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Association of ear and eye findings

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ASSOCIATION OF EAR AND EYE FINDINGS

by

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DEDICATION

I would like to dedicate this work to my father, Hatem Mustafa, who encouraged me to complete my work and studies even when he was in the hospital because he wanted me to pursue my goals despite the obstacles faced.

ACKNOWLEDGMENTS

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ABSTRACT

The ear and eye are both special sensory organs that are derived from the neural ectoderm and develop closely together during the fourth week of embryogenesis. The structure of these organs is related to their functions and therefore each of the components must be able to effectively operate in order to function efficiently. The role of genetic and environmental factors that affect the development of both the ear and eye have been identified and studied, which allows researchers to better understand the association of the ear and eye. Currently, there are syndromes (such as Goldenhar and CHARGE) that are known to affect both systems concurrently. However, there is a possibility that there are more undiscovered syndromes that also affect the ear and eye simultaneously, where there are still unexplored associations between various eye and ear disorders. Identifying and understanding these syndromes allows clinicians to better diagnose and treat patients who originally present with one or the other disorder and have not been further tested. The ear and eye have also been associated with the central nervous system, where disorders in the systems might indicate neurodevelopment or neurological issues because of abnormalities in the development of their common origin.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AVs .... Active Zones

BL .... Blindness

CHD7 .... Chromodomain Helicase DNA-binding protein 7

CHL.. Conductive Hearing Loss

iGluR.. Ionotropic Glutamate Receptors,

MHL.. Mixed Hearing Loss

MPAS.. Minor Physical Anomalies

NDP.. Norrie Disease Pseudoglioma

OAVS... Oculo-Auriculo-Vertebral Dysplasia

POM.. Periocular Mesenchyme

RPE .... Retinal Pigment Epithelium

SE.. Surface Ectoderm.

SNHL .... Sensorineural Hearing Loss

SVI .... Severe Visual Impairment

SVs.. Synaptic Vesicles

TGFβ.. Transforming Growth Factor Beta

UNHS.. Universal Newborn Hearing Screening

USH.. Usher Syndrome

WHO .... World Health Organization

INTRODUCTION

In the first part of this thesis, ear and eye findings will be explored, including congenital development and the various factors that may cause prevalent ear or eye disorders. Next, currently established relationships of ear and eye disorders, such as conditions that involve both systems, will be assessed from the data in the literature. In the following introduction, the relationship between structure and function in the ear and eye organs, the embryological relationship between the derivation of these two organs and the clinical relevance of ear and eye disorders will be detailed.

The Relationship Between Structure and Function in the Ear and Eye

Both the ear and the eye are special sense organs that use sensory receptors to convey information regarding the external environment to the central nervous system (Mescher. 2018). Figure 1 (Steinberg, 2019) illustrates the anatomy of the ear and the structures of its three main compartments; the external ear is comprised of the auricle and external ear canal, the middle ear is comprised of the auditory ossicles and eustachian tube, and the inner ear is comprised of the vestibular apparatus, cochlea, and vestibulocochlear nerve. For the ear to efficiently function for sound perception, every compartment of the ear must be able to effectively operate. The external ear collects and amplifies sounds that are transmitted to the middle ear, which transforms the sound vibrations into mechanical waves that the internal ear can process into electrical nerve impulses that are transmitted to the brain via the auditory nerve (Bickley, 2017).

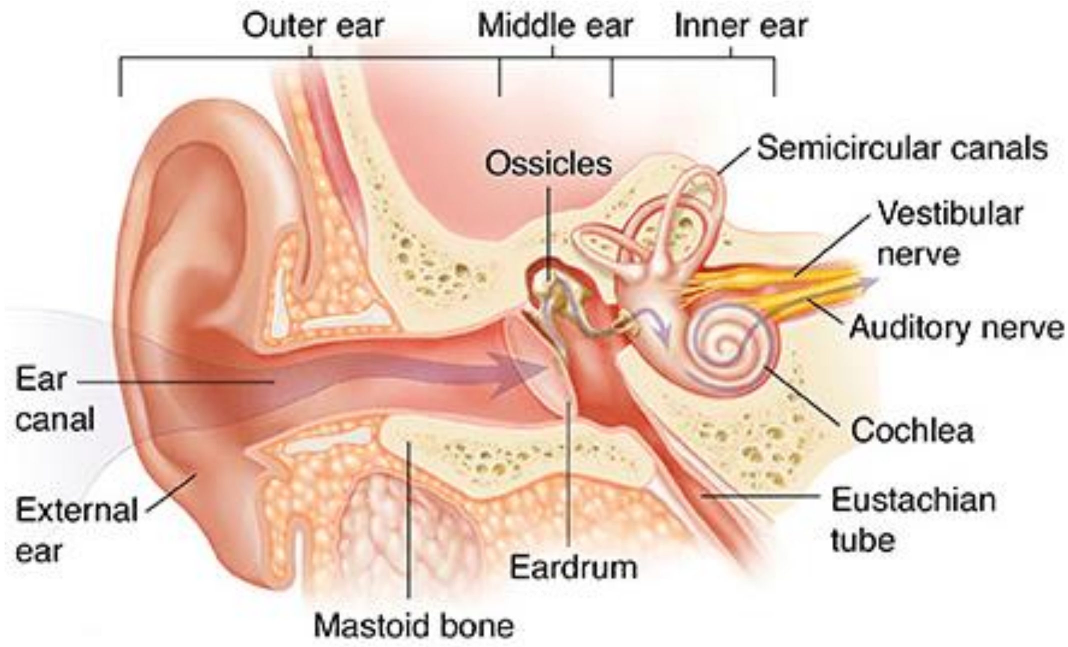

Figure 1: Anatomy of the Ear (Steinberg, 2019)

Similarly, each layer of the eye must effectively operate for efficient visual perception. Figure 2 illustrates the anatomy of the eye and the layers it comprises of. The external layer comprises of the sclera which protects the delicate structure of the eye and the cornea which refracts incoming light; the middle layer comprises of the choroid which blocks the entrance of light into any part of the eye other than the pupil, the ciliary body which allows for visual accommodation that changes the shape of the lens which affects the focus of light on the retina, and the iris which regulates the amount of light that is exposed to the retina; the inner layer of the eye (the retina) comprises of the pigmented layer (which has several functions including absorbing extraneous light passed through the retina to prevent reflection and removing free radicals) and the neural retina which detects and processes the incoming rays of light into nerve signals that are then transmitted to the brain via the optic nerve (Mescher. 2018).

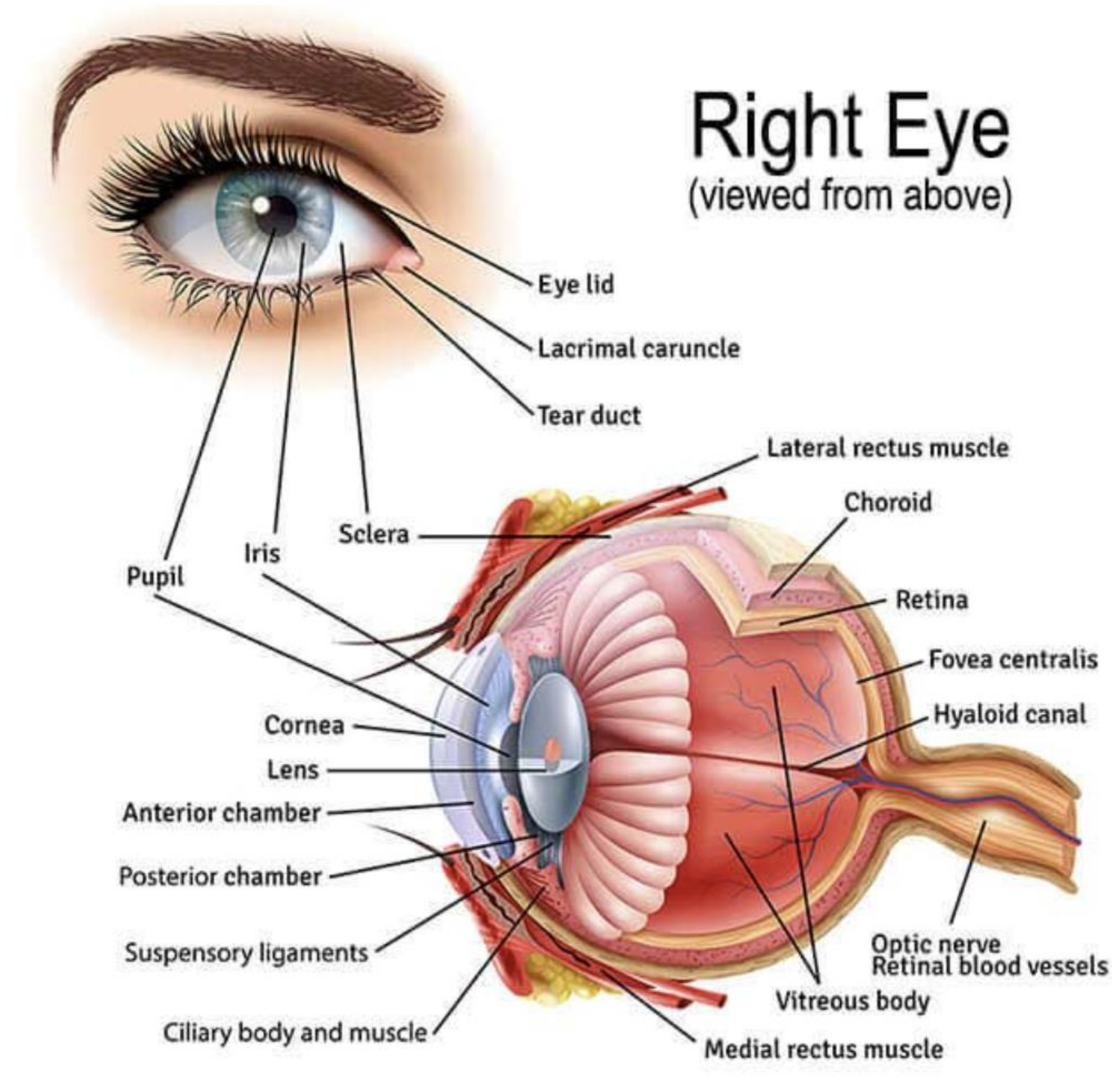

Figure 2: Anatomy of the Eye (Glacial Multimedia, 2020)

