Title: *Normal and abnormal foveal development*

Authors: Mervyn G Thomas MBChB, PhD,[1]* Eleni Papageorgiou MD, PhD,[2] Helen J Kuht BMedSci,[1] Irene Gottlob MD, FRCOphth,[1]*

[1]Ulverscroft Eye Unit, Department of Neuroscience, Psychology and Behaviour, University of Leicester, Leicester, UK.

[2]University Hospital of Larissa, Larissa, Greece

*Correspondence to: Ulverscroft Eye Unit, Department of Neuroscience, Psychology and Behaviour, University of Leicester, Leicester, UK. mt350@le.ac.uk and ig15@le.ac.uk

Abstract

Normal foveal development begins *in utero* at midgestation with centrifugal displacement of inner retinal layers from the location of the incipient fovea. The outer retinal changes such as increase in cone cell bodies, cone elongation and packing mainly occur after birth and continues till 13 years of age. The maturity of the fovea can be assessed *in-vivo* using optical coherence tomography, which in normal development, would show a well-developed foveal pit, extrusion of inner retinal layers, thickened outer nuclear layer and long outer segments. Developmental abnormalities of various degrees can result in foveal hypoplasia. This is a characteristic feature for example in albinism, aniridia, prematurity, Foveal Hypoplasia with Optic Nerve Decussation defects with or without anterior segment dysgenesis without Albinism (FHONDA) and optic nerve hypoplasia. In achromatopsia there is disruption of the outer retinal layers with atypical foveal hypoplasia. Similarly, in retinal dystrophies there is abnormal lamination of the inner retinal layers sometimes with persistent inner retinal layers. Morphology of foveal hypoplasia provides clues to diagnoses and grading correlates to visual acuity. The outer segment thickness is a surrogate marker for cone density, in foveal hypoplasia this correlates strongly with visual acuity. In preverbal children grading foveal hypoplasia can help predict future visual acuity.

Normal Foveal Development

Introduction

The macula is an elliptically shaped area of the human retina, about 5.5 mm in diameter, which includes the foveal, parafoveal, and perifoveal retina.[1] The fovea (Latin for “pit”) is a highly specialized region at the centre of the macula.[2] Although it occupies only about 0.02% of the total retinal area, about 50% of the primary visual cortex processes information provided by the fovea.[3,4] The foveal region is characterised by an avascular zone (FAZ), the displacement of inner retinal neurons forming the foveal pit, increased cone density, and an absence of rod photoreceptors.[4] The adult human retina contains around 4.6 million cones and 92 million rods, and the average horizontal diameter of the rod-free zone is 0.35 mm with a peak foveal cone density of 199.000 cones/mm^2.[5] The maturation of the human fovea is a long and developmentally complex process, which begins at midgestation and continues till around 13 years of age. An understanding of the mechanisms involved in the maturation of the central retina is crucial in the management of congenital ocular anomalies, which could affect vision during the "critical period".[6-8]

Histological studies

The human macula lutea was discovered by Buzzi in 1782.[9] Few years later the fovea was described by Sömmerring as “foramilunum centrale retinae” and by Buzzi as a localized thinning of the retina.[10,11] Preliminary histological studies identified a fully developed fovea at 8 months postpartum.[12,13] Later reports suggested that the fovea is underdeveloped at birth, but is identifiable between 14-22 weeks gestation, and reaches maturity between 15-45 months of age.[6,14,15]

More recent studies concluded that the formation of the *fovea centralis* is a protracted process beginning before midgestation and continuing for several years after birth.[15-17] The fovea can be identified as early as fetal week 11, as a single layer of cones covering over 1 mm of central retina with all retinal layers present.[18] Hendrickson and Yuodelis identified three developmental events in the morphological maturation of the human fovea.[15,19] The first is the centrifugal migration of the inner retinal layers (IRLs) to form the foveal depression, which starts before 24-26 weeks gestation, and reaches completion until around 15 months postpartum.[15,20] Two later events, centralward migration and cone elongation may extend even after 45 months of age.[15] Cones move centripetally toward the pit centre, leading to the central crowding of cones, the thickening of the foveal outer nuclear layer (ONL) (figure 1 and supplementary figure 1), cone elongation, and the reduction in size of the foveal cone mosaic.[13,15,17,19,20] Most of this cone packing occurs after birth and is completed by 4–6 years of age, creating an adult cone density that is 20–30 times higher than fetal cone density.[19,20] The foveolar cone density increases from 18 cones/100 µm at 1 week postnatal to 42 cones/100 µm in the adult. Additionally, the foveolar cone diameter reduces from 7.5 µm at 5 days postnatal to 2 µm by 45 months.[19]

Developmental changes have been found in the rods as well. The rod-free zone or foveola is over 1000 µm in diameter before birth, but it becomes progressively narrower and reaches the adult diameter of 650-700 µm by 45 months of age.[17] The maximum rod density is observed in the region surrounding the foveal cone mosaic, indicating centripetal migration of both rods and cones until adulthood.[17]

Virtual engineering models by Springer and Hendrickson predicted that the foveal

pit emerges within the fetal area of high acuity (AHA) because it contains an avascular zone (FAZ). The absence of vasculature makes this area more deformable than the surrounding retina.[21] Molecular changes, intraocular pressure (IOP) and retinal stretch are possible forces that generate the pit and high cone density of the AHA.[21-24]

Optical coherence tomography studies

Although these histological studies provided valuable data, there were some limitations, such as limited number of eyes, tissue shrinkage, mechanical distortion, and methodological differences.[15,18-20,25] The advent of noninvasive optical coherence tomography (OCT) enabled *in vivo*, high-resolution, real-time visualization of the foveal architecture. The first adult OCT studies highlighted remarkable interindividual variation in several aspects of the foveal pit.[7,21,24,26,27]

As handheld OCT for pediatric use became available, several signs of immaturity were illustrated in premature and term neonates: a shallow foveal pit, a thin photoreceptor layer (PRL), and persistence of IRLs.[28] Between 31 and 42 weeks postmenstrual age (PMA), the thickness of IRLs at the foveal center decreases, due to centrifugal migration of inner retinal cells, while there is progressive formation of the IS and OS band in the opposite direction.[25,28] The IS and OS cannot always be visualized at the fovea before 46 weeks PMA.[25,28] Similarly, in very preterm infants the ellipsoid zone (EZ) develops in the foveal centre only in 14% of preterm compared to 47% of term babies.[29] These findings are confirmed by histological studies, which show progressive thickening of the foveal ONL after birth, as cone packing and elongation of IS and OS occur.[20] Subsequent research also presented good agreement between pediatric OCT images and age-matched

histological sections.[25,27] Dubis et al. demonstrated a single hyper-reflective band, representing cone pedicles, at the fovea in all infants less than 42 weeks PMA. The characteristic four hyper-reflective bands are evident across the fovea by 17-24 months postnatal age, and mature into childhood until 13-16 years of age.[25,27]

Further OCT studies on normal foveal development in term infants and young children demonstrated that the ONL continues to increase in thickness at least until 12 years of age, which may reflect ongoing increases in the number of foveal cone photoreceptors.[30] We have shown examples of original OCT scans from birth to 30 years of age to demonstrate the dynamic changes during development (figure 1). This observation is in line with histological studies, which have shown that cone-packing density at the fovea only reaches half adult values at 45 months, hence development may continue until adulthood.[19]

In summary, histology and OCT largely agree on the sequence of events during foveal development. Between 31 and 42 weeks PMA the thickness and number of IRLs at the foveal center decrease due to inner retinal cell migration centrifugally (see supplementary figure 2).[25,28] This causes deepening of the foveal pit. Over the postnatal period in the first years of life, the pit becomes wider and shallower with no neurons in the center except for cone cell bodies. As the infant grows, there is progressive centripetal growth of the photoreceptor subcellular structures that extend into the foveal center.[31] The height of the PRL increases progressively from infancy to adulthood, so that the foveal center has thin and long cones and the rod outer segments also become long with eccentricity.[31]

Abnormal Foveal Development

Definition and terminology

The hallmark of foveal hypoplasia is the continuation of inner retinal layers (IRLs) posterior to the foveola (see examples in figure 2).[32] Broadly it can be divided into typical foveal hypoplasia and atypical foveal hypoplasia (also referred to as foveal maldevelopment). In atypical foveal hypoplasia there is disruption of the outer retinal layers or abnormal lamination pattern. With the advent of OCT, it is now possible to document the varying degrees of foveal hypoplasia that are likely to represent the different stages of arrested development of the fovea. This has introduced various terms, such as fovea plana, foveal dysgenesis, and foveal aplasia, to describe the structural variability associated with abnormal development of the fovea.[33] Foveal hypoplasia is a more appropriate term rather than aplasia because hypoplasia encompasses both the partial and complete absence of a structure.[34] However the terms fovea plana, foveal dysgenesis and foveal aplasia have been replaced by the foveal hypoplasia grading system.[32]

Grading of foveal hypoplasia

Based on when the developmental arrest occurs, typical foveal hypoplasia can be divided into four grades and an additional grade for atypical foveal hypoplasia (figure 3). This grading system has only been applied to albinism, idiopathic infantile nystagmus, *PAX6* mutations and achromatopsia. It is yet to be used in retinopathy of prematurity (ROP), optic nerve hypoplasia (ONH) and photoreceptor dystrophies. Grade 1 foveal hypoplasia is associated with a shallow foveal pit, outer nuclear layer (ONL) widening, and outer segment (OS) lengthening relative to the parafoveal ONL and OS length, respectively. In Grade 2

foveal hypoplasia, all features of grade 1 are present except the presence of a foveal pit. Grade 3 foveal hypoplasia consists of all features of grade 2 foveal hypoplasia except the widening of the cone outer segment. Grade 4 foveal hypoplasia represents all the features seen in grade 3 except there is no widening of the ONL at the fovea. In atypical foveal hypoplasia (or foveal maldevelopment) there is a shallower pit with disruption of the inner segment ellipsoid (ISe), a sign of photoreceptor degeneration.[32,35,36] Based on quantitative measurements Wilk et al. proposed further subdividing grade 1 into grade 1a (normal pit metrics within 2 SDs of the normal average) and grade 1b (pit is a shallow indent, pit metrics outside of 2 SDs of the normal average).[37] Grading gives an indication of the stage at which foveal development was arrested, provides a prognostic indicator for visual acuity and is applicable across a range of disorders. Recently the grading system has been expanded to divide grade 1 based on Wilk et al. proposed subdivision[37] and has been validated in preverbal children to predict future visual acuity.[38]

Disorders associated with foveal hypoplasia

Typical foveal hypoplasia

The disorders commonly associated with foveal hypoplasia are albinism, *PAX6* mutations, *SLC38A8* mutations, ROP, ONH, and isolated cases (figure 2). The common genetic differentials associated with foveal hypoplasia and the mode of inheritance is shown in figure 4.

