Axenfeld-Rieger Syndrome

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Axenfeld-Rieger syndrome is primarily an eye disorder, although it can also affect other parts of the body. This condition is characterized by abnormalities of the front part of the eye, an area known as the anterior segment. For example, the colored part of the eye (the iris), may be thin or poorly developed. The iris normally has a single central hole, called the pupil, through which light enters the eye. People with Axenfeld-Rieger syndrome often have a pupil that is off-center (corectopia) or extra holes in the iris that can look like multiple pupils (polycoria). This condition can also cause abnormalities of the cornea, which is the clear front covering of the eye.

Keywords: genetic conditions

1. Introduction

About half of affected individuals develop glaucoma, a serious condition that increases pressure inside the eye. When glaucoma occurs with Axenfeld-Rieger syndrome, it most often develops in late childhood or adolescence, although it can occur as early as infancy. Glaucoma can cause vision loss or blindness.

The signs and symptoms of Axenfeld-Rieger syndrome can also affect other parts of the body. Many affected individuals have distinctive facial features such as widely spaced eyes (hypertelorism); a flattened mid-face with a broad, flat nasal bridge; and a prominent forehead. The condition is also associated with dental abnormalities including unusually small teeth (microdontia) or fewer than normal teeth (oligodontia). Some people with Axenfeld-Rieger syndrome have extra folds of skin around their belly button (redundant periumbilical skin). Other, less common features can include heart defects, the opening of the urethra on the underside of the penis (hypospadias), narrowing of the anus (anal stenosis), and abnormalities of the pituitary gland that can result in slow growth.

Researchers have described at least three types of Axenfeld-Rieger syndrome. The types, which are numbered 1 through 3, are distinguished by their genetic cause.

2. Frequency

Axenfeld-Rieger syndrome has an estimated prevalence of 1 in 200,000 people.

3. Causes

Axenfeld-Rieger syndrome results from mutations in at least two known genes, *PITX2* and *FOXC1*. *PITX2* gene mutations cause type 1, and *FOXC1* gene mutations cause type 3. The gene associated with type 2 is likely located on chromosome 13, but it has not been identified. The proteins produced from the *PITX2* and *FOXC1* genes are transcription factors, which means they attach (bind) to DNA and help control the activity of other genes. These transcription factors are active before birth in the developing eye and in other parts of the body. They appear to play important roles in embryonic development, particularly in the formation of structures in the anterior segment of the eye.

Mutations in either the *PITX2* or *FOXC1* gene disrupt the activity of other genes that are needed for normal development. Impaired regulation of these genes leads to problems in the formation of the anterior segment of the eye and other parts of the body. These developmental abnormalities underlie the characteristic features of Axenfeld-Rieger syndrome. Affected individuals with *PITX2* gene mutations are more likely than those with *FOXC1* gene mutations to have abnormalities affecting parts of the body other than the eye.

Some people with Axenfeld-Rieger syndrome do not have identified mutations in the *PITX2* or *FOXC1* genes. In these individuals, the cause of the condition is unknown. Other as-yet-unidentified genes may also cause Axenfeld-Rieger syndrome.

3.1. The genes associated with Axenfeld-Rieger syndrome

- FOXC1
- PITX2

4. Inheritance

This condition is inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder.

5. Other Names for This Condition

- ARS
- Axenfeld and Rieger anomaly
- Axenfeld anomaly
- Axenfeld syndrome
- AXRA
- AXRS
- Rieger anomaly
- Rieger syndrome

References

1. Chang TC, Summers CG, Schimmenti LA, Grajewski AL. Axenfeld-Rieger syndrome:new perspectives. Br J Ophthalmo l. 2012 Mar;96(3):318-22. doi:10.1136/bjophthalmol-2011-300801.
2. D'haene B, Meire F, Claerhout I, Kroes HY, Plomp A, Arens YH, de Ravel T,Casteels I, De Jaegere S, Hooghe S, Wuyts W, van den Ende J, Roulez F,Veenstra-Knol HE, Oldenburg RA, Giltay J, Verheij JB, de Faber JT, Menten B, DePaepe A, Kestelyn P, Leroy BP, De Baere E. Expanding the spectrum of FOXC1 andPITX2 mutations and copy number chang es in patients with anterior segmentmalformations. Invest Ophthalmol Vis Sci. 2011 Jan 21;52(1):324-33. doi:10.1167/i ovs.10-5309.
3. Hjalt TA, Semina EV. Current molecular understanding of Axenfeld-Riegersyndrome. Expert Rev Mol Med. 2005 Nov 8; 7(25):1-17. Review.
4. Idrees F, Vaideanu D, Fraser SG, Sowden JC, Khaw PT. A review of anteriorsegment dysgeneses. Surv Ophthalmol. 2 006 May-Jun;51(3):213-31. Review.
5. Phillips JC, del Bono EA, Haines JL, Pralea AM, Cohen JS, Greff LJ, Wiggs JL. A second locus for Rieger syndrome m aps to chromosome 13q14. Am J Hum Genet. 1996Sep;59(3):613-9.
6. Strungaru MH, Dinu I, Walter MA. Genotype-phenotype correlations inAxenfeld-Rieger malformation and glaucoma pati ents with FOXC1 and PITX2mutations. Invest Ophthalmol Vis Sci. 2007 Jan;48(1):228-37.
7. Tümer Z, Bach-Holm D. Axenfeld-Rieger syndrome and spectrum of PITX2 and FOXC1mutations. Eur J Hum Genet. 2 009 Dec;17(12):1527-39. doi: 10.1038/ejhg.2009.93.
