



GENESIS OF AXENFELD RIEGER SYNDROME: A REVIEW

Amrita Kumari¹, Jyoti Kumari¹, Ekta Singh² and Swapnil Sharma¹

¹Department of Pharmacy, Banasthali University -304022, Rajasthan, India.

²Department of Food Science and Nutrition, Banasthali University -304022, Rajasthan, India.

*Corresponding author's E-mail: swapnilsharma1978@gmail.com

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ABSTRACT

Axenfeld-Rieger syndrome is an autosomal dominant disorder with high penetrance but variable expressivity associated with systemic as well as ocular developmental abnormalities secondary to genetic defects resulting from derangement in neural crest cell differentiation and migration. Systemic findings include mild craniofacial dysmorphism, dental and cardiovascular abnormalities, and redundant umbilical skin. The most common ocular manifestations include a spectrum of posterior embryotoxon, iris atrophy, corectopia, and ectropion uveae with 50% of patients developing glaucoma. There are three types of ARS: Type 1, Type 2, Type 3 which result due to mutation in gene PITX2 on chromosome 4, gene FOXC1 on chromosome 13, and FOXC1 on chromosome 6 respectively. Various clinical trials are being done to identify other genes related to this syndrome. Till date no specific treatment is known except the beta blockers, alpha agonist, carbonic anhydrase inhibitors and some prostaglandin analogues.

Keywords: Peter Anomaly, Corectopia, Trabeculotomy, Glaucoma.

INTRODUCTION

Axenfeld-Rieger syndrome (ARS) is an autosomal dominant genetic condition characterized by anterior segment dysgenesis and systemic abnormalities. The syndrome was named after the two ophthalmologists Theodor Axenfeld (Germany) and och Herwig Rieger (Austria), who described it in 1920 and 1935 respectively. Axenfeld characterized the anomaly which described posterior embryotoxon and iris strands adherent to the anteriorly displaced Schwalbe's line.⁵ Rieger described patients with congenital iris abnormalities including, corectopia, iris hypoplasia and polycoria, which is referred as Rieger anomaly.⁵ Rieger anomaly, associated with systemic findings, such as maxillary hypoplasia, umbilical abnormalities, dental, facial bone defects including, or pituitary involvement is known as Rieger syndrome.³⁻⁴ The combination of Axenfeld anomaly, and Rieger syndrome is known collectively as Axenfeld-Rieger syndrome. This disorder is seen in approximately 1/200,000 live births. Several cases are diagnosed during infancy or childhood; however, glaucoma typically occurs in late childhood or adulthood.⁵ In April 2008, the UKGTN published a review of service provision within genetic ophthalmology. The report highlighted that some genetic testing in ophthalmology existed in a research setting with no provision for transferring to main stream genetic testing. Bristol Eye Hospital (BEH) established a service Axenfeld-Rieger syndrome during a period of research (WAVE (scanning) point mutation analysis (PITX2 and FOXC1)).⁵

Epidemiology and Pathogenesis

The syndrome is caused by developmental defects of the eyes and teeth, during the first three months of pregnancy. Mutations in certain genes have been identified. Approximately 40 per cent of individual

showed genetic mutation, while no genetic abnormalities have been identified in the remaining individuals. Axenfeld-Rieger syndrome (ARS) is autosomal dominant in most cases, but can also occur sporadically. It is associated with a 50% risk of glaucoma.⁶⁻⁷ ARS is a genetically heterogeneous group of abnormalities which is a result of mutations in at least 4 different gene loci. Mutations in PITX2 on ch 4q25, FOXC1 on 6p25, PAX6 on 11p13, and FOXC1 on 13q14 have been associated with formation of ARS.⁸⁻⁹ FOXC1 and PITX2 both encode for transcription factors which regulate expression of downstream genetic targets by binding to specific DNA sequences and activating transcription. In mouse models, both FOXC1 and PITX2 are expressed in the ocular organs and structures affected in ARS during embryogenesis.¹⁰⁻¹¹

There are 5 reported loci as shown in figure 1 which have been associated with ARS. RIEG was identified and cloned in 1996, and later renamed as PITX2. FOXC1, second loci of ARS, was identified in 1998. 40% ARS cases was reported in both PITX2 and FOXC1 which occurred due to point mutations and copy number variations. Two loci have been identified but the genes remained unknown.