Albinism

Albinism is a genetically heterogeneous disorder arising due to abnormalities of melanin biosynthesis. Hypopigmentation can be diffuse involving skin, hair and eyes (oculocutaneous albinism) or localised to the eyes (ocular albinism). Almost all patients with albinism have foveal hypoplasia.[39] There is significant phenotypic variability with all four grades of foveal hypoplasia seen.[32,39,40] Typically albinism is associated with higher grades of foveal hypoplasia with majority having grade 2 or worse foveal hypoplasia.[32,39] However, there have been rare reports of cases of features of albinism without foveal hypoplasia, which raises the possibility of carrier manifestations in albinism.[39,41]

PAX6 mutations

PAX6 mutations are associated with panocular phenotypes with significant phenotypic heterogeneity.[42] Aniridia is the characteristic phenotype described with *PAX6* mutations. However normal iris structure and subtle iris defects have also been described with PAX6 mutations.[43-45] Similarly the foveal structure can be variable in *PAX6* mutations.[32,42,45,46] Hingorani et al. showed that 37/43 (86%) patients with *PAX6* mutations had foveal hypoplasia.[42] Similarly, Sannan et al. showed that in 24/33 (72%) patients with *PAX6* mutations had foveal hypoplasia.[46] The grades of foveal hypoplasia described in *PAX6* mutations can range between grades 1-4.[32,46] In the study by Sannan et al. 22/24 (92%) patients had grade 3 or 4 foveal hypoplasia.[46] Although strong genotype-phenotype correlations have been described in relation to the anterior segment disease,[42,46] no significant correlations have been observed with grades of foveal hypoplasia and the genotype.[46]

***SLC38A8* mutations**

SLC38A8 mutations were described in patients with foveal hypoplasia, optic nerve decussation defects and anterior segment dysgenesis (FHONDA) syndrome.[47] This is a rare cause and anterior segment dysgenesis is not always present.[48] One of the distinguishing features from albinism is the presence of normal skin and ocular pigmentation.[47] Majority of cases reported have a high grade foveal hypoplasia (grade 3 or 4).[48] Since normal pigmentation is present in these patients it is hypothesized that loss of SLC38A8 represents a melanin-independent component essential for development of the macula and visual pathway.[47]

Prematurity

Prematurity is associated with immature retinal vasculature and can be associated with abnormal development of the macula. Previous studies have shown a small FAZ in patients with a history of prematurity[49,50] and attenuated central retinal responses on multifocal ERG in individuals with ROP.[51] One of the earliest studies by Hammer et al. reported that in the majority of patients with ROP there was a broad and shallow foveal pit with incursion of IRLs.[52] Absent foveal depression and retention of IRLs at the foveola has also been described in later ROP studies.[53-55] Foveal architecture and FAZ diameter does not correlate with visual acuity.[56] Unlike the genetic causes of foveal hypoplasia (such as albinism and *PAX6* mutations), the foveal morphology and foveal specialization characteristics in pre-term born children are distinct.[57-59] Specifically, macular developmental arrest has been reported in 44% of spontaneously regressed ROP and in 27% of preterm infants without ROP.[57]

Optic nerve hypoplasia

ONH is a developmental disorder characterised by a significant reduction in the population of retinal ganglion cell axons.[60] It can arise from genetic mutations (for example *PAX6* or *PAX2* mutations)[42,61] or other external causes (for example maternal drug abuse). Pilat et al. reported foveal hypoplasia in 18/22 (82%) of eyes with ONH,[62] all with a foveal depression or indent suggestive of a grade 1 (predominantly grade 1b) foveal hypoplasia. In contrast, Katagiri et al. described a lower incidence of foveal hypoplasia (7/29 (24%)) in ONH, however with a wider spectrum of foveal defects including higher grades with completely absent foveal pits and absence of outer segment lengthening.[63] Katagiri et al. grouped the patients into three morphological groups: subnormal fovea, foveal hypoplasia, and an atypical foveal abnormality. Subnormal fovea represents a normal foveal depression that seemed shallow due to thinning of the ganglion cell complex around the fovea. Atypical foveal abnormality represents a wide and irregular foveal depression.[63]

Isolated cases

Isolated cases represent foveal hypoplasia with no other associated abnormalities as described above.[32,64,65] This can be associated with or without nystagmus.[64,66,67] Although a specific gene for isolated foveal hypoplasia has not yet been identified, the advent of next generation sequencing has identified specific pathogenic mutations in some of these cases identified as idiopathic previously. For example, Saffra et al. described a family with autosomal recessive isolated foveal hypoplasia[68] which was subsequently identified as pathological *SLC38A8 mutation*[69] after the report of mutations in *SLC38A8* and foveal hypoplasia.[47] Thus isolated foveal hypoplasia could represent a heterogeneous group of genetically

unsolved cases. It could potentially arise from hypomorphic *PAX6* mutations,[44,70] *SLC38A8* mutations,[47,48] *FRMD7* mutations,[71] hypomorphic mutations in genes associated with albinism or novel genes.[39,41] OCT angiography studies have revealed a lack of FAZ in isolated cases similar to that observed in albinism.[64] Recently homozygous mutation of *AHR* has been associated with autosomal recessive isolated foveal hypoplasia, nystagmus and no chiasmal misrouting.[72] The mouse model of this disorder ($Ahr^{-/-}$) exhibits congenital pendular nystagmus.[73]

Although not a hallmark of the disease, foveal hypoplasia has also been described in Incontinentia Pigmenti,[74,75] Stickler syndrome,[76] Prader-Willi syndrome,[77] Down syndrome,[78] Wolf-Hirschorn syndrome,[79] Dandy Walker syndrome,[80] microcephaly,[81] nanophthalmos,[82,83] Åland island eye disease and incomplete congenital stationary night blindness.[84,85] The pathophysiology of arrested retinal development in these disorders is yet to be elucidated.

Atypical foveal hypoplasia and abnormal morphology

In atypical foveal hypoplasia (foveal maldevelopment) there is continuation of the IRLs posterior to the foveola but it is also associated with outer retinal disruption.[32,35,86,87] Thus atypical foveal hypoplasia is seen in photoreceptor dysfunction syndromes such as achromatopsia and other cone-rod dystrophies.

Achromatopsia

Achromatopsia arises from mutations of genes involved in the phototransduction cascade.[88] OCT shows a spectrum of outer retinal changes including disruption of the inner segment ellipsoid (ISe) signal, hyporeflective zone and outer nuclear thinning.[35,36,89] Foveal hypoplasia is reported in between 52% - 80% of cases with achromatopsia.[35,36,89] In patients with *ATF6* mutations and achromatopsia all

patients had foveal hypoplasia.[90] There is some debate about whether the retinal changes seen in achromatopsia are progressive. Two cross sectional studies have shown that there is progressive outer retinal changes in particular the outer nuclear layer thickness and changes to inner segment ellipsoid early in life.[35,36] Sundaram et al. did not find any progressive changes in their cross sectional study in achromatopsia.[89] The first longitudinal study in achromatopsia showed that there is progressive retinal changes particularly in the first decade of life.[87] Further longitudinal studies suggest that achromatopsia may be progressive, but progression is slow and subtle.[91,92] Further longitudinal studies are needed to understand the natural history of this disorder to determine whether a therapeutic window for gene therapy exists.