The Embryological Development of the Ear and Eye

Previous research suggests that neural crest cells (migratory multipotent cells) and cranial placodes (specialized regions of ectoderm) both help with the development of the ear and eye. During midgestation of the embryo, mesenchyme that is derived from neural crest cells will accumulate at symmetrical and bilateral locations and the mesenchyme at some of these sites will contribute to the development of sensory organs such as the eyes and ears; more specifically, the choroidal cells, cornea, scleral, middle ear bones and epithelia, and inner ear. Neural crest cells also generate Schwann cells, melanocytes, and even in some cases, vascular cells (LaMantia, 2020; Theveneau & Mayor, 2014).
The cranial placodes give rise to the three sensory placodes (the olfactory, lens, and otic placodes), which differentiate and also help contribute to the development of the special sense organs such as the ear, eye, nose, and lateral line (Basch et al., 2016; Scholsser, 2006). Developing next to the future retina, the lens placode generates the eye's crystalline lens, which is composed of both lens epithelial cells and lens fibre cells. The entire inner ear (endolymphatic duct, cochlea, and semicircular canals) is derived from the otic placode; as well as the sensory hair cells, innervating neurons, and all the supporting and endolymph secreting cells (Streit, 2008).

During the fourth week of embryological development, the branchial arch system (which is composed of six paired branchial arches that each have an inner mesodermal core that is surrounded by neural-crest-derived mesenchyme that is internally lined with a layer of pharyngeal endoderm and externally lined with a layer of ectoderm) is formed and thus, the development of both the ear and eye begin. As illustrated in Figure 3, the internal ear develops from surface ectoderm during week four, while the middle and external ear's development is interconnected as they later develop from pharyngeal arches 1 & 2, the pharyngeal groove, pharyngeal pouch 1, and the pharyngeal membrane.

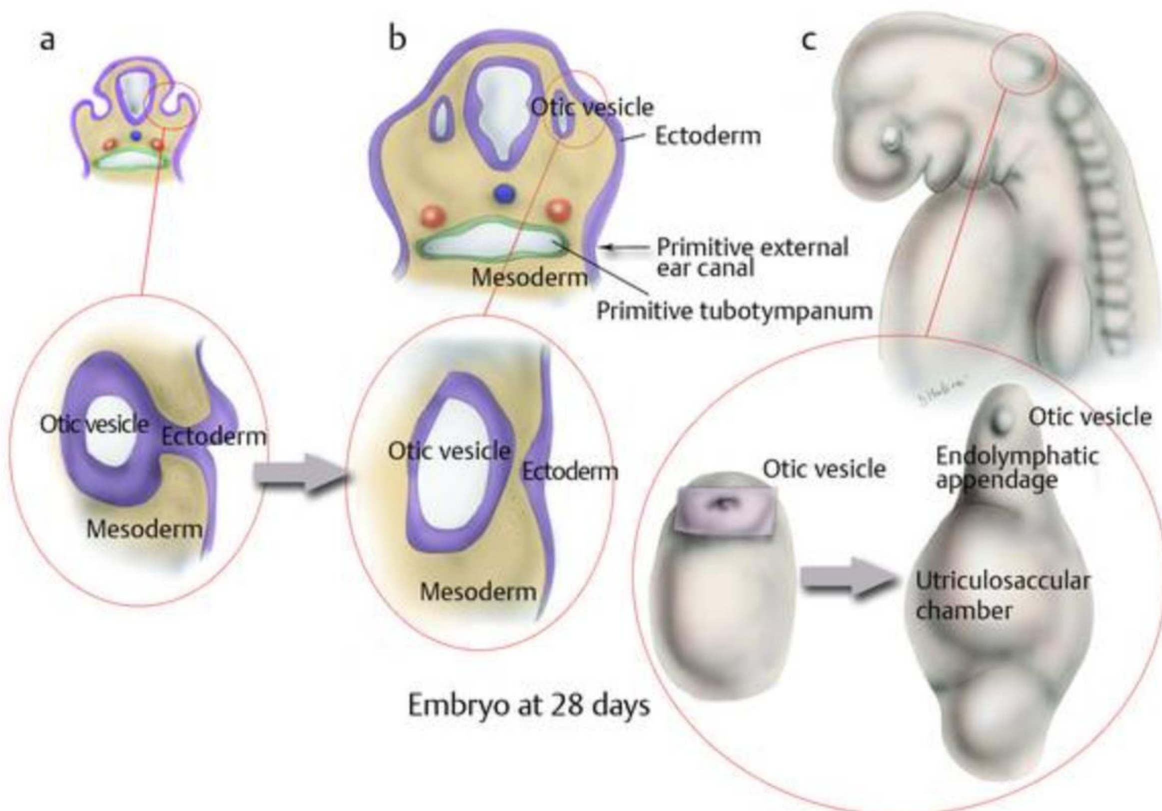

Figure 3: Embryological Development of the Ear (Thieme, 2016)

The eye begins to develop during week four, at day 22, when the forebrain region's neural plate begins to fold and forms a closed neural tube. During week four, at day 28, a two layered optic cup of neuroectoderm forms and soon after, the mesenchyme starts to surround the optic cup and forms the choroid (a vascular tunic developed from mesenchyme directly around the optic cup) and the sclera (a fibrous tunic formed from the outermost mesenchyme) (Dudek & Harrel, 2019). The ear and the eye have a strong likelihood of affecting one another due to the common origin and close development; meaning that an abnormality occurring during the development of the ear could indicate a possible abnormality during the development of the eye.

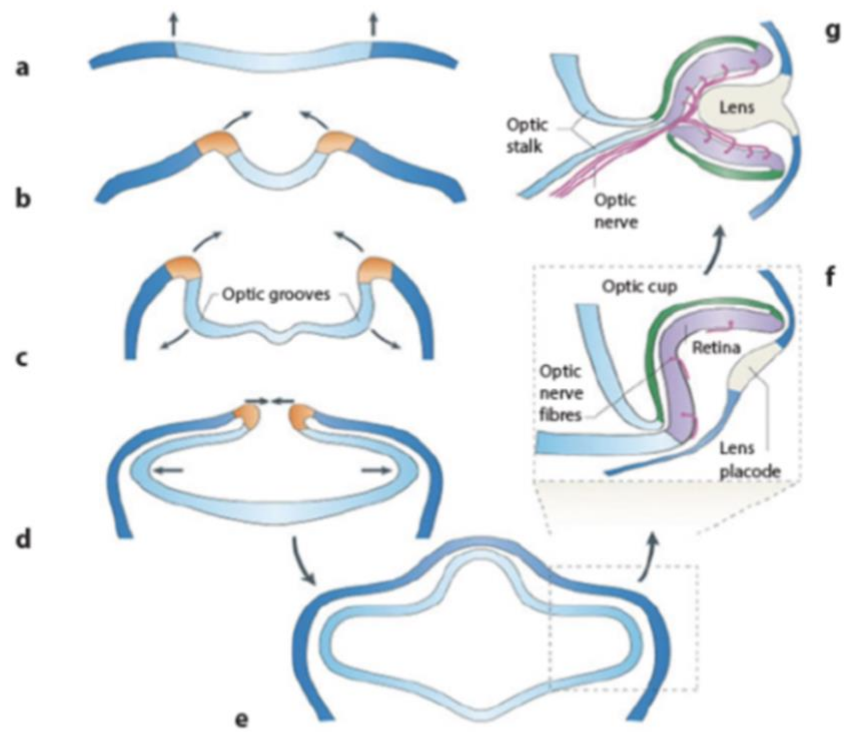

Figure 4: Embryological Development of the Eye (Cook, 2015)

The Significance of Ear and Eye disorders

One of the most prevalent chronic conditions in children is congenital hearing loss, which occurs when the ear is unable to transmit electrical nerve impulses to the brain. An audiogram is used to identify where the transmission of signal is hindered and categorizes the hearing loss into three main groups. Sensorineural Hearing Loss (SNHL) indicates dysfunction of the transmission between the inner ear and brain, Conductive Hearing Loss (CHL) indicates dysfunction of the transmission between the external ear and middle ear, and Mixed Hearing Loss (MHL) is a combination of both SNHL and CHL (Korver et al., 2018). Hearing loss is also classified by severity, which is based on decibel (dB) hearing levels. The World Health Organization's (WHO) classification for hearing impairment was first created in 1986 but was revised in 2008 because the original thresholds of normal hearing placed did not agree with the functional experience of people with mild hearing impairment and the original classification did not include people with unilateral hearing loss at any severity, nor people who suffered with mild bilateral hearing loss. Table 1 shows WHO's newly revised classification and grading of hearing impairment (Olusanya, 2019).

