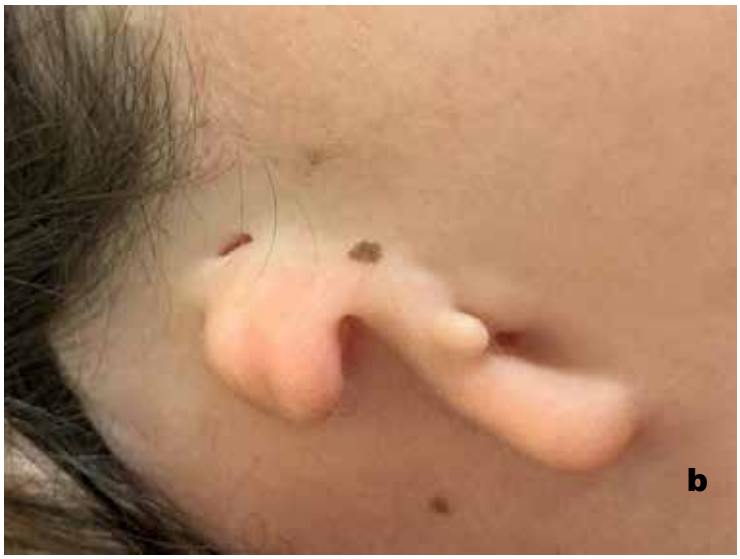
Table 2: A characteristic auricular shape or other associated findings can be the key to a particular genetic diagnosis. The distinctive features are in bold in Table 2:

Modified from Cox TC et al., 2014 (3)

HL: hearing loss; CHL: conductive hearing loss; SNHL: sensorineural hearing loss

Figure 1 a, b, c, d: This child with Cat-Eye syndrome has bilateral microtia (a, b) with a preauricular fistula on the upper right ear (b). There is a skin tag on the right cheek (c) and coloboma of the left iris (d).

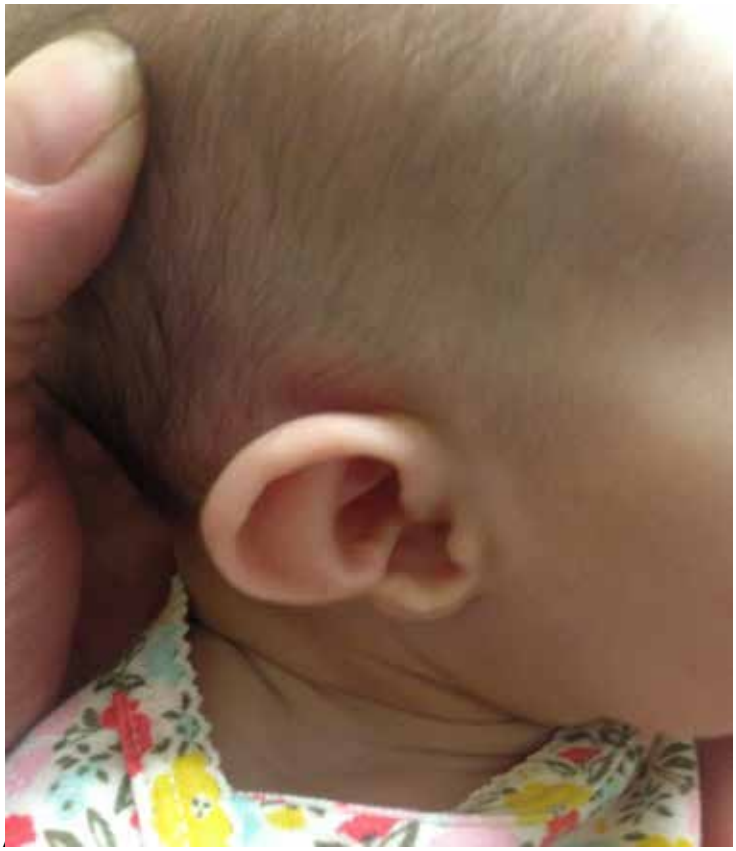




QUIZ

Match the lettered photos of ear anomalies with the numbered syndromes. Use hints provided in Table 2. The answer key is below the author boxes.