Cone-rod dystrophy

In cone-rod dystrophy, there is loss of the interdigitation zone (IZ) signal with decreased intensity of the ISe.[93] The IZ signal represents the interdigitation between the outer segments and the apical processes of the retinal pigment epithelium.[94] Abnormal retinal lamination patterns have also been described in retinal dystrophy and is hypothesized to arise due to interruption of the naturally occurring developmental apoptosis.[95] The clinical features, genetics and retinal imaging findings have recently been reviewed.[96] The spectrum of changes in retinal dystrophy can be variable and can include but are not limited to retinal atrophy, dystrophic changes, retinoschitic changes, cystoid macular oedema and atypical foveal hypoplasia (foveal maldevelopment).[97-102]

Functional and clinical implications

Previous studies have shown that visual acuity is correlated to the different grades of foveal hypoplasia in albinism, *PAX6* mutations and isolated cases. [32,37] Grade 1 foveal hypoplasia is associated with the best visual acuity followed by grade 2, 3 and 4 respectively.[32,37] This is because the developmental arrest occurs at different stages and thus peak cone density varies between the different grades of foveal hypoplasia.[32,37] Wilk et al. showed that grade 1 foveal hypoplasia is associated with the highest peak cone density, this is progressively reduced in grades 2, 3 and 4.[37] Outer segment length is a surrogate measure for peak foveal cone density.[8] Consistent with this observation a strong correlation is observed between visual acuity and outer segment thickness in albinism.[40] Recent work suggests that the grading of foveal hypoplasia can be extended to preverbal children to predict future vision.[38]

The use of handheld OCT in paediatric ophthalmology is considered an extension of the clinical examination and is now possible to obtain high resolution foveal and optic nerve scans in paediatric patients.[102] Based on the macular and optic nerve morphology rapid differential diagnosis is possible and subsequent testing strategy can be devised.[102] We have presented a diagnostic algorithm to aid with the differential diagnoses and investigations of abnormal retinal development (figure 5). Similarly, the use of next generation sequencing (NGS) panels in ophthalmology allows targeted testing based on phenotypes,[41,103] thus reducing the need for some of the traditional investigations. Using an NGS panel as a frontline diagnostic test has many advantages, however the variants generated need to be interpreted in the clinical context and thus still relies on good phenotyping. In some instances, there remains a significant challenge of differentiating pathogenic from non-pathogenic variants.

Conclusion

The advent of high-resolution imaging using OCT and adaptive optics has provided a deeper understanding of normal and abnormal retinal development. This has built on previous histological studies and given us insight into the clinical implications of arrested retinal development. Using a combination of NGS and high-resolution imaging (handheld OCT) has simplified the diagnostic process in paediatric ophthalmology. Further genotype-phenotype studies are needed to understand how genomic variants interact and affect biological pathways and thus retinal development. Predicting future visual acuity in preverbal children based on macular morphology will have great clinical utility and impact in the practice of paediatric ophthalmology.

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Funding: This work was supported by the Ulverscroft Foundation (05/38), Fight for Sight (grant ref: 5009/5010 and 24NN181), Academy of Medical Sciences (SGL021/1066) and the Medical Research Council (MRC), London, UK (grant number: MC_PC_17171, MR/J004189/1 and MRC/N004566/1). MGT is supported by NIHR (CL-2017-11-003).

Competing Interests: None

Contributors: Conception and design: MGT and IG. Literature review and manuscript drafting: MGT, EP and HJK. Critical appraisal and final approval: MGT, EP, HJK and IG. Overall responsibility: MGT and IG.

Figure legends:

Figure 1: *Original foveal optical coherence tomography scans showing normal foveal development from birth (38 weeks post menstrual age (38w PMA)) to 30 years of age. At birth there is continuation of inner retinal layers at the foveola, a thin outer nuclear layer (yellow annotation) with no outer segment lengthening. Over the first two months of life the outer nuclear layer gradually thickens (note the increasing size of the yellow annotation) and by 3-6 months the outer segment lengthening is morphologically visible on OCT. Over this period the inner retinal layers are displaced as the foveal pit deepens. The cone photoreceptors continue to specialize evidenced by the outer nuclear layer thickening and outer segment lengthening, as shown in the examples from 12 months to 12 years. Abbreviations: NFL = nerve fibre layer, GCL = ganglion cell layer, IPL = inner plexiform layer, INL = inner nuclear layer, OPL = outer plexiform layer, ONL = outer nuclear layer, ELM = external limiting membrane, ISe = inner segment ellipsoid, RPE = retinal pigment epithelium.*

Figure 2: *Examples of foveal abnormalities associated with different disorders. The hallmark of foveal hypoplasia is the continuation of inner retinal layers posterior to the foveola. Albinism, SLC38A8 mutations, PAX6 mutations, prematurity and isolated cases are associated with typical foveal hypoplasia. There exist some retinal degenerations presenting with abnormal foveal morphology including Alström disease and cone-rod dystrophy. Achromatopsia is associated with a disruption of the inner segment ellipsoid and atypical foveal hypoplasia. All OCT examples of foveal abnormalities have been captured from individuals above the age of five years. Abbreviations: FH = foveal hypoplasia, ONH = optic nerve hypoplasia, CRD = cone rod dystrophy, BBS = Bardet Biedl syndrome*

Figure 3: *Foveal hypoplasia grading scheme using optical coherence tomography (OCT). Top panel shows features of foveal specialization seen on OCT. Grades 1 – 4 are seen in typical foveal hypoplasia where different degrees of foveal specialization are seen. Grade 4 foveal hypoplasia has no evidence of specialization and resembles peripheral retina. Grade 3 foveal hypoplasia has only outer nuclear layer (ONL) widening. Grade 2 foveal hypoplasia has outer segment (OS) lengthening in addition to ONL widening. Grade 1b foveal hypoplasia has a very shallow pit (or indent) in addition to specialization features seen in grade 2.*

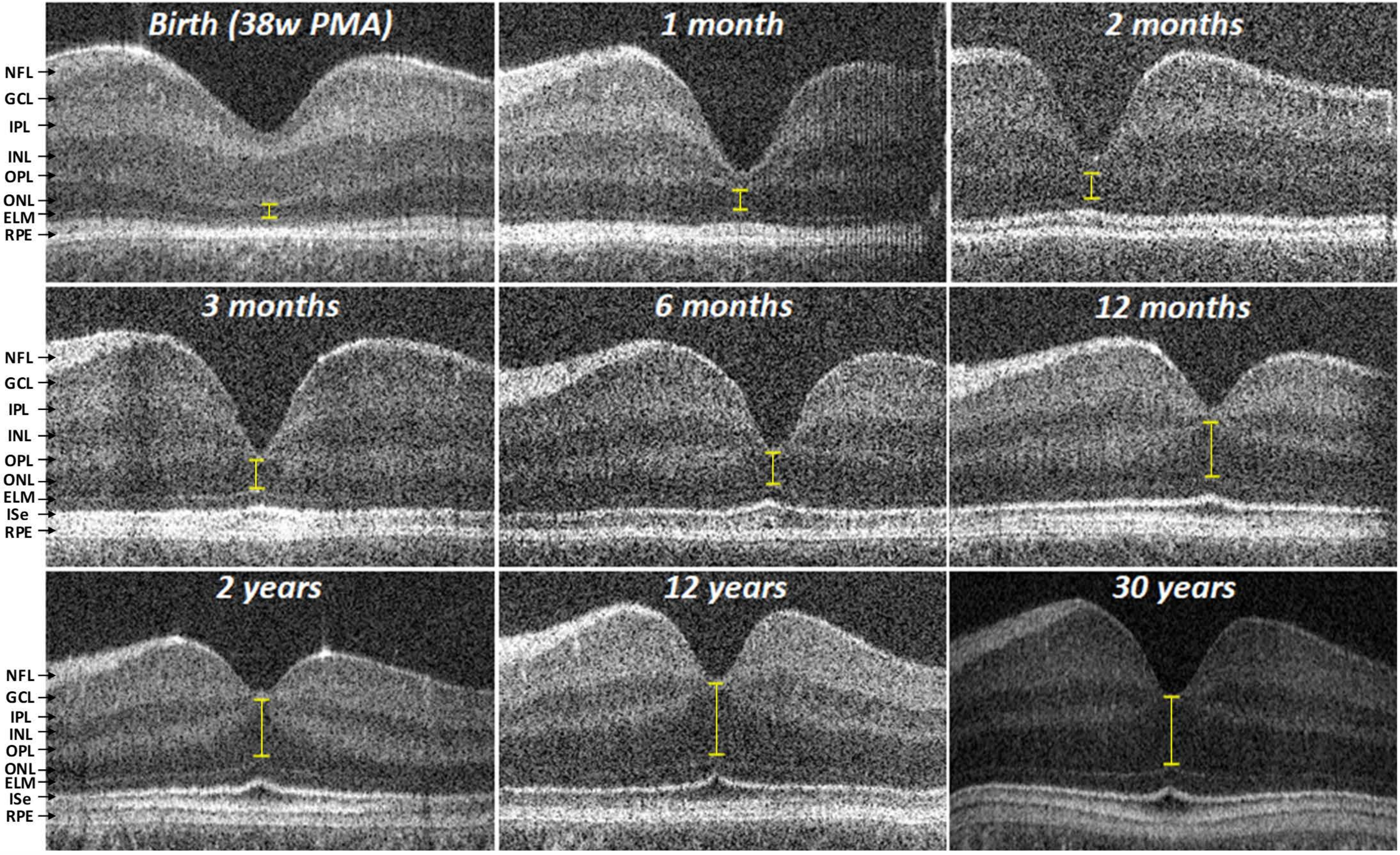
Grade 1a foveal hypoplasia has a near normal foveal pit (however with the presence of inner retinal layers posterior to the foveola) and all other features of specialization seen in grade 2. Atypical foveal hypoplasia is characterized by disruption of the inner segment ellipsoid (ISe) and a shallow foveal pit. ELM = external limiting membrane; GCL = ganglion cell layer; ILM = internal limiting membrane; INL = inner nuclear layer; IPL = inner plexiform layer; OPL = outer plexiform layer; RNFL = retinal nerve fiber layer; RPE = retinal pigment epithelium. Adapted and reproduced with permission from Thomas MG, Kumar A, Mohammad S, et al. Structural grading of foveal hypoplasia. Ophthalmology. 2011;118(8):1653–1660. Copyright © 2011 Elsevier.