Grade of impairment	**Corresponding audiometric ISO value**	**Performance**	**Recommendations**	**Comments added to the previous classification**
0: no impairment	25 dB or better	No or very slight hearing	None	20 dB also recommended.

		problems. Able to hear whispers		People with 15 – 20 dB levels may experience hearing problems. People with unilateral hearing losses may experience hearing problems even if better ear normal
1: slight impairment	26–40 dB	Able to hear and repeat words spoken in normal voice at 1 m	Counselling. Hearing aids may be needed	Some difficulty in hearing but can usually hear normal level of conversation
2: moderate impairment	41–60 dB	Able to hear and repeat words using raised voice at 1 m	Hearing aids usually recommended	None
3: severe impairment	61–80 dB	Able to hear some words	Hearing aids needed. If no	Discrepancies between pure-tone

		when shouted into better ear	hearing aids available, lip-reading should be taught	thresholds and speech discrimination score should be noted
4: profound impairment including deafness	81 dB or greater	Unable to hear and understand even a shouted voice	Hearing aids may help in understanding words. Additional rehabilitation needed. Lip-reading and sometimes signing essential	Spoken speech distorted, the degree depending on the age at which hearing was lost

Table 1: WHO's Grades of hearing impairment (Olusanya, 2019)

Studies have shown that at least 1:1000 or 2:1000 children at birth are affected with permanent hearing loss which severely impacts their development (Voss et al., 2019). Vision is an important sense for deaf people to communicate, as it has been shown that the development of communication and cognitive skills in patients with both vision and hearing loss was negatively impacted (Ostadimoghaddam et al., 2015). 14 million children in the world are estimated to be blind. Blind (BL) children are more likely to have delayed or disordered development, be hospitalized, and die young compared to non-BL children. Visual Impairment (VI) Classification is also important to note, as previous studies have shown that a majority of BL children will have other non-ophthalmic impairments or disorders, but it is unknown whether the same can be said about children with moderate VI. The international classification for Disease definition of visual impairment, coined by the WHO, is shown in table 2 (Solebo et al., 2017).

Category of impairment	
Mild or no VI	Vision better than or equal to 0.48 logMAR (6/18 Snellen)
Moderate VI	Vision worse than 0.48, but equal to or better than 1.0 (6/60 Snellen)
SVI	Vision worse than 1.0, but equal to or better than 1.3 (3/60 Snellen)
BL	Vision worse than 1.3

Table 2: WHO International Classification for Disease classification of visual impairment (VI), severe visual impairment (SVI) and blindness (BL)

(Solebo et al., 2017)

In the following thesis, the association between ear and eye disorders will be explored, as well as the various factors on the congenital development of the ear and eye and the effects these disorders can have.

Specific Aims

Specific aims of the following thesis include:

1. Comprehensive review of the literature to characterize the association between congenital development of the ear and eye and how various factors can impact the development and cause eye and ear disorders.
2. Investigation of established relationships between ear and eye disorders based on currently known disorders that have been identified to affect both the ear and eye.
3. Exploration of potential associations between ear and eye disorders that have not yet been established.

Ear and Eye Malformations

It is important to understand the wide range of ear and eye abnormalities presented in order to better identify and diagnose the affected patients. Ear malformations may occur congenitally or be acquired, and they can be broadly classified as external ear abnormalities, middle ear abnormalities, or inner ear abnormalities. External ear abnormalities refer to malformations of the auricle and/or external ear canal. Malformations of the auricle can affect its size, orientation, relief pattern, and position. Microtia is an example of a malformation of an auricle that is smaller and underdeveloped, there are different grades of microtia depending on the severity of the malformation and how underdeveloped the auricle is (Zhang, 2019). In some cases, there is a complete absence of the auricle (which is known as anotia) and that may occur with a more narrowed or missing ear canal. In extreme cases, the external auditory canal can be absent or underdeveloped, which typically referred to as aplasia or hypoplasia. Other malformations of the external ear are ear tags, ear pits, and ear sinus that are found anterior to the auricle. Middle ear abnormalities include any malformation of the size and configuration of the middle ear space as well as the configuration, size, and number of ossicles. Abnormalities affecting the development and structure of the oval or round window are also considered middle ear abnormalities. Inner ear abnormalities may include hypoplasia, aplasia, or other malformations of the sensory patches and labyrinth as well as enlarged or narrowed vestibular aqueducts. Inner ear abnormalities also often include reduced numbers of vestibular ganglion cells (which innervate the vestibular hair cells), displaced arteries and nerves, and a malformed internal auditory canal.

The eye, ocular adnexa (which is composed of the eyelids, lacrimal apparatus, conjunctiva, and orbital soft tissue), and orbit may also be malformed congenitally and can cause severely impaired vision or simply only have a cosmetic significance (Guercio & Martyn, 2007). Similar to the ear, any part or layer of the eye may be congenitally malformed. Anopthalmia (which is the absence of one or both of the eyes), Microphthalmia (which is when one or both eyes are abnormally small), and coloboma (which is when there is a hole in the iris, optic disc, retina, or choroid due to the fissure failing to close) are the most common congenital eye malformations (Bovolenta & Martinez-Morales, 2019). Other common congenital eye malformations include aniridia (which is when the iris is absent or partially developed), optic nerve hypoplasia (which is when the optic nerve is underdeveloped), congenital aphakia (which is when the lens is absent), and congenital cataracts (Ludwig et al., 2021).

Malformations of both the ear and eye can show up in various ways, as any grouping of ear or eye malformations can occur simultaneously. However, certain subsets of coexisting ear/eye malformation groupings are more likely to occur than others because of their origin, morphology, and genetic alterations. Although the exact causes of eye and ear malformations are not clearly understood yet, some causes are speculated to include genetic and environmental factors. Environmental factors can include insufficient blood supply to the eye or ear during fetal development, exposure to toxins or medications (especially teratogen exposure), and viral infections. Genetic factors of ear and eye malformations include single-gene defects, growth factors, secretion factors, transcription factors, cell adhesion proteins, receptors, and other ligands or molecules

(Bartel-Friedrich, 2008; Boyadjiev Boyd, 2020; Rosa et al., 2011). Understanding the various causes of ear and eye malformations allows researchers to consider the various factors and the other possible consequences that may also occur in the affected patients.

Chromodomain Helicase DNA-binding protein 7 (CHD7) gene

Neural crest cell differentiation, specification, and migration has been found to be controlled by the Chromodomain Helicase DNA-binding protein 7 (CHD7) gene through its effect on guidance and transcription factors. The CHD7 gene functions at specific stages of neural crest development, it activates the transcriptional network that is required for neural crest specification and migration. Loss of function mutations of the CHD7 gene (which affect neural crest development) have been identified as one cause of CHARGE and Kabuki syndromes, which both include coexisting abnormal or hindered development of the eye and ear systems (Pauli, 2017). The CHD7 gene can also affect ear and eye development because it has been studied to cooperate with the polybromo- and BRG1- associated factors of an ATP-dependent chromatin remodeling complex called BAF/PBAF that controls gene expression that is important for the development of neural crest cells. The apoptosis signal regulating kinase 1 and inhibitor p21 is suppressed by BRG1, which inhibits apoptosis and promotes the proliferation of neural crest cells, respectively (Butcher et. al, 2017; Pauli, 2017). Although the syndromes CHARGE and Kabuki do not exclusively affect the ear and eye systems, understanding some of the genetic causes and identifying the role of the CHD7 gene in the ear and eye systems' development is essential for researchers to understand and identify syndromes with clinical overlaps such as ear and eye disorders. Therefore, identifying any mutations or loss of function of the CHD7 gene is important, as it would allow researchers to know if there might be consequential coexisting ear and eye abnormalities that they should look for when assessing a patient.

