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Genetics of the anterior segment dysgenesis

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Abstract:

The anterior segment dysgeneses are a broad group of heterogeneous disorders characterized by developmental abnormalities of the anterior segment of the eye, including primary congenital aphakia, Peters sequence, aniridia, and Axenfeld–Rieger spectrum. These conditions can have overlapping phenotypes and both genotypic and phenotypic heterogeneity. This article provides a strategy for both phenotyping and then genotyping using a targeted stepwise approach.

Keywords:

Anterior segment mesenchymal dysgenesis, cornea, lens

Introduction

Anterior segment dysgenesis (ASD) encompasses a broad group of developmental disorders affecting the anterior part of the eye, particularly the cornea, iris, and lens. Understanding these conditions can be particularly complex due to variable expression, overlapping phenotypes, and both genetic and phenotypic heterogeneity. ASD relies on an accurate diagnosis and management. This paper will suggest a strategy for identifying the phenotype of these patients and how this can lead to appropriate genotyping to arrive at a final diagnosis.

Similar to other genetic conditions, a stepwise approach will achieve the most accurate phenotyping and genotyping. A comprehensive and accurate medical and family history associated with a complete systemic and ophthalmic examination is a key to establishing the phenotype, which will be the foundation of the most efficient genotyping process. By opting for this strategy, the clinician is also able to lower the risks inherent to genetic testing and minimize the false genotype rate.[1] It is essential to emphasize the role of genetic counseling during this process, before and after genetic testing.

We will focus on the most common and well-recognized disorders. Other less frequent disorders are summarized in Table 1.

Clinical Evaluation of Anterior Segment Dysgenesis

Clinical phenotyping of ASD requires a careful slit lamp examination, intraocular pressure, and, where indicated, imaging, to establish the clinical diagnosis. Figure 1 suggests a flow diagram to approach the identification of the phenotype. The first question the clinician should ask is whether a lens is present. This may require ultrasound biomicroscopy (UBM) or anterior segment optical coherence tomography (aOCT). If there is not, the most probable diagnosis is primary aphakia. Other clues to this diagnosis would include retinal dysplasia, a silvery gray appearance of the cornea, and a high likelihood of glaucoma. If a lens is present, the ophthalmologist may then ask a second question, if an iris is present. If there is little or no iris, perhaps only a residual stub or peripheral iris, the patient has aniridia. If a significant iris is present,

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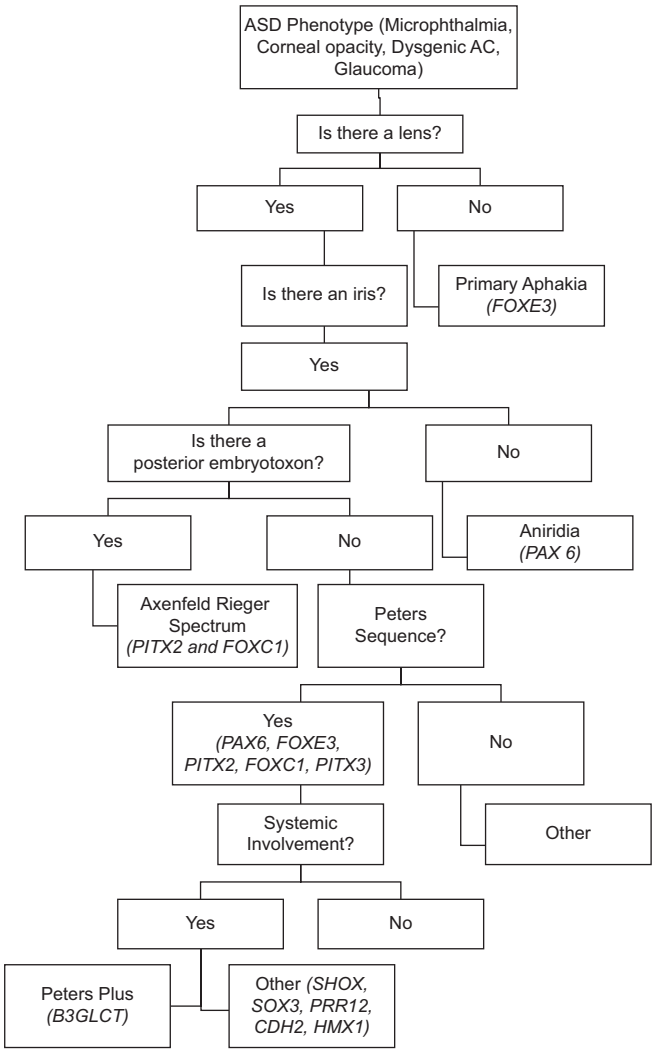