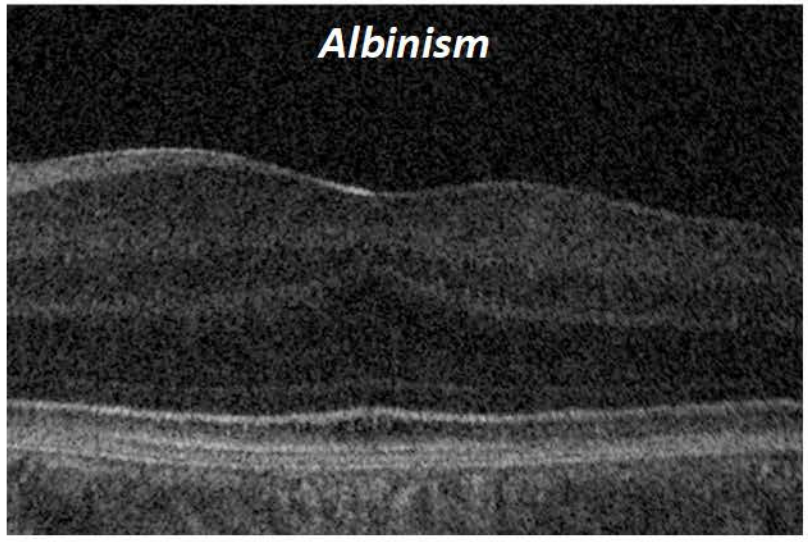
Figure 4: *The common genetic differentials for foveal hypoplasia. PAX6 mutations are inherited in an autosomal dominant manner and are often associated with aniridia. GPR143 mutations cause ocular albinism and is X-linked. There are many genes associated with oculocutaneous albinism (OCA) and can include syndromic forms as well. SLC38A8 and AHR mutations are rarer forms of autosomal recessive foveal hypoplasia but without hypopigmentation.*

Figure 5: *Clinical diagnostic algorithm for abnormal retinal development. The hallmark of typical foveal hypoplasia is continuation of inner retinal layers posterior to the foveola. Outer retinal changes or abnormal lamination suggests an inherited retinal dystrophy (IRD). Electroretinogram (ERG) or IRD gene panels can differentiate between the IRD subtypes. Foveal hypoplasia (FH) gene panels can readily differentiate the genetic subtypes that can cause FH. In the absence of genetic panels, visual evoked potentials (VEP) is helpful in broadly differentiating the diagnoses based on chiasmal misrouting. In some cases of albinism* (hypomorphic mutations or carriers) normal VEP responses maybe present. ONH = optic nerve hypoplasia, IIN = idiopathic infantile nystagmus*

Supplementary figure 1: *Foveal pit formation and movement of retinal cells during formation of the area of high acuity. The laminar retinal structure prior to foveal pit formation is shown in (A). The inner retinal layers were displaced centrifugally (away from the future fovea) during foveal pit formation (B). The cone photoreceptors migrate centripetally (towards the fovea) and form the pure cone area (C). Arrows point in the direction of movement of the cellular layers. The magnified laminar structure with the different retinal cell types and the inner segment & outer segment (IS & OS) of the photoreceptors are shown in (D). NFL = Nerve Fibre Layer; GCL = ganglion cell layer; IPL = inner plexiform layer; INL = inner nuclear layer; OPL = outer plexiform layer; ONL = outer nuclear layer. (A, B, C are based on developmental theory proposed by Springer and Hendrickson[21]. Figure adapted from: Springer AD, Hendrickson AE. Development of the primate area of high acuity. 1. Use of finite element analysis models to identify mechanical variables affecting pit formation. Visual neuroscience 2004;21(1):53-62.)*

Supplementary figure 2: *Original foveal optical coherence tomography scans showing foveal morphology at 32 weeks post menstrual age (PMA) to 42 weeks PMA.*