PAX genes

The Pax gene family, most of which have a paired box DNA-binding domain that is highly conserved, has been shown to be essential for controlling embryonic development and encoding transcription factors. Mutations in the Pax6, Pax 3, and Pax 1 genes have been studied to result in eye, nose, muscular, nervous system, and skeletal abnormalities (Heanue, et. al., 2002). In specific regions during embryogenesis, the mesoderm inducts the neuroectoderm and creates subdivisions of the brain. The neural tube is subdivided and differentiated into six different divisions: metencephalon, telencephalon, spinal cord, diencephalon, myelencephalon, and the mesencephalon. These subdivisions have varying functions, composition, morphologies, and are only possible because of the pattern of Pax genes that are expressed during development which allow for cell differentiation and specification (Chalepakis, et.al., 1993; Wang, et. al., 2008). Figure 5 shows the spacial limitations of the Pax genes expression of the embryonic central nervous system during midgestation, where the olfactory epithelium (oe), telencephalon (t), diencephalon (d), Posterior commissure (PC), pons (pn), Rhombencephalic Isthmus (RI), Cerebellum (cb), Spinal cord (sc), myelencephalon (my), and mesencephalon (ms) locations are marked to better illustrate the pax genes specialized for their respective areas (Chalepakis, et.al., 1993) The PAX2 gene is expressed in the rhombencephalic isthmus, where the otic vesicle is derived from, and has been studied to play a role in allowing the parts of the inner ear (cochlea, vestibula, and endolymphatic duct) to specialize, differentiate, and develop from the otic vesicle. Expression of PAX6 genes has also been studied in the diencephalon, where the optic vesicle is derived from, and have been shown to play a role in the differentiation and specification of the vesicle of the eye, optic stalk, lens, and retina **(**Hanson, 2008)

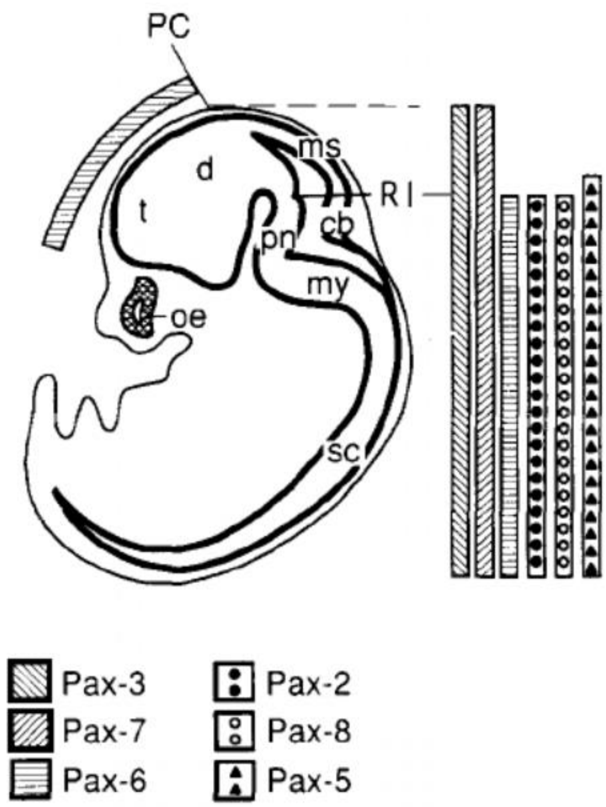

Figure 5: Longitudinal plane of the developing neural tube illustrating the expression spacial expression limits of the Pax genes (Chalepakis, et.al., 1993)

Norrin and Frizzled-4 Ligand Receptor Pair

Mutations of the Norrie Disease Pseudoglioma (NDP) gene were identified as the cause of Norrie disease, an x-linked congenital retinal dysplasia that presents with blindness at birth and is usually accompanied with sensorineural deafness or hearing loss. The NDP gene encodes the small protein product, Norrin, with a cysteine-knot motif (Braunger et.al., 2012). The Norrin protein is able to bind to the frizzled-4 (Fz4) protein receptor and although it is unrelated to Wnt, it activates the Wnt/ β-catenin signaling cascade which is essential for the retinal cellular specialization and the vascularization of both the retina and inner ear. Figure 6 illustrates the Wnt/ β-catenin signaling cascade in cells, where the proteins' complex degrades β-catenin when the cascade is off. When the cascade is on, the DVL protein binds to the FZD receptor and the phosphorylated Lipoprotein related receptor protein associates with Axin through the DVL's DIX domain and causes the complex of proteins to dissociate; this allows β-catenin to stabilized, bind to the TCF (T cell factor), and upregulate the target genes in the nucleus (Nusse, et. al., 2017). Norrin and Fz4 have been studied and were concluded to operate as ligand/receptor pairs because they were found to have a high specificity and affinity for each other, have had their single mutations that occurred in one protein or the other yield similar vascular phenotypes, studies showed that Norrin induced the activation of the Wnt's Fz4/Lrp dependent pathway with high efficiency, and Norrin's function was observed to be similar to Wnt's function as they both required a Fz and Lrp receptor, binded to the Fz protein's cysteine rich domain with high affinity, and had similar affinities to the ECM (extracellular matrix) which also imposed similar constraints to their range of action (Xu, et al., 2004).

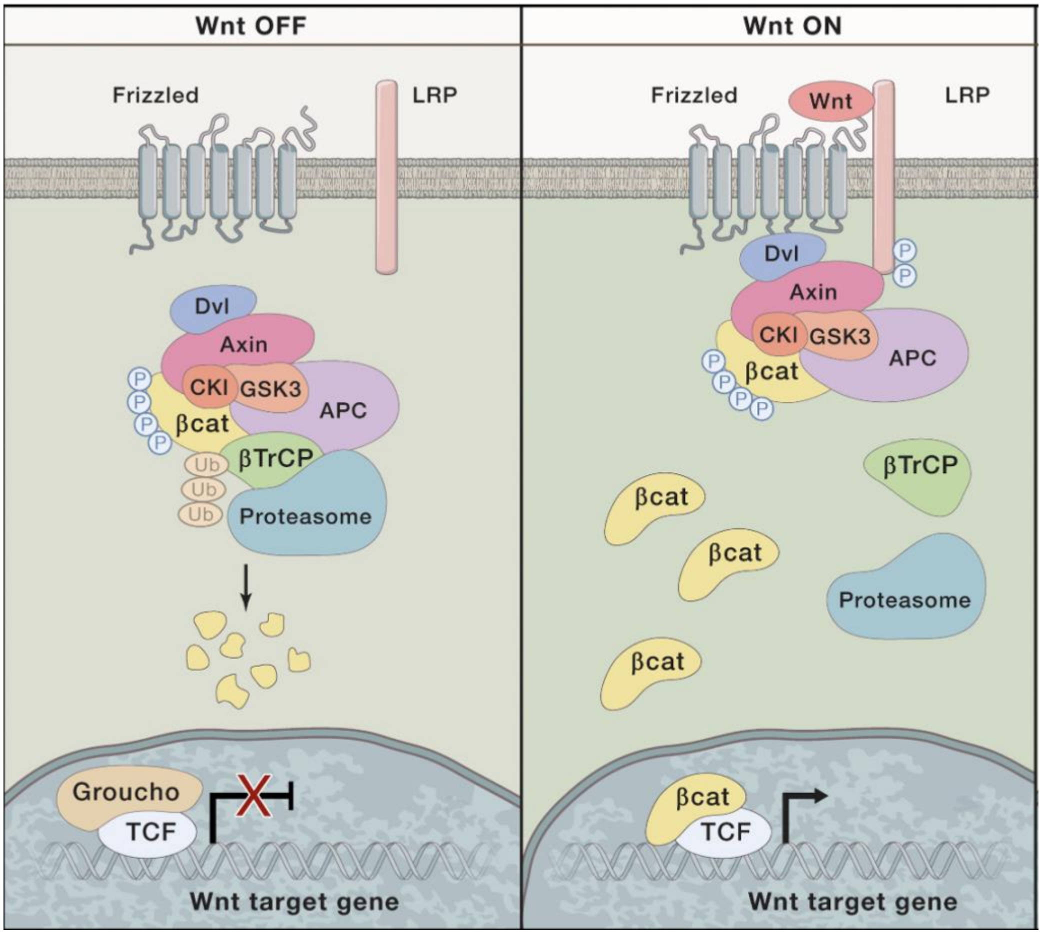

Figure 6: Wnt/ β-catenin signaling cascade found in cells. The left illustrates the signaling cascade when it is off while the right shows the cascade and it's effect when it is on. (Nusse, et. al., 2017)

The development of the early lens and retinal pigment epithelium (RPE) resulting from the WNT/ β-catenin signaling cascade is illustrated in figures 7 and 8, respectively. In figure 7, the transforming growth factor beta (TGFβ) is secreted by the POM (periocular mesenchyme) and signals the non-lens SE (surface ectoderm). The lens fate is suppressed by repressing the Pax6 gene when activating the WNT/ β-catenin signaling cascade by the induction of WNT2b through the secretion of TGFβ. On the right of figure 7, the lens development can be seen to be initiated when the Pax6 gene inihibits the WNT/ β-catenin in the lens placode. In figure 8, the WNT/ β-catenin signaling cascade in the retinal pigment epithelium is activated when WNTs are secreted by the SE; this causes the Otx2 and Mitf genes to be induced and cooperate with the Pax6 gene to control the development of the RPE **(**Fujimura, 2016).