A:



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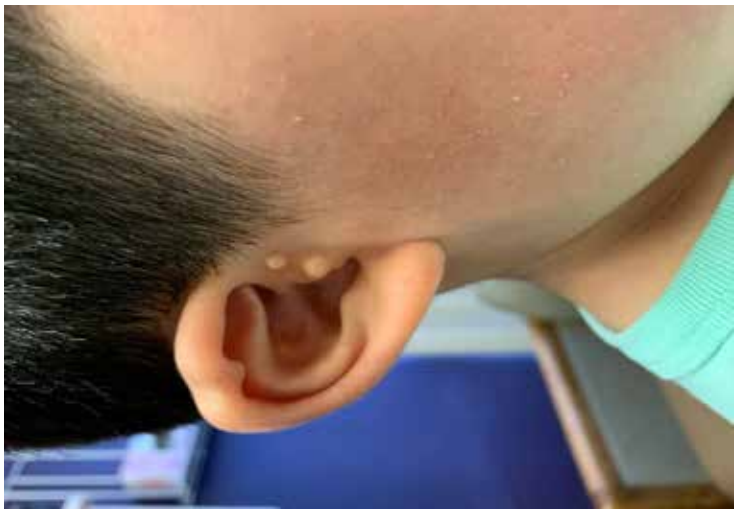
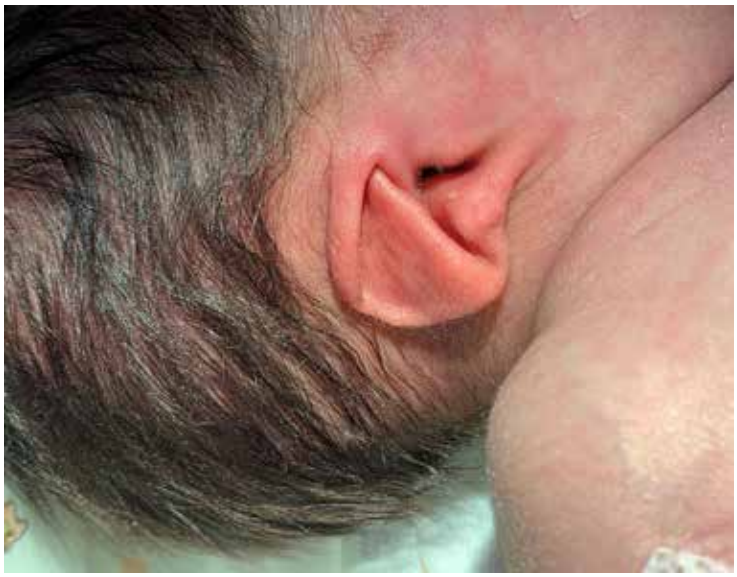


C:



D:

1. Treacher-Collins syndrome
2. Auriculocondular dysplasia
3. Beckwith-Wiedemann syndrome
4. CHARGE syndrome

Reference:

1. *OMIM #115479: Cat-Eye-syndrome*
2. *Bartel-Friedrich S. Congenital Auricular Malformations: Description of Anomalies and Syndromes. Facial Plast Surg. 2015 Dec;31(6):567-80. doi: 10.1055/s-0035-1568139. Epub 2015 Dec 14. PMID: 2666763*
3. *Cox TC, Camci ED, Vora S, Luquetti DV, Turner EE. The genetics of auricular development and malformation: new findings in model systems driving future directions for microtia research. Eur J Med Genet. 2014 Aug;57(8):394-401. doi: 10.1016/j.ejmg.2014.05.003. Epub 2014 May 29. PMID: 24880027; PMCID: PMC4143470.*

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ANSWER KEY FOR THE MICROTIA QUIZ:

A-2 Auriculocondylar dysplasia

B-3 Beckwith-Wiedemann syndrome

C-4 CHARGE syndrome

D-1 Treacher-Collins syndrome