Birth (38w PMA)
1 month
2 months
3 months
6 months
12 months
2 years
12 years
30 years
NFL
GCL
IPL
INL
OPL
ONL
ELM
ISe
RPE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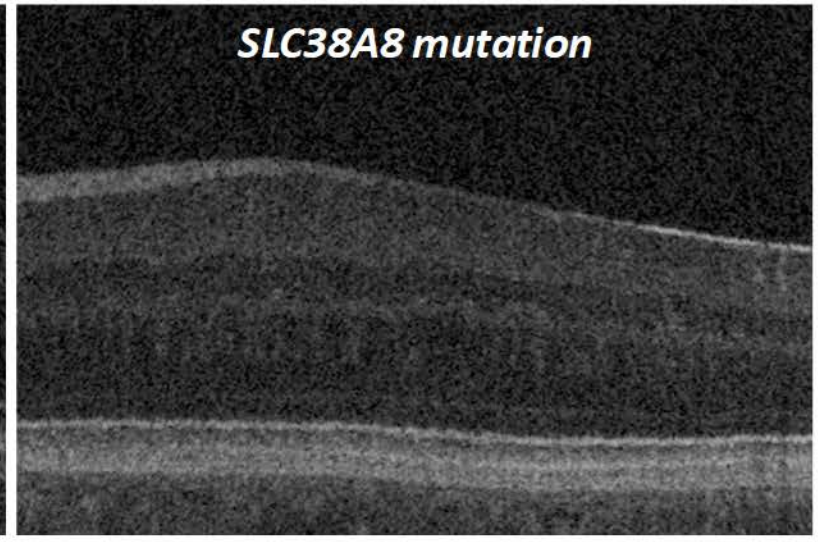
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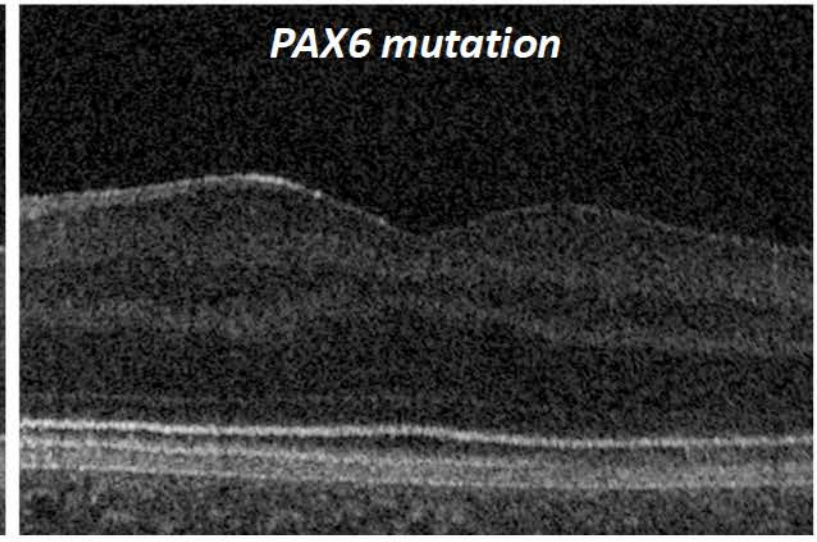
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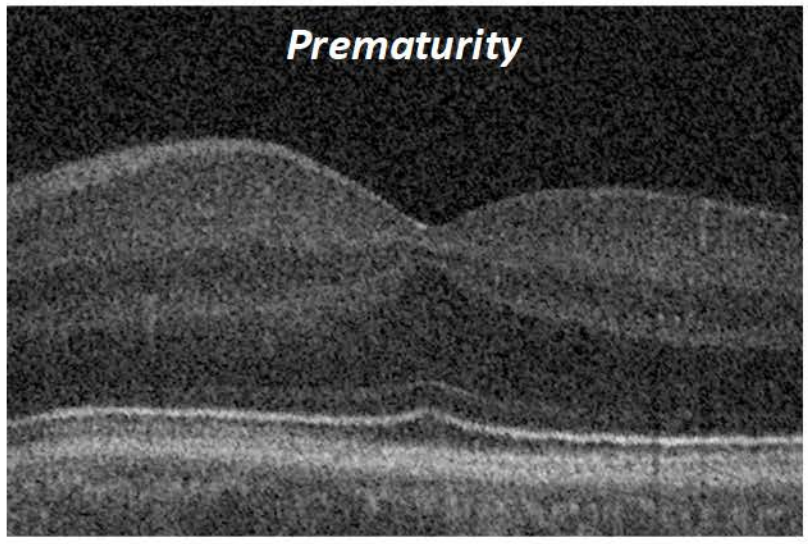
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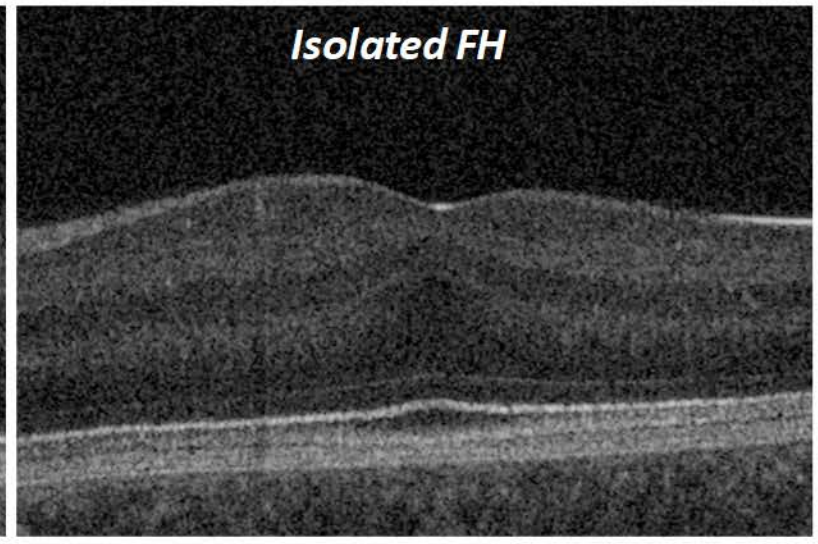