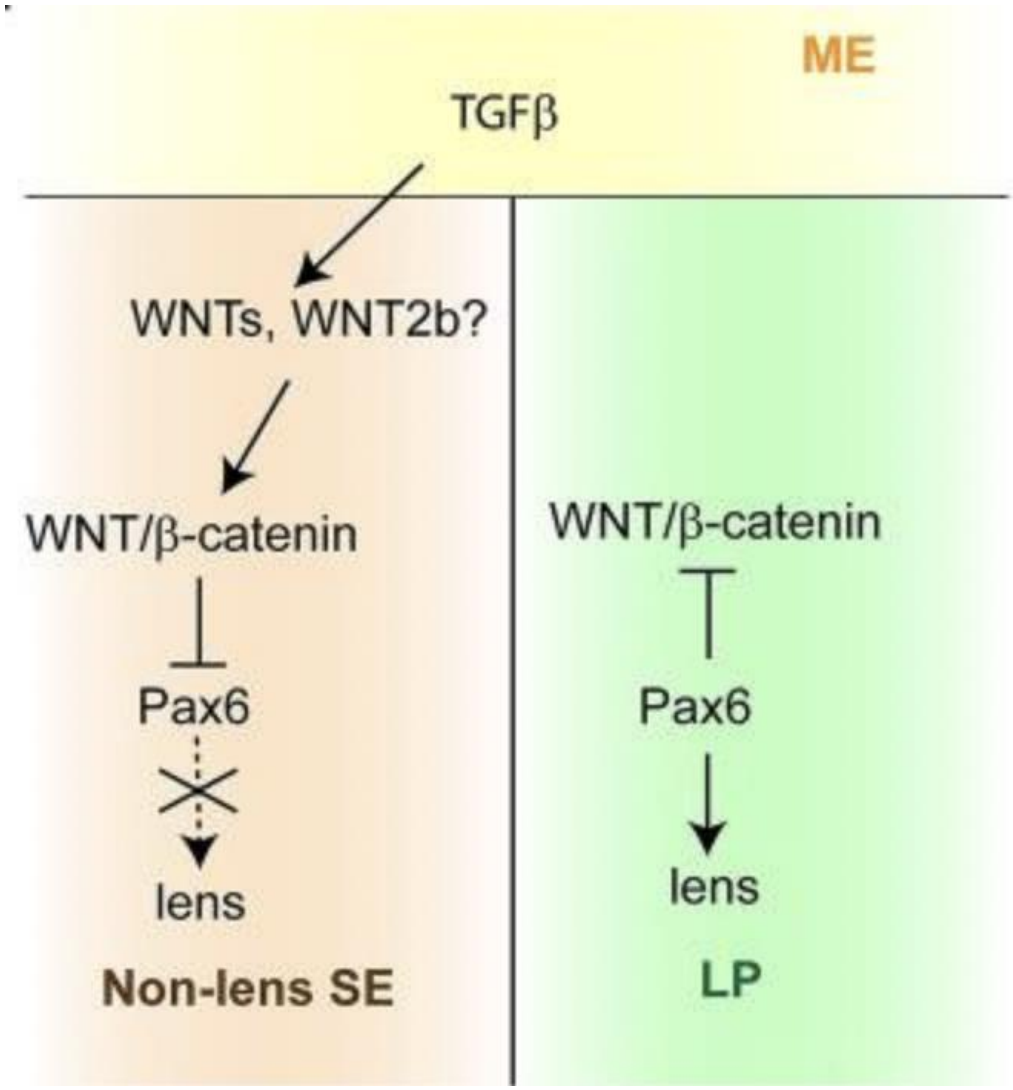

Figure 7: The development of the early lens resulting from the WNT/ β-catenin signaling cascade **(**Fujimura, 2016).

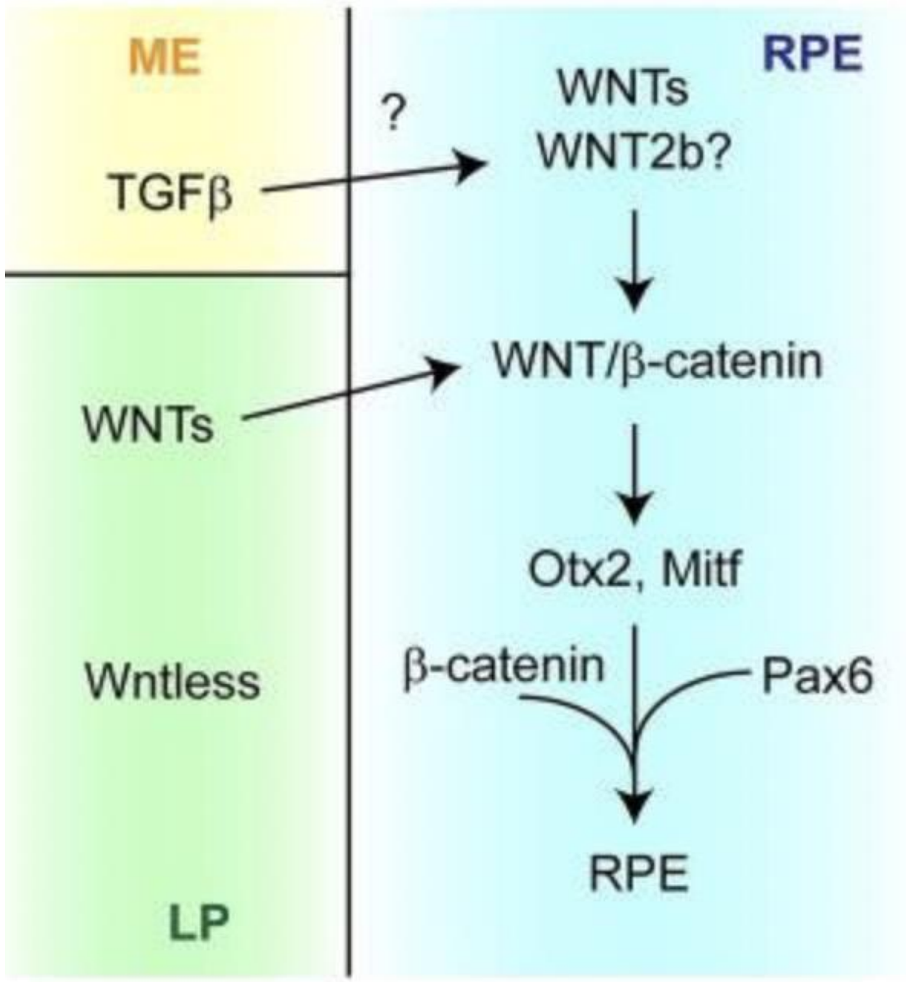

Figure 8: The development of the retinal pigment epithelium (RPE) resulting from the WNT/ β-catenin signaling cascade **(**Fujimura, 2016).

Although neither the WNT/ β-catenin signaling cascade nor Fz4 have been identified as a required protein for the initial development of the inner ear, Fz4 has been noted as a necessary protein for cochlear survival and maintenance. Fz4 was also found to be expressed in the inner hair cells and is speculated to also play a direct role in the survival of the hair cells (Xu, et al., 2004).

Mutation in the Human Homeobox Gene NKX5-3

In Switzerland, three out of fourteen siblings were born with ophthalmic abnormalities (such as rod-cone dystrophies, microphthalmia, cataracts, retinal pigment epithelium abnormalities, and colobomas) and cleft ear lobules. Figure 9 illustrates the macular hypoplasia, retinal dysplasia, and coloboma seen in of the siblings while figure 10 shows the external ear abnormality auricular deformation that was seen in all three of the patients. A mutation screening and linkage analysis showed that the NKX5-3 gene's first exon had a homozygous deletion of 26 nucleotides in all three of the siblings. This analysis, as well as a knockout study conducted on the gene, showed that is a new and previously unestablished oculo-auricular syndrome. Expression of the NKX5-3 gene, which is also known as the HMXI transcription factor, has been studied in both the ear and eye. Normally, the NKX5-3 gene represses EPHA3, which targets retinal axons in the lateral part of the geniculate nucleus. However, when the NKX5-3 gene is mutated or deleted, it is unable to inhibit EPHA3 and thus the polarity of the retina is further modified and generates the ophthalmic abnormalities seen in the patents. The gene expression of NKX5-3 has also been observed as the ear is differentiated and derived into the external ear and mutations in the NKX5-3 yielded abnormalities in only the external ear compartment of the ear (the middle and inner ear were observed to have no abnormalities despite the NKX5-3 loss of function) (Schorderet, et. al., 2008).