Figure 1: Diagnostic algorithm for phenotyping and genotyping anterior segment dysgeneses. Most frequent genes indicated

the next question arises: is there posterior embryotoxon? Although this finding is seen in 8%–32% of the general population,[1,10] it is suggestive of the Axenfeld–Rieger spectrum. If there is no posterior embryotoxon, one can look for other diagnostic indicators such as iridocorneal adhesions and a posterior scallop on the cornea on UBM or aOCT suggestive of Peters anomaly. Thereafter, other findings such as pupil position, persistent fetal vasculature on the iris, or a coloboma-like iris defect can help identify alternate phenotypes.

Congenital primary aphakia

Congenital primary aphakia is a severe panocular dysgenesis characterized primarily by aborted lens development during the 4th week of gestation due to failure of lens placode induction from the surface ectoderm.[11] As the lens has a critical role in the induction and stromal differentiation of the cornea,[10-13] this results in severe dysgenesis of the anterior segment and microphthalmia.[14] Often these patients present with a silvery corneal appearance probably secondary to thin corneal stroma and disorganized collagen lamellae.[15] As the anterior and posterior structures visualization usually is poor, aOCT or UBM can identify the absence of a lens. Some patients present with buphthalmos due to glaucoma, which can occur in over 20%.[16] Patients may also present with features of Peters anomaly and/or retinal dysplasia.

Congenital primary aphakia is due to pathologic variants in *FOXE3*. This gene encodes a transcription factor with a DNA-binding domain, the forkhead domain. In a 2022 series, 82% of patients showed pathogenic heterozygous variants in this gene.[12] There have been reports of autosomal dominant and recessive inheritance. Usually, nonsense variants follow an autosomal recessive pattern, with more severe ocular and systemic manifestations. Autosomal dominant variants usually result in a C-terminal extension of the protein, with a milder and isolated ocular phenotype. Reported extraocular manifestations to include Arnold–Chiari malformation, global developmental delay, polycystic ovary syndrome, ventricular septal defect, and renal pelvic dilation. Variants in this gene have also been associated with thoracic aortic aneurysms.[17]

Aniridia

Aniridia is an autosomal dominant disorder, almost always secondary to heterozygous variants or deletions in *PAX6*, with high penetrance, variable expression, and phenotypic heterogeneity.[12,18] *PAX6* is the master control gene for eye morphogenesis, so pathogenic variants result in a broad spectrum of eye manifestations.[19] The principal clinical manifestation is the underdevelopment of the iris, but the disorder is also associated with cataracts, keratopathy, glaucoma, nystagmus, and optic nerve and foveal hypoplasia.[20] Aniridia secondary to large deletions may involve both *PAX6* and the Wilms tumor gene (*WT1*), resulting in WAGR syndrome: Wilms tumor, aniridia, genitourinary abnormalities, and the relative difference in development. Genetic testing gives critical information about cancer risk: either through chromosomal microarray that identifies a deletion involving *WT1* or sequencing of *PAX6* identifying intragenic pathogenic variants. In cases where genetic testing is unavailable, abdominal ultrasound screening protocols should be used.[21] Deletion of the region downstream of *PAX6* and *WT1,* involving the genes *ELP4* and/or *DCDC1,* which affect the expression of *PAX6*, may also result in aniridia. The presence of aniridia plus posterior embryotoxon should suggest the rare aniridic form of the Axenfeld–Rieger spectrum due to deletions or duplications involving 6p25.[22] There have been reports of a condition characterized by blepharophimosis and ASD, including near-total absence of the iris, microphthalmia, and macular