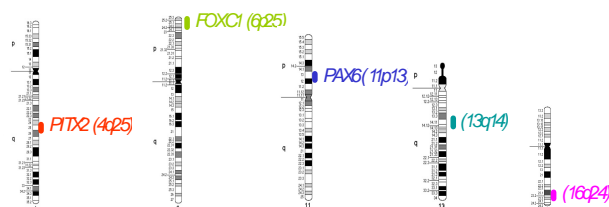


Figure 1

More than 44 mutations related to FOXC1 is reported till date. Chromosomal aberration due to missense, nonsense, insertion/deletion and duplication of genes



were observed. Majority of mutations resided in the fork head domain.

More than 40 mutations related to PITX2 are reported till date. Chromosomal aberration due to missense, nonsense, splice-site mutation and insertion/deletion of genes were observed. Majority of mutations resided in the homeodomain as shown in figure 2.⁵

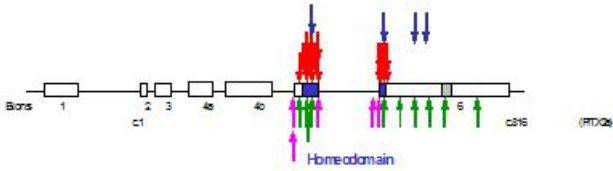


Figure 2

Case Study

Case 1: Rieger syndrome case with all the typical dysmorphic features and the molecular genetic finding was described by use of FISH analysis of the PAX6 gene. An eight-year old girl with iridogoniodysgenesis, iris stroma hypoplasia, corectopia, underdeveloped premaxilla and a congenital absence of nine teeth in the maxilla. The mandibular front teeth were in the peg-shaped and all teeth were small. There was failure of involution of the periumbilical skin. FISH analysis using probes for the PAX6 gene showed a small deletion for the PAX6 gene on one homologue of chromosome 11. Hence it was concluded that Rieger syndrome can in addition to PITX2 gene mutations and abnormalities at chromosome 13q14 can be associated with PAX6 gene abnormalities.¹²⁻¹³

Case 2: A 13 year old girl got FOXC1 deletion and was observed with enhanced surveillance of glaucoma and was referred to cardiology as well as prenatal testing in future.

Case 3: Figure 3 shows PITX2 Splice-site Mutation in 44 year old male was observed with bilateral secondary glaucoma and hydrocephalus.

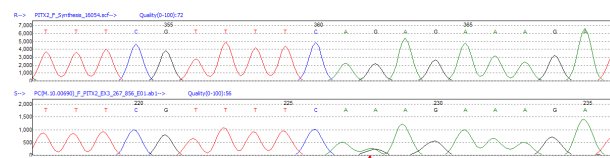


Figure 3

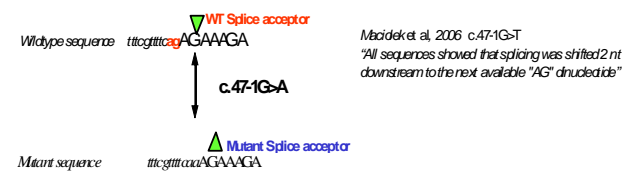
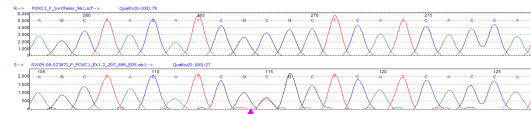


Figure 4

PITX2 point mutation analysis lead to the identification of splice-site mutation in PITX2 c.47-1G>A as shown in figure 4. Previously reported mutations affected position c.47-

1G>T and c.47-1G>C. Functional studies in these cases reported that protein were poorly expressed and truncated.

Case 4: Figure- 5a and b shows, FOXC1 Unclassified Variant was seen in 23 year old male



Point mutation analysis of FOXC1 identified a UV; c.254C>T, p. Ala85Val.