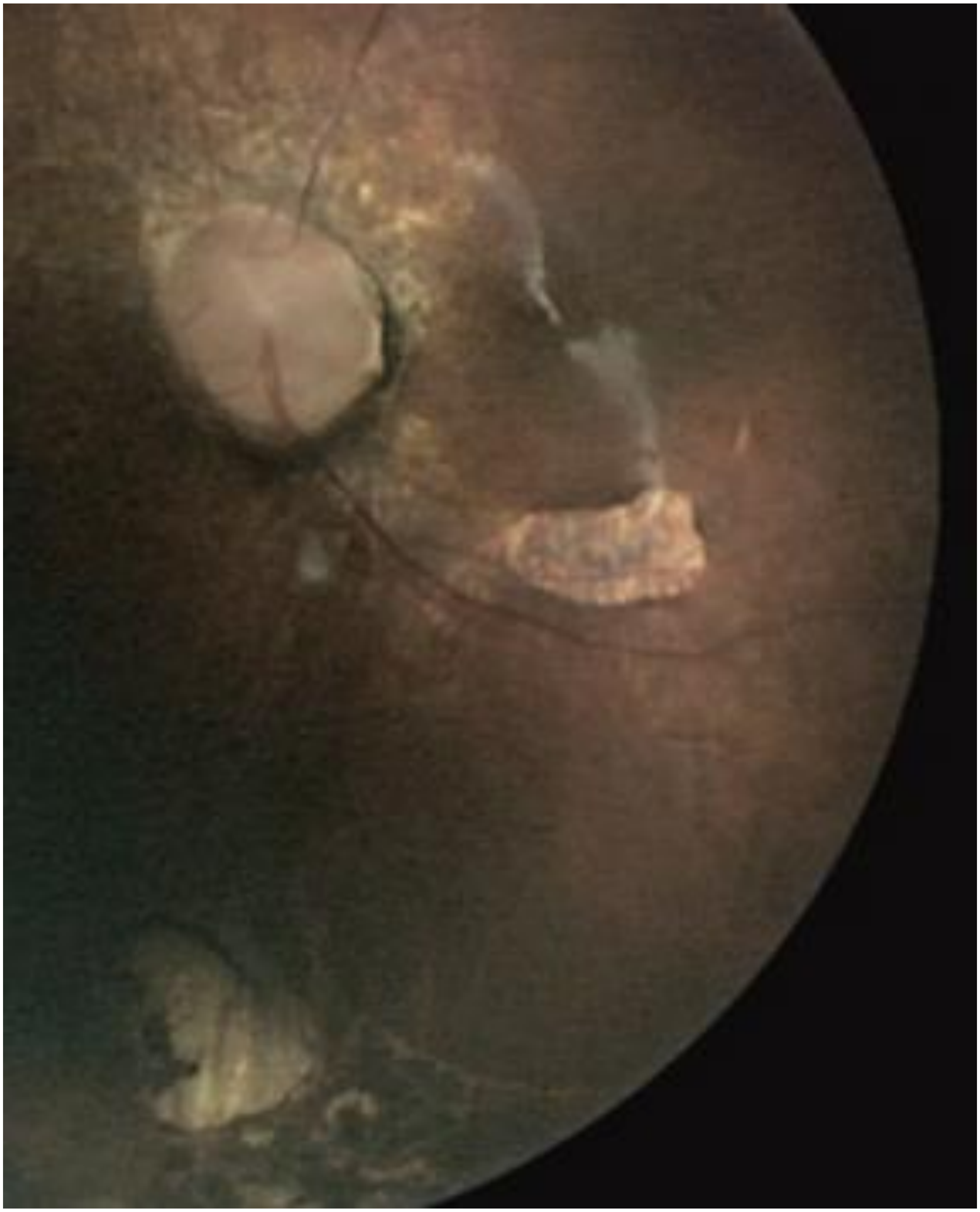

Figure 9: The characteristic macular hypoplasia, retinal dysplasia, and coloboma seen by Fundus photography (Schorderet, et. al., 2008).

Figure 10: Characteristic external ear auricular abnormality of the new oculo-auricular syndrome (Schorderet, et. al., 2008).

Gestational folic acid deficiency

Folic acid (also referred to as vitamin B9 or folate) has been observed to be essential for the development of the eye during embryogenesis. Taking folate acid during pregnancy is encouraged to decrease the risk of neural tube defects occurring during development. In the study conducted by Sijilmassi, the embryos from mothers who had a folic acid deficient diet during the first two weeks of gestation (D2) and before pregnancy by six weeks and 2 weeks after pregnancy (D8) were studied and compared among embryos from mothers who did not have a folic acid deficient diet. In figure 11A, microphthalmia is not observed in the control group where the mother did not have a folic acid deficient diet. However, figure 11B showed microphthalmia in at least one eye, which was seen in 42% of the D2 group. Figure 11C illustrates observed microphthalmia in both eyes, ocular interactions (as the eye was rotated and the lens was absent), and nervous system abnormalities in 68.4% of the D8 group that had the longest folic deficient diet (Sijilmassi, et. al, 2021).

Figure 11: Comparison of head overview to document eye microphthalmia over the groups (Sijilmassi, et. al, 2021).

For the ear, folic acid has been observed to protect the elevated hearing threshold as well as prevent the reduction in the density of the vessel by reducing the deposition of the abundance of collagen and oxidative stress experienced in the inner ear. Folate is one of the strongest medication determinants of the level of Hcy in plasma, which is helpful to get rid of because Hcy is significantly associated with poor hearing (Kundu,, et. al, 2012).

Ush1c gene

Mutations in the Ush1c gene has been studied and observed as the cause of Usher syndrome (USH), which is one of the most common causes of deaf and blindness. There are varying levels of severity (USH1, USH2, and USH3), which are shown in table 3, but the incidence of the most severe form (USH3) is about 3-6:100,000. The inner ear's hair cells and retina's photoreceptor cells have a macromolecular protein network is formed within them from USH gene products as they bind to PDZ domains encoded in the scaffold protein harmonin. The mechanoreceptor hairs in the inner ear had USH1 genes that helped with the specification and differentiation of the hair cells (Reiners, et. al, 2005). The ear was observed to have much higher Ush1c gene expression than the ear did, which implied that the function of the Ush1c gene in the ear might be different than its function in the eye (Tian, et. al, 2010).

	USH1	USH2	USH3
Hearing loss	Severe to profound Congenital Stable	Moderate to severe Congenital Stable	Moderate to severe Progressive
Vestibular function	Altered	Normal	Variable
RP onset	Usually prepubertal	Around puberty or post pubertal	Around puberty or post pubertal
Language	Unintelligible	Intelligible	Intelligible

Table 3: Usher Syndrome clinical features (Tian, et. al, 2010)

Ribbon Synapses in the Retina and the Cochlea

Hair cells and photoreceptors drive receptor potentials at chemical synapses to code any vestibular, visual, and auditory information. For efficient temporal precision and reliability, the transmission of synapses requires both molecular and cellular specializations. AZs, or active zones, are used for synaptic transmission and they are presynaptic plasma membrane regions that are specialized and have electron dense projections that allow the transmitter filled SVs (synaptic vesicles) to tether to them. A ribbon synapse distinctly varies from a conventional synapse because it allows for more SVs to tether to or near the AZ. For ribbon synapses to form, the protein Ribeye must be expressed. So far, ribbon synapses have only been observed in vertebrates. Specifically, ribbons in mammals are found in vestibular hair cells, cone and rod photoreceptors, and cochlear outer and inner hair cells. The main purpose of ribbon synapses is to collect information from the environment and surroundings, which may be difficult to keep up with at times. Therefore, ribbon synapses may use continuous or fast release and efficient synaptic vesicle replenishment mechanisms to keep up with the environment and process information of sounds or images. The outer layer of the retina of the eye contains photoreceptors which use bipolar cells, as seen in figure 12, to send the collected signals to the inner retina for processing. IGluRs, or excitatory ionotropic glutamate receptors, are able to send signals as fast as by a sub millisecond and they are used by postsynaptic HCs (horizontal cells) and OFF bipolar cells. The release signals and sustained release of the stimuli will affect the duration and intensity of the signals collected (Moser, et. al., 2020; Nouvian, et. al., 2006).

Ribbon Synapses in the Retina and the Cochlea

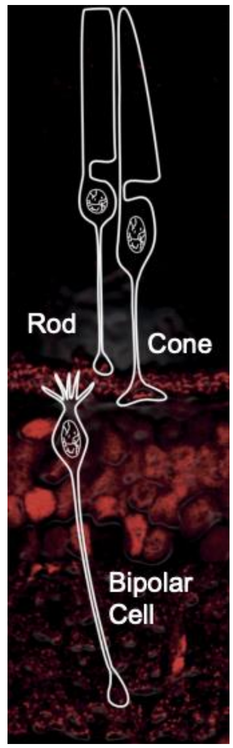

Figure 12: Rod photoreceptors, cone photoreceptors, and bipolar cells forming ribbon synapses in the retina for image processing (Moser, et. al., 2020).