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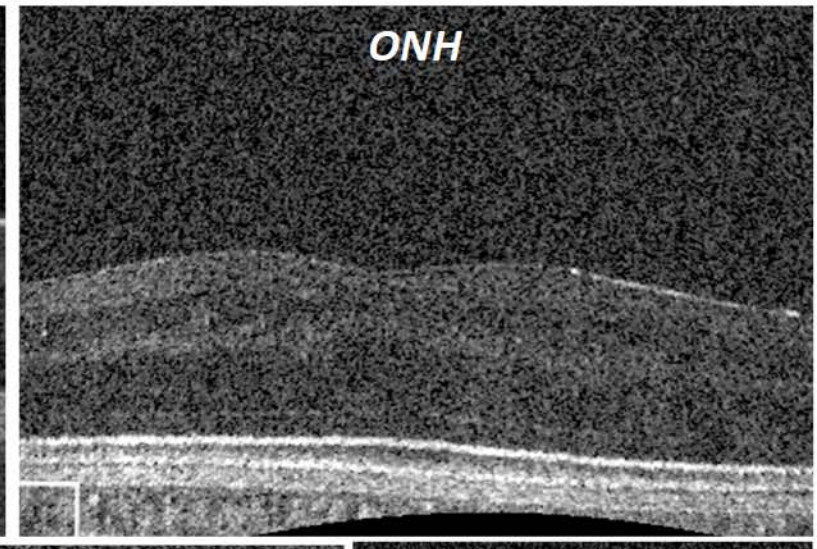
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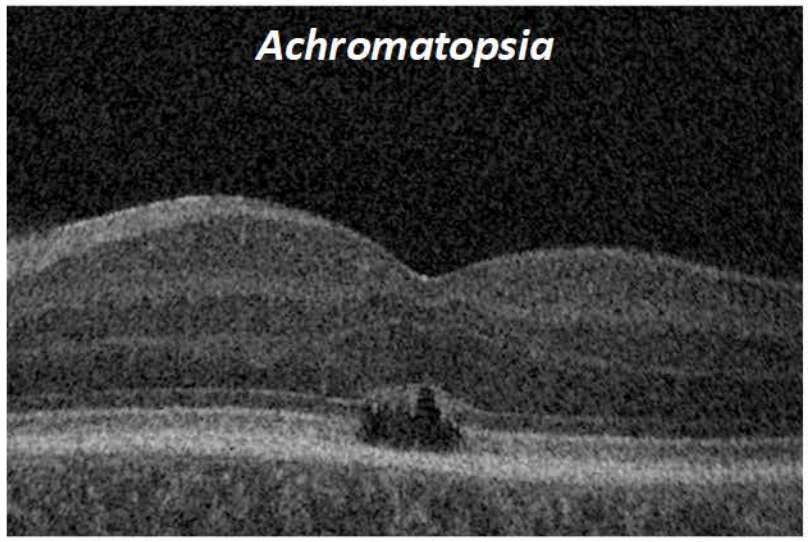
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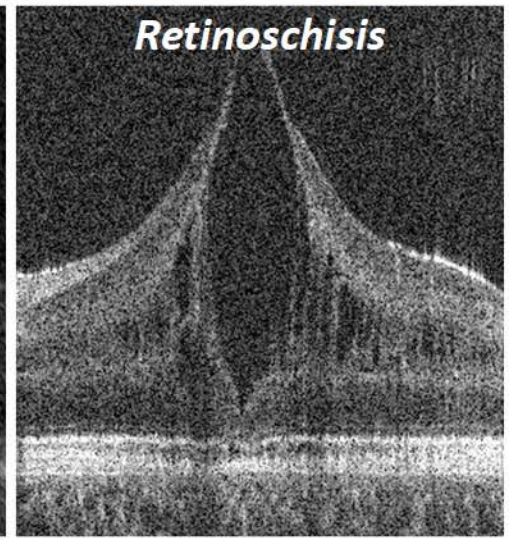
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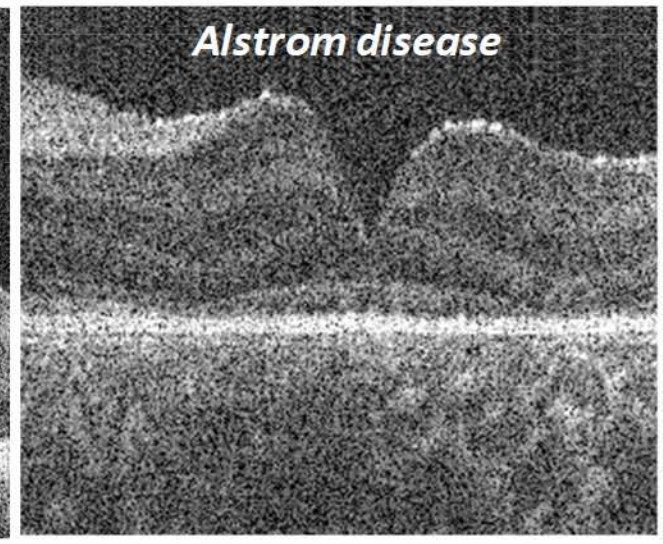
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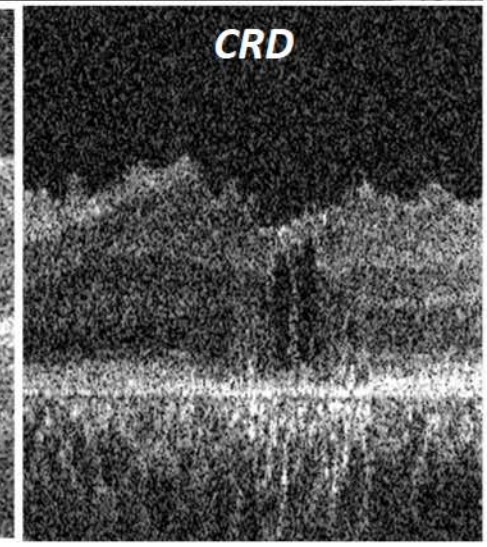
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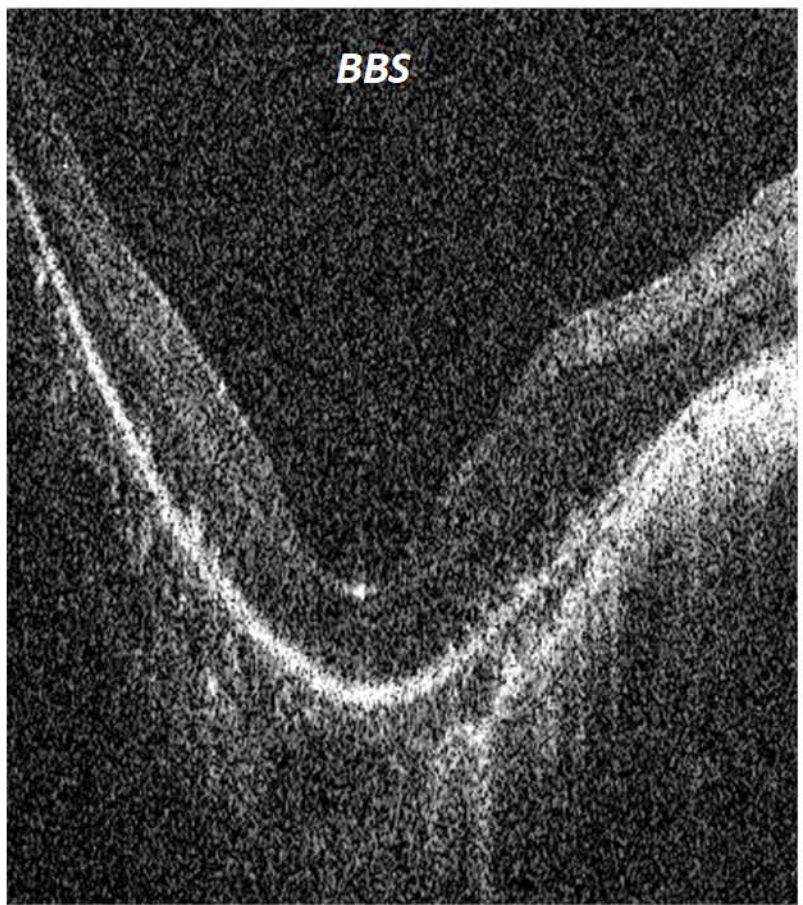