Table 1: Less common anterior segment dysgeneses

Disorder	Inheritance	Genes*	Systemic manifestations†
Coloboma[2]	AR, AD, XLr, XLd	ALG3 *SCKL* *TMEM67* *POMT1* *PITX2* *PQBP1*	Microcephaly, developmental delay, Pai syndrome, Renpenning syndrome, Skeletal dysplasia, Brain malformations
Cornea plana[3]	AD, AR	*KERA*	None reported
Anterior segment mesodermal dysgenesis[4]	AD	*PITX3*	None reported
Congenital iris ectropion[5]		*PAX6*	Neurofibromatosis type 1, Prader–Willi
Megalocornea[6]	XL, AD, AR	*CHRDL1* dup22q. 11.2	Mucolipidosis, Neuhauser syndrome, Osteogenesis imperfecta
Microcornea[7,8]	AD, AR	*EPHA2* *FOXE3* *GJA8* *CRYGD* *CRYGC* *MAB21L2* *ATOH7, SLC16A12* *BEST1* *ARL2* *MIP* *GJA3* *MAF* *CRYAA* *CRYBB3* *CRYBB2* *CRYBB1, CRYBA4* *NHS* *SOX2*	Ehlers–Danlos syndrome, Marfan syndrome, Norrie syndrome, Turner syndrome, Waardenburg syndrome, Alport syndrome, Oculodentodigital syndrome
Autosomal dominant anterior stromal iris hypoplasia[9]	AD	*PITX2*	None reported
Iris traction band		Unknown	None reported

*Most commonly associated genes with the isolated ASD; †Syndromes listed in association although the genes for these syndromes are not typically associated with the listed ocular findings as an isolated finding. Nomenclature: AD, AR, XLd, XLr. AD=Autosomal dominant, AR=Autosomal recessive, XLd=X-linked dominant, XLr=X-linked recessive

dysgenesis/hypoplasia due to missense variants in gene *MAB21L1*.[23]

Axenfeld–Rieger spectrum

This spectrum is characterized by the variable combination of posterior embryotoxon, iridocorneal adhesions, iris hypoplasia, and corectopia/polycoria. Systemic features include anomalies of the teeth, redundant periumbilical skin, facial dysmorphism, hearing impairment, and heart abnormalities.[24] It is autosomal dominant with high penetrance and variable expression.[25] Pathogenic variants in *PITX2*, a fundamental transcription factor in eye development, are more often associated with systemic manifestations. Congenital heart defects and hearing loss are more common with pathogenic variants in *FOXC1*. These two genes may be disease causing by deletion or duplication as well. They are responsible for approximately 70% of cases.[13,24] Less frequent genes in which pathogenic variants have been associated with Axenfeld–Rieger spectrum phenotypes include *RIEG2*,[26] *GJA1*,[27] *COL4A1*,[28] *FGD1, PIK3R1*,[29] and *FOXC2, CYB1P1, LAMB2*.[30]

Isolated posterior embryotoxon, usually without iridocorneal adhesions, can be an isolated finding in between 8% and 32% of the general population.[10] One systemic association is Alagille syndrome secondary to *JAG1* variants.[31]

Peters anomaly/sequence

Peters anomaly/sequence is characterized by posterior corneal defects with secondary opacity associated with iridocorneal and possible keratolenticular adhesions with or without cataracts. This condition is the result of a defective lens formation from surface ectoderm, followed by secondary disruption of neural crest migration during embryogenesis.[32] The majority of cases are sporadic, but autosomal recessive and dominant inheritance has been described.[33] This spectrum is characterized by broad genotypic heterogeneity. The genes more frequently involved in this condition are *PAX6, FOXE3, PITX2, FOXC1*, and *PITX3*. However, there have been reported variants in *COL4A1, CYB1P1, FLNA, HCCS, NDP, SLC4A11*, and *TFAP2*.[34]

Peters-Plus syndrome refers to several disorders. The designation most accurately describes autosomal recessive Peters sequence in the setting of skeletal dysplasia, developmental delay, and other malformations due to biallelic disruption of function of the *B3GLCT* on 13q.[35] Peters sequence can also be seen with a variety of other malformations, in particular cardiac, due to disruption of a variety of genes (e.g., *SHOX, SOX3, PRR12, CDH2,* and *HMX1)*, some of which have yet to be discovered. Genetic testing should be driven by the specific systemic phenotype.