Figure 5a

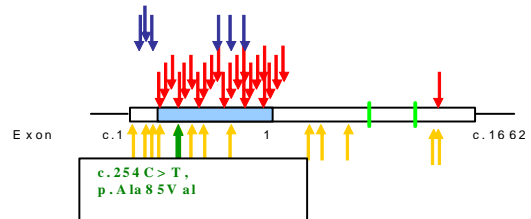


Figure 5b

Evidence confirmed variant resides in the functional forkhead domain of the protein. Reports showed mutation affecting the same codon but a different nucleotide (c.253G>C, p.Ala85Pro) were associated with eye and heart defects in two family members.⁵

Types of Axenfeld Rieger Syndrome

Type 1:

Systemic features: Dental anomalies and mid-facial hypoplasia secondary to underdeveloped maxillary sinuses are among the most common systemic features. The nasal root often appears abnormally broad and the lower lip appears to protrude. The teeth become small and conical in shape with wide spaces between them (diastema). Some teeth may be missing. The umbilicus may fail to involute normally and retains excessive, redundant skin which sometimes leads to the erroneous diagnosis of an umbilical hernia. Hypospadias is frequently present while anal stenosis, cardiac defects and sensorineural deafness, are less common.

Genetics: Type 1 is caused by a mutation in the homeobox transcription factor gene, PITX2, located at 4q25-q26. A type of iris hypoplasia (IH)/ iridogoniodysgenesis (IGDS) (IRID2) disorder has been classified separately but is caused by a mutation in PITX2 as well and many cases have the same systemic features. Mutations in the same gene have also been found in ring dermoid of the cornea and in some cases of Peter’s anomaly. RIEG2 is rare but a deletion of 13q14 has been reported in several cases. Mutations in the FOXC1 gene (6p25) may be responsible for RIEG3.¹⁷⁻¹⁹

Type 2:

Systemic features: Dental and hearing defects, mild craniofacial dysmorphism, hydrocephalus,



cryptorchidism, fetal lobulation of kidney, congenital heart defect, and congenital hip abnormalities.

Genetics: Deletion of 13q14 performed linkage analysis of a large 4-generation family and demonstrated that Rieger syndrome was not linked to 4q25 but to markers on 13q14. Phillips *et al.* (1996) pointed to forkhead (FOXO1A) as an excellent candidate for the site of the mutation in this form of Rieger syndrome. They stated that if such mutations are found, this would be an example of a gene that can function both as an oncogene (producing rhabdomyosarcoma) and as a 'teratogene' (producing RIEG2).

HGNC Approved Gene Symbol: RIEG2 whose cytogenetic location is 13q14 and which had Genomic Coordinates (GRCh37): 13:40,100,000 - 55,300,000.²⁰⁻²¹

Type 3:

Systemic features: Patients are less likely to have the systemic anomalies such as craniofacial and dental defects often seen in RIEG1. They often have a sensorineural hearing deficit and many have cardiac valvular and septal defects not usually seen in RIEG1.

Genetics: They result from a mutation in the FOXC1 gene located at 6p25. Mutations in the same gene also cause iris hypoplasia/iridogoniodysgenesis (IGDA) (IRID1).¹⁸

Symptoms

Axenfeld-Rieger syndrome is a bilateral, heterogeneous condition and may include developmental abnormalities in the anterior chamber angle, iris, and trabecular meshwork. Posterior embryotoxon, an increased intraocular pressure, correctopia, polycoria and ectropion uveae, are common ophthalmologic findings with ARS. Photophobia may be a symptom resulting from the pupillary and iris abnormalities. The most commonly recognized clinical manifestations of ARS are the iris correctopia/atrophy, and posterior embryotoxon. Typically, the remainder of the cornea is clear. Occasional patients have megalocornea or microcornea. The posterior embryotoxon may not be visible with the slit lamp examination.³ The iris strands adherent to the posterior embryotoxon can range from fine threadlike strands to broad bands of iris tissue. Likewise, the iris stroma may be grossly abnormal including generalized atrophy with correctopia, ectropion uveae, and often is similar in clinical appearance to iridocorneal endothelial syndrome (ICE).⁴ Systemically, mild craniofacial dysmorphism, dental abnormalities, and redundant umbilical skin are observed. The facial abnormalities include hypertelorism, telecanthus, maxillary hypoplasia, and a broad, flat nasal bridge. Dental abnormalities include hypodontia, microdontia or oligodontia. Patients may have hypospadias, anal stenosis, pituitary abnormalities, growth retardation, and cardiac valvular abnormalities.^{5, 14} Abnormalities of the pituitary gland and other surrounding areas are less common, but more serious findings.