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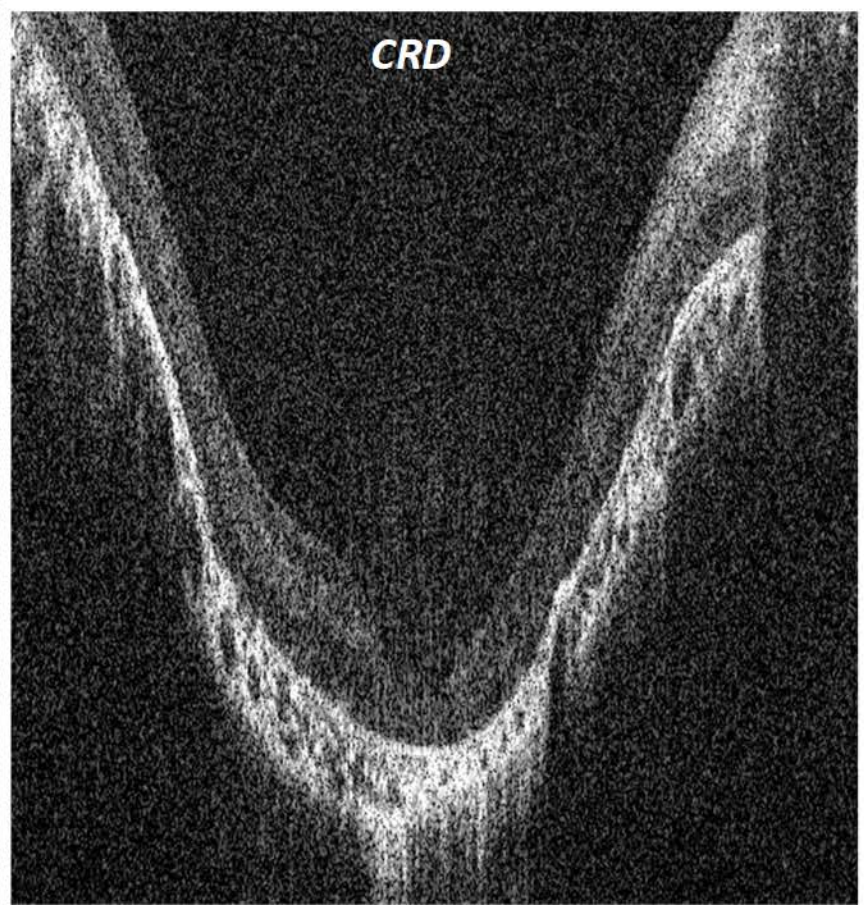
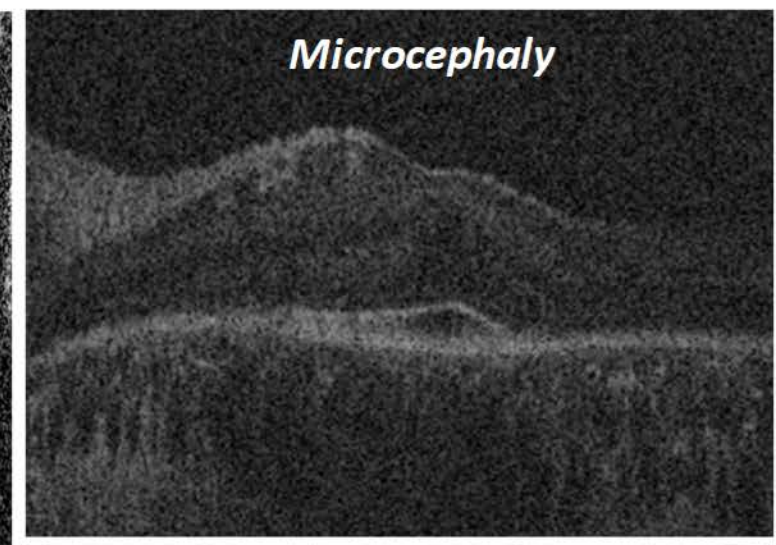
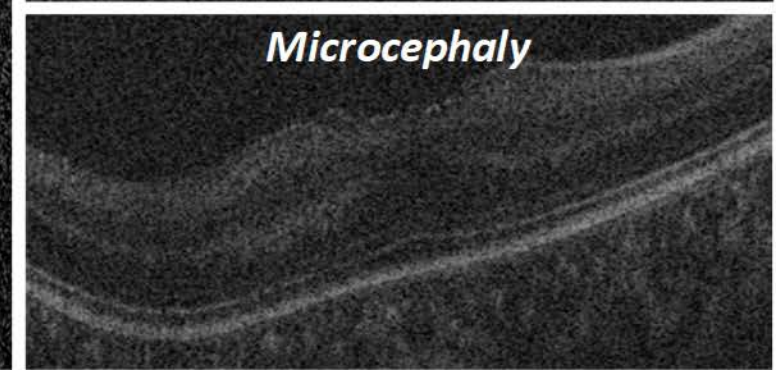
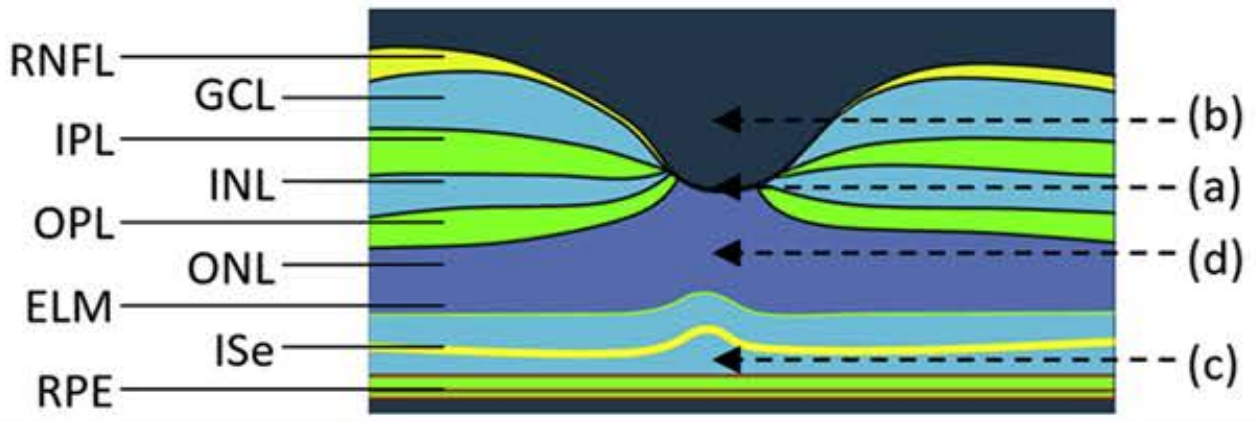
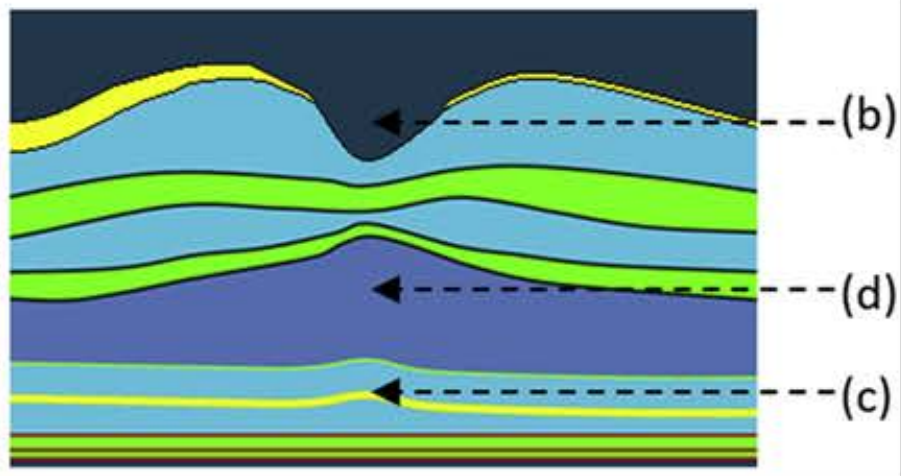
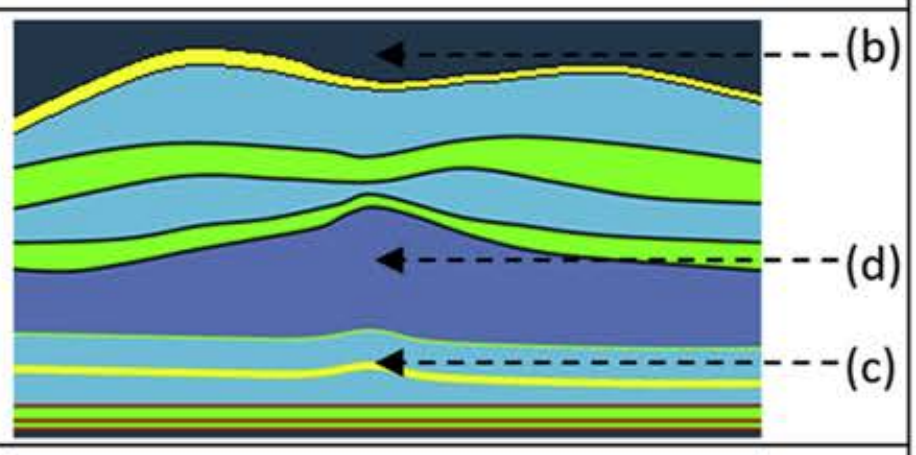
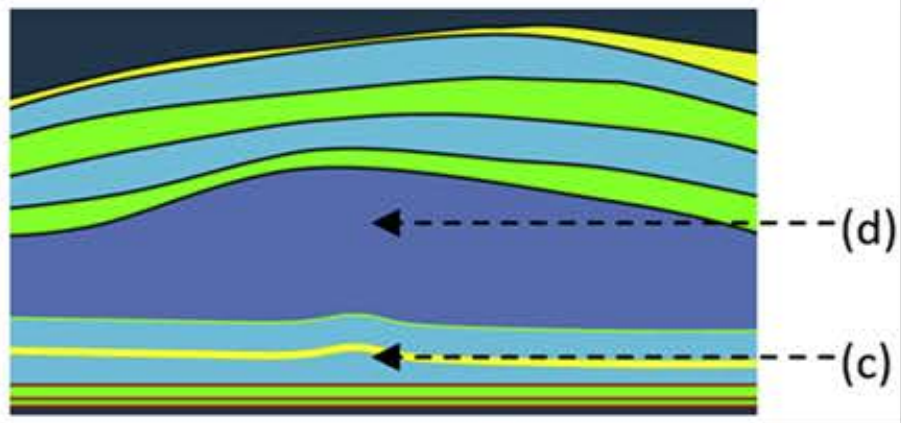
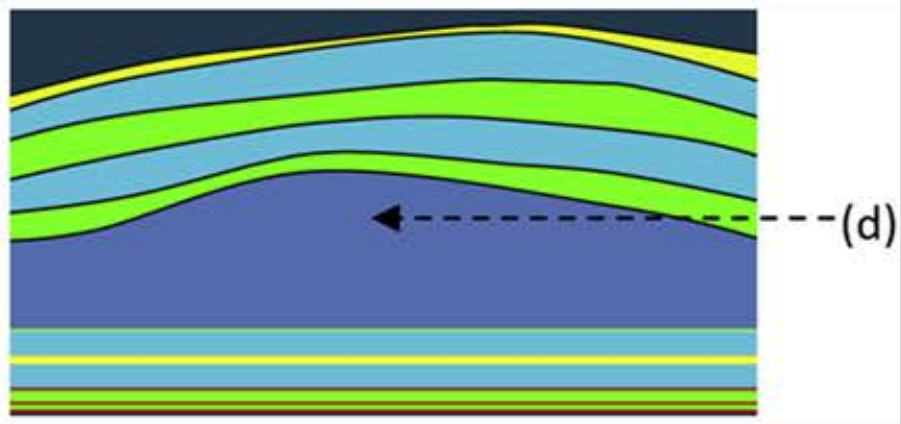
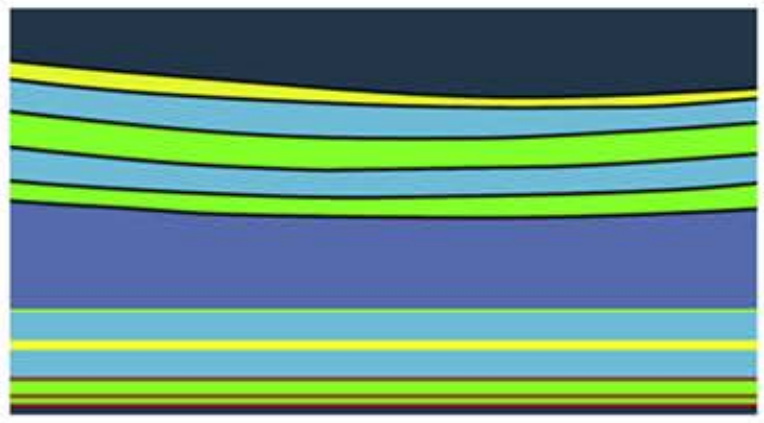
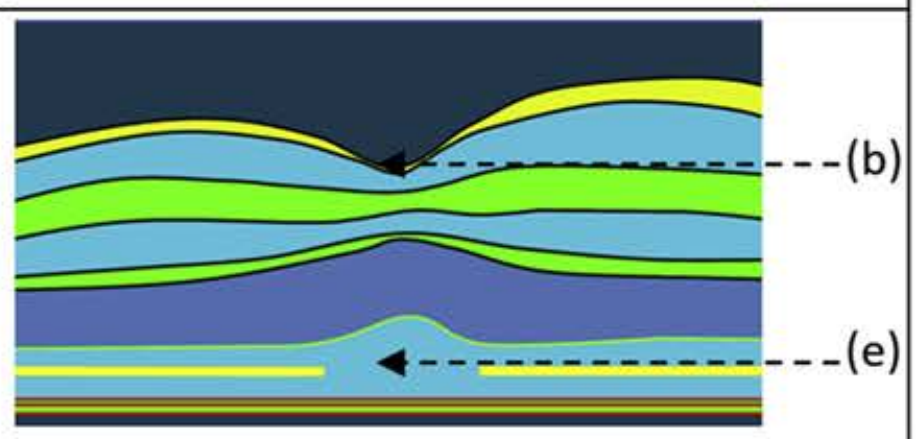
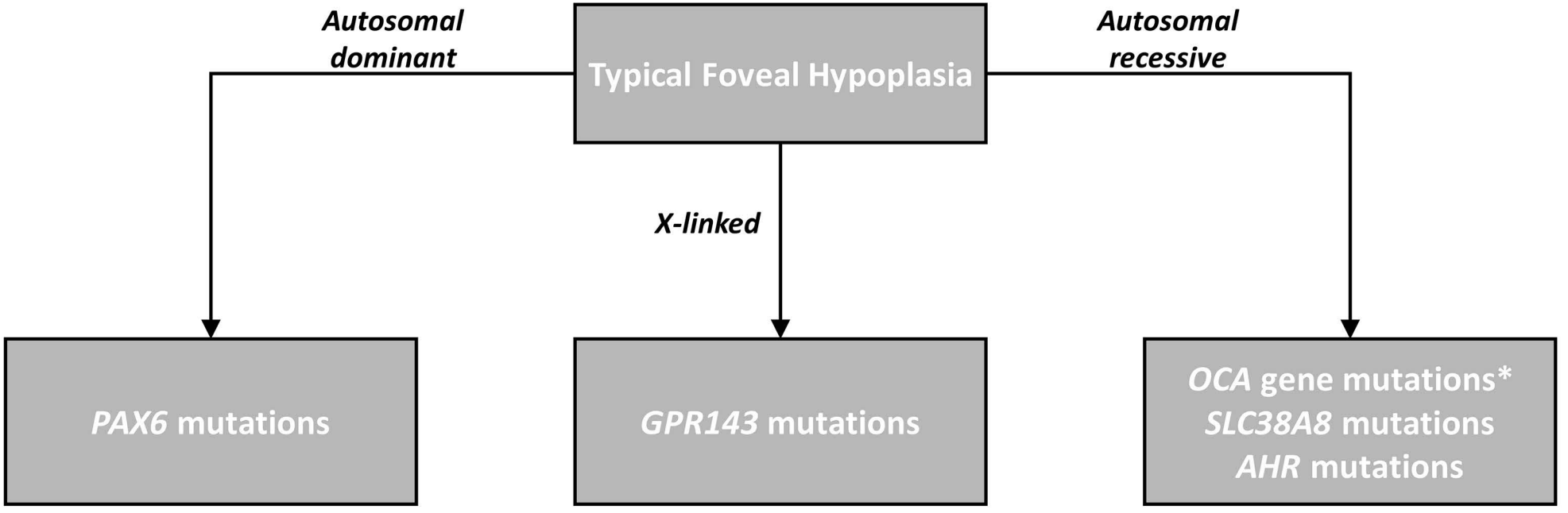