Iris coloboma is often isolated but may be part of a larger picture, including ocular coloboma with microphthalmia, optic nerve involvement, and other ocular developmental disorders such as cataract, persistent fetal vasculature, and uncommonly glaucoma, with or without systemic manifestations.[36] The genetic testing strategy is informed by the complete phenotype. Cornea plana is characterized by flattening of the corneal surface, associated with variable degrees of hyperopia, peripheral corneal opacity with or without glaucoma.[37] Anterior segment mesodermal dysgenesis is characterized by variable degrees of corneal opacity, posterior embryotoxon, and corneal-irido-lenticular adhesions. It has been associated with the development of glaucoma, making routine screening examinations mandatory.[38] Congenital iris ectropion is an isolated, often unilateral, disorder associated with angle dysgenesis with secondary development of glaucoma.[5] The main diagnostic criteria for megalocornea are a corneal diameter >12.5 mm in the presence of normal pachymetry and axial length. This can be associated with radial iris transillumination. It is not associated with glaucoma, but the differential diagnosis of primary congenital glaucoma should be considered. Microcornea features a corneal diameter <10 mm (<9 mm in newborns) with/without other ocular and/or systemic malformations.[7] Genotyping is again targeted toward the complete phenotype. Autosomal dominant anterior stromal iris hypoplasia is characterized by a poorly developed iris stroma that allows for the baring of the iris sphincter. There is a high incidence of glaucoma.[9]

Genotyping

Once a complete phenotype has been established, genetic testing can proceed, preferably using a strategy with a narrow gene hypothesis to minimize the false genotype rate.[1] This process should only be pursued with proper pretest genetic counseling. The goals of genetic counseling are to provide complete information about testing options, recurrence risk, risk to other family members, cost, expectations for result accuracy and timing, incidental results, and possible variants of uncertain significance. Genetic counseling aims to be nondirective.[39] Genetic counselors have expertise in facilitating appropriate test selection, incorporating the phenotype information from the ophthalmologist, and considering other factors, including patient preference and motivations, certification and licensing standards met by performing laboratories, and insurance coverage and payment options. They can also identify research opportunities or other supportive resources for patients and families.[40]

Genetic counseling is also essential after the results are received. One of the fundamental steps in this whole process is the interpretation of results. The results should be interpreted following the American College of Genomics and the Association of Molecular Pathology guidelines who define a five-tier framework of classification of gene variants as: pathogenic, likely pathogenic, uncertain significance, likely benign, and benign.[41] This analysis should be comprehensive, looking at the function of the gene involved, if the variants identified are reported in medical literature, population frequency of the variant, evolutionary conservation of the affected gene location, and other characteristics. While testing laboratories generally provide interpretation according to these guidelines, it is important for the clinical team to review this carefully and analyze the match between the genotype and phenotype observed in their patient to ensure consistency. Testing of other family members may be necessary to understand the results of the proband. This process requires a team with expertise in interpreting genomic variant results and disclosing them to patients and families in a meaningful way. It is the latter which requires proper genetic counseling to effectively communicate, and interpret the impact of, the genetic test results to the patient and their family.

Conclusion

The anterior segment dysgeneses are a complex and sometimes the overlapping collection of developmental disorders which may be isolated or occur in the setting of associated systemic disease. A comprehensive clinical evaluation is mandatory to achieve a robust phenotype which can then lead to appropriate genetic testing. The process should be supported by genetic counseling.

Data availability statement

Data Sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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Conflicts of interest

The authors declare that there are no conflicts of interests of this paper.

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