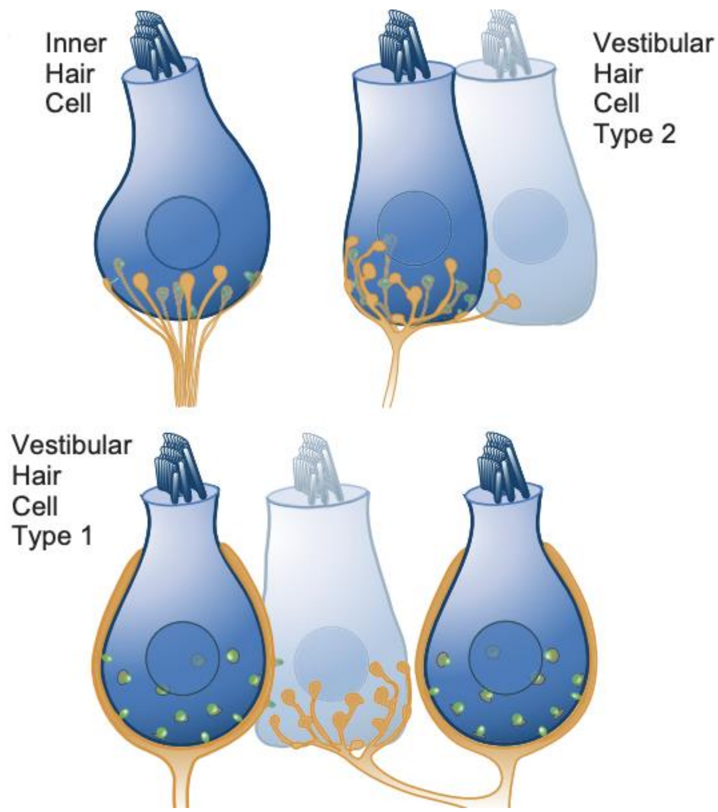

Figure 13: Various synapses formed by hair cells that are found in the inner ear (Moser, et. al., 2020)

Figure 13 illustrates how one synapse (such as the type I vestibular hair cell with multiple AZs) or many synapses with either one or more post synaptic elements (such as the type I vestibular hair cell, cochlea's outer and inner hair cells, avian papilla's tall hair cells, or lower vertebrate hair cells) may be formed by a hair cell. Mammals' hair cells and bipolar spiral ganglion neurons form and share several monosynaptic connections with each other. Glutamate is usually released by hair cells of the inner ear's vestibular and auditory epithelia in response to the graded receptor potential and certain glutamate receptor subtypes, such as GluR2, were discovered to only become expressed around the onset of hearing (Moser, et. al., 2020; Nouvian, et. al., 2006).

Genetic Connections Consistent With Evolution Of Hearing And Seeing

Eyes and ears have been observed to share developmental pathways in killifish medaka when ectopic expression of the Six3 gene resulted in the appearance of an eye or lens in the same area as the otic vesicle. The linkage of syndromes that affect both the eyes and ears, such as usher syndrome which presents with retinal degeneration and deafness, will connect both senses (Piatigorsky, 2003). The eye and ear have the ability to change images and sounds, respectively, into signals that are meaningful and then allow for communication and improved human interactions (Fritzsch, et. al, 2007).

Even in the brain, auditory and visual connections have been established and are consistent with the concept of the marriage of systems. There was observed to be a region in the brain where both visual and auditory signals converged and neurons in the region were able to evoke or create interactions that were multisensory on the level of a single cell in response to auditory or visual cues. In certain species, like barn owls, it is the visual system that trains the auditory system to translate both cues while hunting prey (Piatigorsky, 2003).

Association of Ear and Eye Abnormalities with the Nervous System

Minor Physical Anomalies, or MPAs, are subtle, clinically insignificant, or cosmetic abnormalities of the head, ear, eye, face, mouth, and limbs that occurred from errors during morphogenesis. MPAs indicate altered embryonic development and are useful markers of abnormal brain development because the areas affected have the same origin and derivation of ectodermal tissue as the central nervous system. (Manouilenko, et. al, 2014; Praharaj, et.al., 2012; Weinberg, et. al., 2007). Ear and eye abnormalities have been associated with neurodevelopmental and neurological disorders such as autism, schizophrenia, and bipolar disorder (Do et.al., 2017; Praharaj, et.al., 2012). An increased incidence of external and middle ear diseases and abnormalities was studied in patients with schizophrenia and bipolar disorder (Mason, et. al., 2008; Praharaj, et.al., 2012).

Although some eye abnormalities and visual impairments have been associated with nervous system disorders, it is also important to differentiate between congenital cortical-origin and peripheral-origin blindness to better understand the patterns and effects of comorbidity. Cortical origin blindness is caused by lesions in the occipital cortex while peripheral origin blindness comes from the globe. There has yet to be any cases identified where a patient with congenital cortical blindness has been diagnosed with schizophrenia; this has suggested to researchers that cortical blindness may have a protective effect against schizophrenia, but this does not seem to apply to patients with congenital peripheral blindness. Blindness originating from different structures has different mechanisms which may affect the mechanisms associated with schizophrenia.

For example, cortical congenital blindness is caused by an impaired connection between the areas of the brain but the thalamic and subcortical structures are still intact in cortical congenital blindness; however, the same is not true for peripheral congenital blindness (Morgan, et. al, 2018). Furthermore, many schizophrenia-associated impaired functions (such as auditory attention, auditory perception, language, and memory) are normally heightened in congenitally blind patients and those compensations that are seen in congenitally cortically blind patients (such as cortical reorganization since the brain structures are still intact) tend to help lower their risk for schizophrenia (Morgan, et. al, 2018; Silverstein, et. al, 2013)

However, this protection does not seem to be double sided or congenitally passed on; as studies have shown that the children of people who were diagnosed or treated for schizophrenia were more likely to be diagnosed with neurological, ear, or eye disease before the age of 10 (Gunnarsdóttir, et. al, 2018).

Currently known syndromes with Coexisting Ear and Eye disorders

Coexisting ear and eye defects have shown an upward trend from 9:10,000 between 2004 to 2006 to 15.3:10,000 between 2010 to 2012. Interestingly, the incidence of nervous system abnormalities has also increased, from 19:10,000 between 2004 and 2006 to 31.9:10,000 between 2010 and 2012. Figure 14 shows the trend of prevalence for groups of congenital abnormalities occurring over the years (Mashhadi et. Al., 2014). Currently, there are several established syndromes identified to affect both the ear and eye; most of which also present with nervous system and/or other organ abnormalities.

Some of the more commonly established and diagnosed syndromes, Goldenhar, CHARGE, Kabuki, and CODAS syndrome will be discussed.

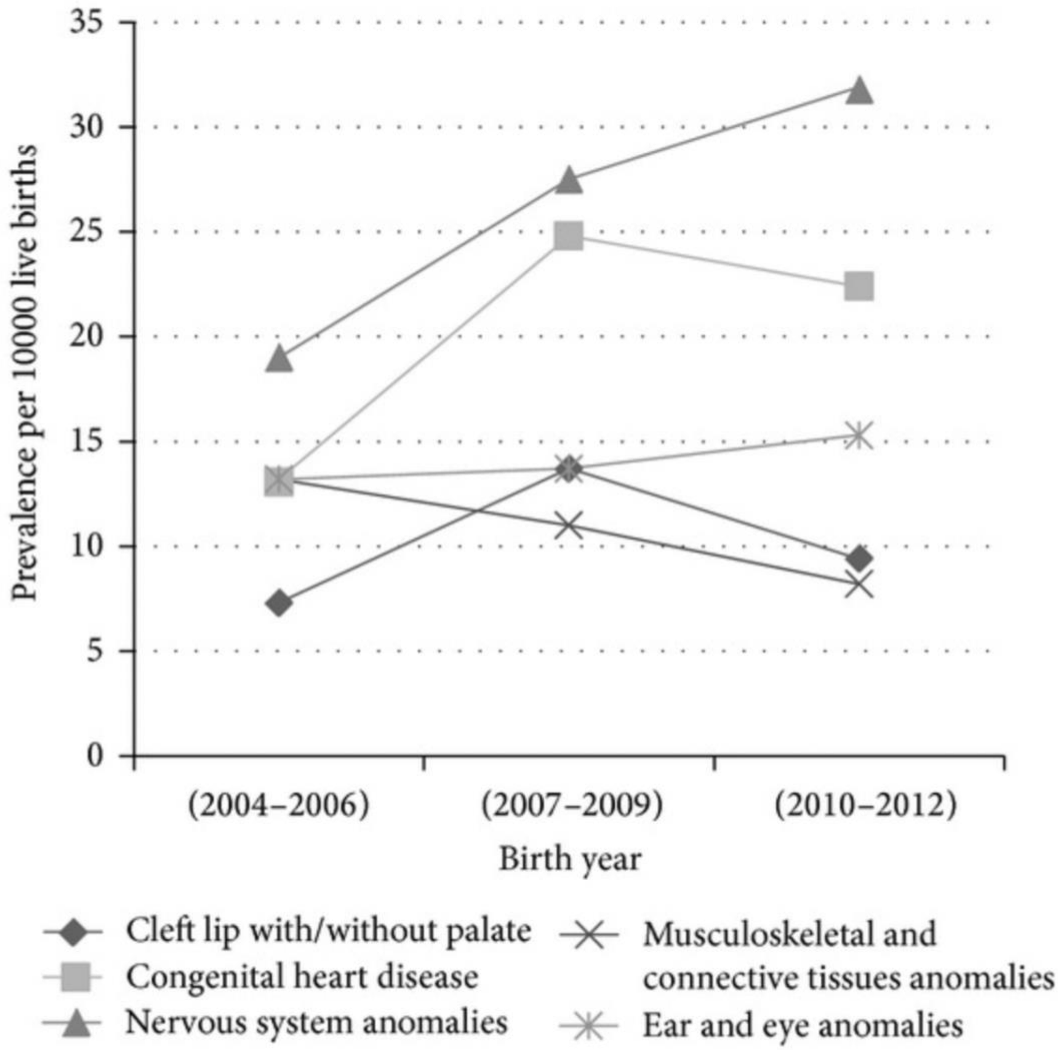

Figure 14: Total prevalence of groups of congenital abnormalities seen over the years (Mashhadi et. Al., 2014).