Diagnosis

Axenfeld-Rieger Syndrome can be diagnosed during an eye examination. The most important signs include: checking the pressure in the eye, examining the drainage angle and looking at the optic nerve. If the pressure is high then Glaucoma is likely. Sometimes small mirror helps to look at the drainage angle. Water in the eye drains out at the drainage angle. Glaucoma looks different from usual. If the angle looks blocked or not fully developed then this might explain why the pressure is high. The optic nerve can also help to make a diagnosis. In Glaucoma damage occurs to the optic nerve which causes some of the wires within it to wear out and disappear. By looking into the eye with a special instrument all these wires can be seen 'end on' as they exit the eye and pass to the brain. This is the 'head' of the optic nerve. If none of the wires are damaged then the 'head' of the optic nerve looks yellow and pink. If many wires are missing then the optic nerve looks pale and white. This is the common appearance in Glaucoma. Eye doctors often describe the damage to the optic nerve head as 'optic disc cupping'. Younger children can be examined easily while they are asleep, under a short anesthetic, the eye doctor can check the pressure in the eye and the appearance of the head of the optic nerve. Axenfeld-Rieger Syndrome is diagnosed if glaucoma is confirmed along with other signs such as a flattened appearance to the nose and face and fewer teeth than normal.²²

ARS Testing Strategy (Figure- 6)

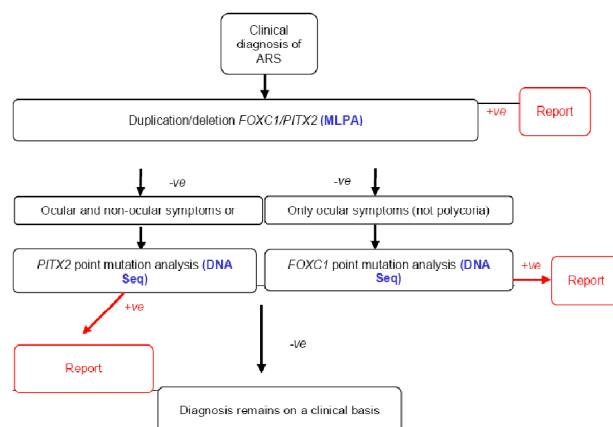


Figure 6

Treatment

The presence of glaucoma requires prompt and vigorous treatment but control is difficult with blindness too often the result. Oral surgery may be beneficial for dental problems. Low vision aids can be useful.

Medical Management

Medical management of congenital and childhood glaucoma is generally used as an adjunct to surgical interventions. Aqueous suppressants, including beta-blockers such as atenolol, propranolol, timolol, betaxolol, levobulolol²³⁻²⁴ and carbonic anhydrase inhibitors such as



acetazolamide, dorzolamide, brinzolamide²⁵ have been shown to be safe and effective. Side effects should be considered. Prostaglandin analogues such as latanoprost may be used to lower IOP and are generally.²⁶⁻²⁷ Alpha-2 agonists such as Clonidine, especially brimonidine, is contraindicated in children less than 2 years of age secondary to their association with potentially serious apnea, bradycardia, hypotension, hypotonia, and CNS depression in this population.²⁸ Praclonidine should be used with caution for the same considerations, but seems to be safer than brimonidine.²⁹

Surgical Management

As in congenital glaucoma, surgical intervention is more efficacious than medical management in ARS.³⁰ Surgical options include, goniotomy, trabeculotomy, trabeculectomy with or without antifibrotic agents, aqueous shunt procedures, or cyclodestructive procedures. In a retrospective review of pediatric glaucoma by Bussieres *et al*, 40% of patients with ARS had goniotomy, 30% had trabeculotomy, and 2% required glaucoma drainage devices. Most of those patients required 1.5 surgeries per eye.^{26,31}

CONCLUSION

ARS is a term that can be used to describe a variety of overlapping phenotype. Till date at least 3 known genetic loci are found which can cause this disorder. The important feature of these phenotypes is that they confer a 50% or greater risk of developing glaucoma. The condition can also lead to gradual and irreversible visual loss and needs specialist care and careful monitoring. Early detection of ARS are measuring potentially elevated intraocular pressure helps physician to prevent visual field loss. Various clinical trials are being done to identify other genes related to this syndrome. Till date no specific treatment is known except the beta blockers, alpha agonist, carbonic anhydrase inhibitors and some prostaglandin analogues so research are being done in this field to specify a particular line of treatment for this syndrome. Novel targets for treatment are now in development with the primary objective of curing it up to the root level. Furthermore, these genetic issues may be utilized in the development of targeted drug therapies for Axenfeld-Rieger syndrome.

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