CRD

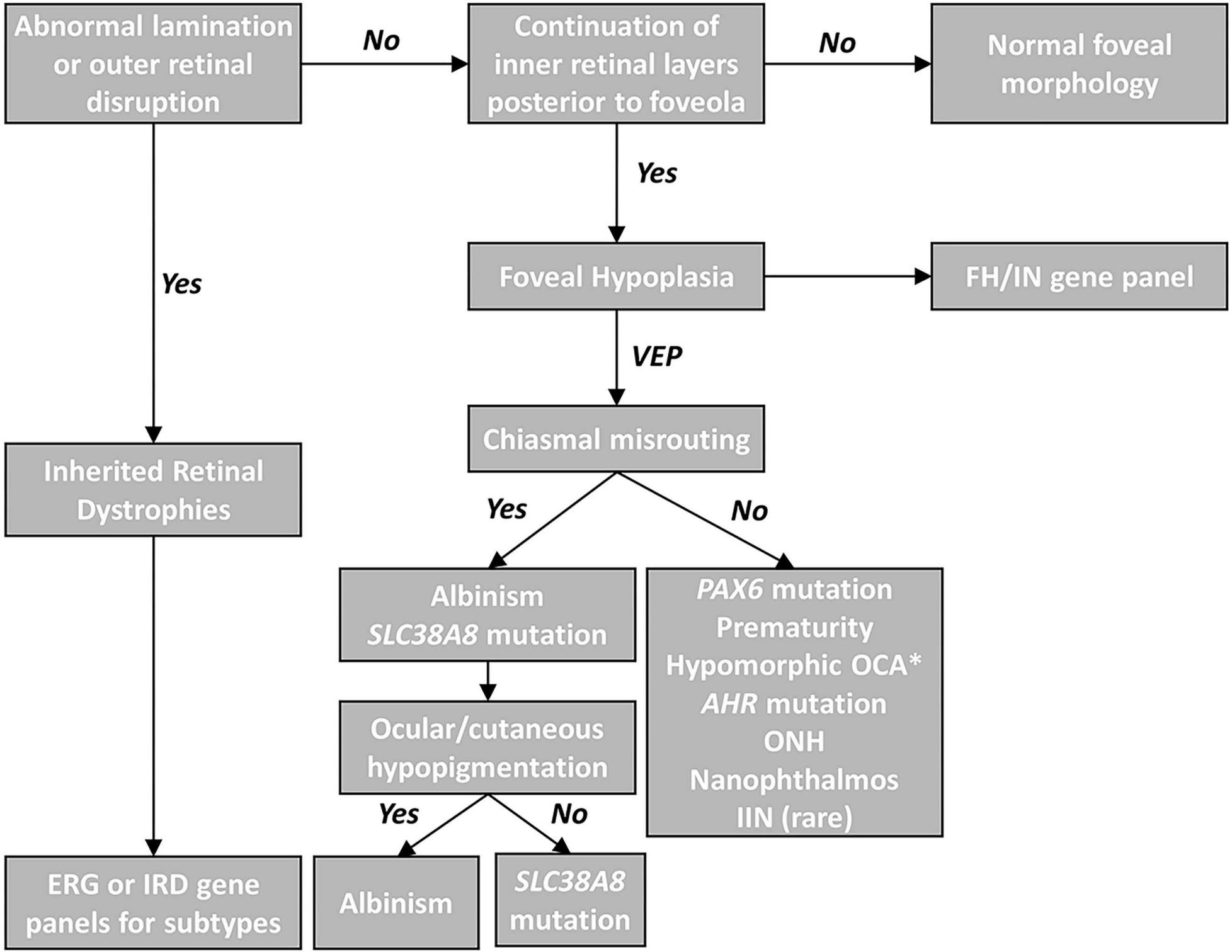

Microcephaly

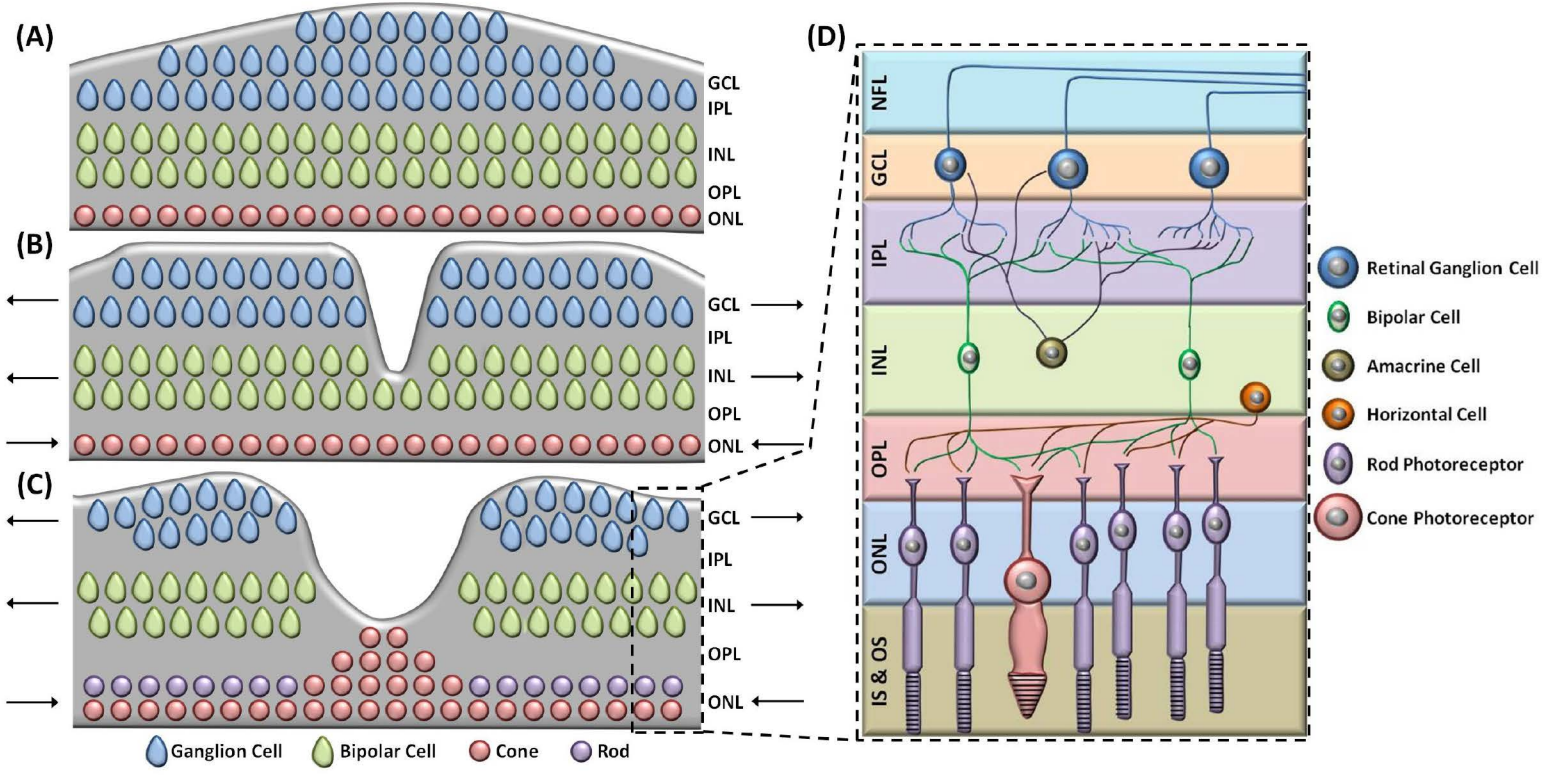

Microcephaly

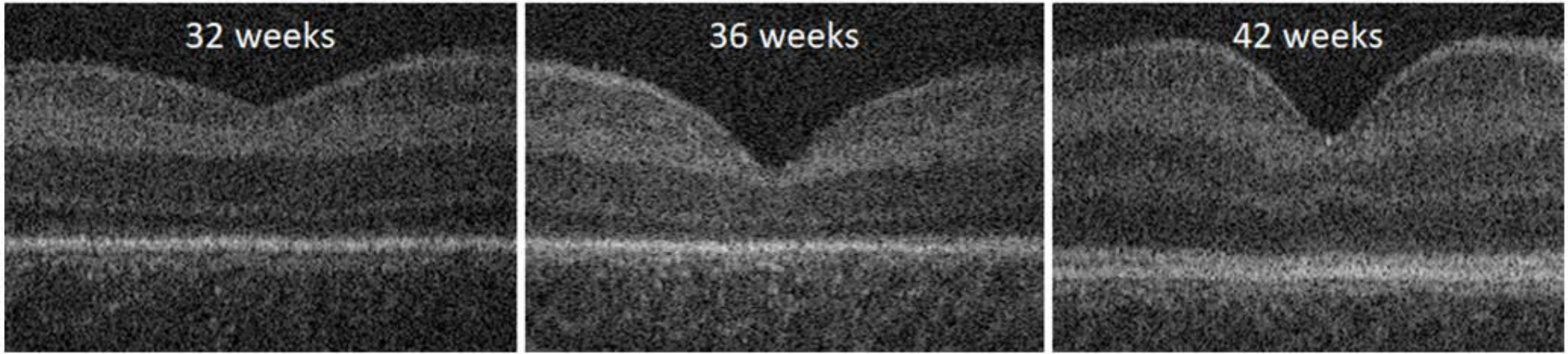
Normal foveal structural features detectable using optical coherence tomography	Illustration
(a) Extrusion of plexiform layers (b) Foveal pit (c) OS lengthening (d) ONL widening	

Grade of foveal hypoplasia	Structural features detected on optical coherence tomography	Present or absent	Illustration
1a	**(a) Extrusion of plexiform layers** **(b) Foveal pit – Nearly normal** (c) OS lengthening (d) ONL widening	**(a) Absent** (b) Present (c) Present (d) Present	
1b	**(a) Extrusion of plexiform layers** **(b) Foveal pit – Shallow indent** (c) OS lengthening (d) ONL widening	**(a) Absent** (b) Present (c) Present (d) Present	
2	**(a) Extrusion of plexiform layers** **(b) Foveal pit** (c) OS lengthening (d) ONL widening	**(a) Absent** **(b) Absent** (c) Present (d) Present	
3	**(a) Extrusion of plexiform layers** **(b) Foveal pit** **(c) OS lengthening** (d) ONL widening	**(a) Absent** **(b) Absent** **(c) Absent** (d) Present	
4	**(a) Extrusion of plexiform layers** **(b) Foveal pit** **(c) OS lengthening** **(d) ONL widening**	**(a) Absent** **(b) Absent** **(c) Absent** **(d) Absent**	
Atypical	**(a) Extrusion of plexiform layers** (b) Foveal pit – Shallow (e) ISe disruption	**(a) Absent** (b) Present (e) Present	


Autosomal dominant
Typical Foveal Hypoplasia
Autosomal recessive
X-linked
PAX6 mutations
GPR143 mutations
OCA gene mutations*
SLC38A8 mutations
AHR mutations


Abnormal lamination or outer retinal disruption
No
Continuation of inner retinal layers posterior to foveola
No
Normal foveal morphology
Yes
Yes
Foveal Hypoplasia
FH/IN gene panel
VEP
Chiasmal misrouting
Inherited Retinal Dystrophies
Yes
No
Albinism SLC38A8 mutation
PAX6 mutation
Prematurity
Hypomorphic OCA*
AHR mutation
ONH
Nanophthalmos
IIN (rare)
Ocular/cutaneous hypopigmentation
Yes
No
ERG or IRD gene panels for subtypes
Albinism
SLC38A8 mutation


(A)
GCL
IPL
INL
OPL
ONL
(B)
GCL
IPL
INL
OPL
ONL
(C)
GCL
IPL
INL
OPL
ONL
Ganglion Cell
Bipolar Cell
Cone
Rod
(D)
NFL
GCL
IPL
INL
OPL
ONL
IS & OS
Retinal Ganglion Cell
Bipolar Cell
Amacrine Cell
Horizontal Cell
Rod Photoreceptor
Cone Photoreceptor


32 weeks
36 weeks
42 weeks