Goldenhar syndrome

Goldenhar syndrome, also referred to as oculo-auriclo-vertebral dysplasia or OAVS, is a congenital disease caused by malformations of the developing first and second branchial arches. Oculo-auriclo-vertebral dysplasia is characterized clinically by facial asymmetry, ENT abnormalities, vertebral anomalies, cardiac abnormalities, ocular abnormalities, and CNS malformations (Schmitzer, et. al., 2018). As illustrated in table 3, the auricular symptoms of OAVS may include various inner, middle, and external ear abnormalities and may or may not present with coexisting loss of hearing. Table 4 lists the various ocular symptoms of Goldenhar syndrome, where upper eyelid colobomas (illustrated in figure 6) are most commonly seen as well as chorioretinal colobomas, subconjunctival dermoids, or epibulbar choristomas. There is a spectrum of severity for Goldenhar syndrome, where some patients have subtle and almost unnoticeable abnormalities while others have extreme defects. The incidence of Goldenhar syndrome has been studied to be between 1:3500 and 1:5600. Patients with Goldenhar syndrome may also present with delayed psychomotor development, low height, speech disorders, autistic behavior, retardation (which is often presented with microphthalmia), and psycho-social problems (Bogusiak, et. al., 2017).

Auricular Symptoms	
accessory tragi	Atresia of the external auditory canal
Preauricular fistulas	Ear dysplasia with or without hearing loss
Preauricular appendages	Middle and inner ear abnormalities
Anotia	Low-set, posteriorly rotated ears
Microtia	Ear asymmetry

Table 4: Auricular Symptoms of Goldenhar Syndrome (Bogusiak, et. al., 2017)

Ocular Symptoms	
Coloboma	Eyes asymmetry/dysmorphy
Cleft eyelid	Lipodermoids
Anophtalmia/Microphtalmia	Lacrimal duct artresia/stenosis
Exophthalmia	Epibular/ Subconjunctival dermoids
Epibulbar choristomas	Strabismus

Table 5: Ocular Symptoms of Goldenhar Syndrome **(**Bogusiak, et. al., 2017)

Figure 15: Upper Eyelid Coloboma (Schmitzer, et. al., 2018).

CHARGE Syndrome

CHARGE Syndrome is a congenital condition that includes Coloboma ocular, Heart defects, Atresia or stenosis of the choanae, Retardation of growth and/or development, Genitourinary anomalies, and Ear abnormalities. Over 90% of patients with CHARGE syndrome are diagnosed with cranial nerve dysfunction, most of which have more than one cranial nerve affected. The cranial nerves affected have been shown to be cranial nerve I (which affects sense of smell), cranial nerve V (which affects swallowing and chewing), cranial nerve VII (which causes facial palsy), cranial nerve VIII (which causes sensorineural hearing loss and balance vestibular issues), and cranial nerves IX & X (which causes swallowing issues). Intellectual, hearing, and visual impairments may present in various severities, from mild to severe. CHARGE Syndrome has been studied to have an incidence between 1:10,000 and 1:15,000 and is one of the most common syndromes that causes combined deafness and blindness. The external ear abnormality shown in figure 16 is a characteristic of CHARGE syndrome as well as inner ear abnormalities such as vestibular and cochlear malformations and an absent olfactory bulb (Hudson et. Al., 2017).

Figure 16: Characteristic External Ear Abnormality seen in CHARGE syndrome (Hudson et. Al., 2017).

Kabuki syndrome

Kabuki syndrome is a congenital syndrome that is characterized by skeletal abnormalities, retardation, cardiac defects, auditory dysfunction, dermatoglyphic anomalies, and ophthalmologic abnormalities such as colobomas. 1 in 32,000 children are born with Kabuki syndrome and they tend to have features such as long palpebral fissures (which are openings between the eyelids that are longer than normal and are illustrated in figure 17, eversion of the lower lateral eyelids, large and prominent ears, malformed auricles, ear pits, otitis media, conductive or sensorineural hearing loss, microphthalmia, ptosis (which is drooping of the eyelid), strabismus (also commonly referred to as "cross eyed"), and/or a blue discoloration of the sclera (Adam, et. al., 2005; Cheon, et. Al., 2015). Patients with Kabuki syndrome have also been studied to have an association with neurological disorders, ADHD, autism, and/or anxiety (Wang, et.al., 2019).

Figure 17: Patient with Kabuki syndrome with characteristic long palpebral fissures and eversion of the lower lateral eyelid (Adam, et. Al., 2005)

CODAS SYNDROME

CODAS syndrome is a rare congenital disorder that includes Cerebral, Ocular, Dental, Auricular, and Skeletal abnormalities. The characteristic features of CODAS include delay of developmental growth, epiphyseal ossification, and tooth eruption; craniofacial abnormalities; cataracts; ptosis; hearing loss with external ear abnormalities such as malformed auricles and helices; and coronal vertebral clefts with short stature. Between the years 1991 (when the first case was described) and 2010, there have only been four reported cases in the world and studies have established LONP1 mutations as the cause. LONP1 is a DNA binding protein, chaperone, and protease that influences mitochondrial inner membrane complex assembly; mutations in LONP1 have been studied to hinder mitochondrial function, cause an accumulation of reactive oxygen species, and increased apoptosis (Dikoglu, et. al., 2015; Strauss, et. al., 2015).

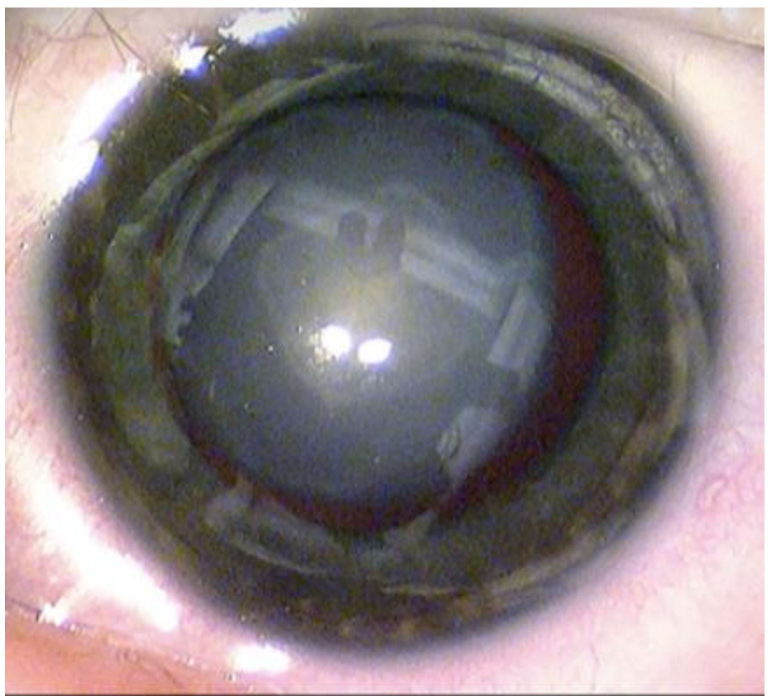

Figure 18: Patients with CODAS syndrome have characteristic bilateral nuclear cataracts that rapidly develop before they are 6 months old (Strauss, et. al., 2015).

Limitations

There are guidelines that help identify and treat congenital hearing loss, such as the universal newborn hearing screening (UNHS), which allows for early intervention and optimal effect of treatment for maximum literacy development and linguistic competence. All newborns and infants are recommended to undergo neonatal hearing screens in the first few days of life so that they are able to receive treatment before the critical period passes. Prior to these guidelines encouraging early newborn hearing screenings, patients were diagnosed at an average of two to three years old with severe hearing loss and around four years old with mild to moderate hearing loss. With the implementation of the newborn hearing screenings, children are able to be diagnosed within the first several months of their life (Wroblewska-Seniuk, et. al., 2017). Although some newborn screenings do not catch and identify all hearing impairments, especially if late onset deafness occurs, it is still a valuable tool that has helped with the diagnosis and early treatment of hearing loss. However, there are no similar neonatal vision screenings that could be given to provide similar results for identifying and treating congenital blindness earlier.

CONCLUSIONS AND FUTURE DIRECTIONS

Understanding ear and eye associations and the factors that affect the systems is essential for clinicians to be able to recognize, diagnose, and treat patients who experienced abnormal development during embryogenesis that presents as ear and eye disorders. Although there are guidelines in place for when patients are diagnosed with either an ear or eye disorder, there are no current guidelines that consider one disorder to be a possible indicator of another and encourage an assessment of both systems. Furthermore, the association of ear and eye disorders with the central nervous system should be more heavily emphasized and assessed as it could allow clinicians to better identify and treat high risk patients that may be affected.

Although there are some currently known syndromes that affect both the ear and eye systems, there is still the possibility of unexplored associations between ear and eye disorders. Future work in the ear and eye field should include identifying patients who present with ear diagnoses and then identifying and assessing whether they were seen or diagnosed by ophthalmology for any eye disorders. Studying and characterizing the incidence and co-occurrence of specific ear and eye disorders in patients would allow researchers to explore and possibly identify previously unknown associated ear and eye disorders, or even to have a better idea of what specific ear and eye abnormality associations have a high co-incidence.

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