Eur J Pediatr (1995) 154 : 795–800

REVIEW

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Aniridia: recent achievements in paediatric practice

Received: 18 August 1994
Accepted: 17 February 1995

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Abstract Aniridia is a rare panocular disorder which primarily involves not only the iris, but also the retina, optic nerve, lens and cornea. Visual acuity deteriorates as a result of nystagmus, glaucoma, cataract, corneal opacities and retinal hypoplasia. Aniridia may appear as an isolated disorder, most often familial with autosomal dominance or sporadically in association with at least 12 syndromes. Both familial isolated and Wilms tumour, bilateral sporadic aniridia, genitourinary abnormalities and mental retardation syndrome-associated aniridia have been traced to a mutation of the PAX6 gene on band 11p13. Since genetic diagnosis of this disorder is already possible, counselling affected families should be preceded by karyotype studies and linkage analysis in familial cases of isolated aniridia. In sporadic cases of isolated aniridia or WAGR syndrome, we suggest that PAX6 mutation analysis be employed.

Key words Aniridia syndromes · WAGR syndrome · PAX6 gene · Genetic counselling

Abbreviation *WAGR* Wilms tumour, bilateral sporadic aniridia, genitourinary abnormalities and mental retardation

Introduction

Aniridia is an ophthalmological disorder which concerns paediatricians and geneticists alike. In the following article we review the epidemiology, ophthalmological findings and associated syndromes of this disorder and the recent genetic achievements made in this area.

Definition

Aniridia, or absence of the iris, was first described by Barrata in 1818 [2]. The condition is often more complex than hypoplasia of the iris. Nelson et al. [30] defined aniridia as a "panocular disorder affecting not only the iris, but the cornea, anterior chamber, lens, retina and optic nerve as well". It may occur as an isolated disorder, when only ocular pathology is observed, or in association with a variety of extra-ocular findings [6, 25, 39]. Aniridia is bilateral in 98% of cases [20].

Epidemiology

Population studies in Michigan and Denmark have revealed that the incidence of aniridia ranges between 1:64 000 and 1 : 100 000 [24, 30]. Two-thirds of all cases are familial, and one-third are sporadic [27, 30, 37]. The majority show an autosomal dominant inheritance pattern with almost complete penetrance but variable expression [7,

37]. In some rare syndromes, aniridia is transmitted in an autosomal recessive manner [28, 31, 41]. Two-thirds of the sporadic cases represent a new autosomal dominant condition [7, 30].

Isolated aniridia is familial in about two-thrids of the cases, while aniridia in association with extraocular pathology is mainly sporadic [5, 21, 22, 25, 29, 35, 40]. No significant sexual or racial predilection has been described [30].

Ophthalmological findings

Although infants and children are generally referred for defective iris structure and nystagmus [30], much more severe ocular findings may be observed in these patients.

The contour of the iris varies from total aplasia to partial hypoplasia. Different grades of severity may be observed in the same family. Even with apparently "complete" or "total" absence, a small portion of the iris tissue can always be found on gonioscopic examination or histologically. Atypical iris colobomas are also included among aniridia disorders [12, 28, 30] (Figs. 1, 2).

Glaucoma is observed in 6%–75% of patients. It usually develops in the first or second decades of life as a result of progression of the postnatal anatomical changes in the angle structure which leads to angle closure. Other causes of elevated intraocular pressure may be abnormal angle function, absence of Schlemm canal, or eye surgery [22, 30, 38].

Cataract develops in the first two decades of life in 50%–85% of patients and may require extraction. There is one report of familial spontaneously resorbed cataract [30, 40].

Ectopic lens occurs in up to 56% of patients, probably caused by a molecular defect of the zonules [19, 30].

Corneal defects such as a grey opacification associated with fine radial vessels in the peripheral superficial layer of the cornea may appear as early as age 2 years. These changes can progress and affect visual function [6, 19, 30]. Microcornea has also been reported [30, 40].

Optic nerve hypoplasia is a common finding. The majority of aniridia patients have at least mildly hypoplastic discs. The poor retinal and macular development seen in aniridic patients is responsible for the visual malfunction and photophobia [19, 30, 33]. However, there are reports of families in which affected members with absence of most of the iris have good visual acuity. This suggests that the primary cause of the retinal maldevelopment is distinct from the mechanisms that lead to aniridia [30, 33, 37].

Pendular horizontal nystagmus is present in most patients and is secondary to macular hypoplasia. Strabismus, usually esotropia, and high refractive errors are also very common.

Impaired vision is the end result of the ocular pathology listed above. The most important factors are the retinal and macular maldevelopment and damage as noted, and the cataracts, glaucoma and corneal opacifications. Of patients with aniridia, 86% are reported to have visual acuity of 20/100 or worse in the better eye [6, 19, 30].

Narrowed palpebral fissures with brow furrowing are generally considered characteristic of affected patients and are attributed to the voluntary grimace used to avoid photophobia. In 1988 Cohen and Nelson [5] reported on a family in which autosomal dominant aniridia was associated with congenital ptosis of the eyelids, probably a result of maldevelopment of the iris and the levator palpebrae superior muscle, as based on their common mesodermal origin. Microphthalmia should also be considered a potential cause of a narrow palpebral fissure [5].

Refractive correction is mandatory in the ophthalmological management of aniridic patients [30]. Although many of them, especially those with familial isolated aniridia, have normal intelligence, they may be considered developmentally delayed because improper attention has been given to correction of their visual needs. Glaucoma, cataract and strabismus are the most common problems [19, 30, 38]. Surgical or topical (for some glaucoma patients) treatment should be instituted as early as possible.

The WAGR syndrome

WAGR (Wilms tumour, bilateral sporadic aniridia, genitourinary abnormalities and mental retardation) syndrome

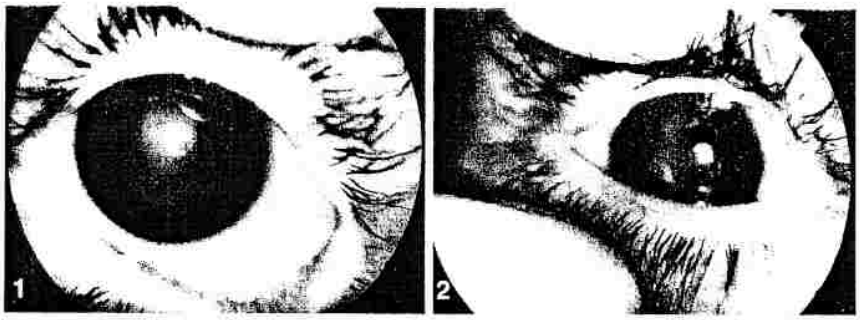

Fig. 1 Left eye: aniridia in a girl. The edge of the lens is visible as well as the cataract

Fig. 2 Right eye: aniridia in the sister's eye. The edge of the lens is visible with its opacities

is the most common and most important of the aniridia syndromes. The association of Wilms tumour with aniridia was first observed by Brusa and Torricelli in 1953 [3]. Its incidence is rarer (1:69) than the association of Wilms tumour with genitourinary abnormalities (4.4%–7%) or hemihypertrophy (2%–3%), but 1000 × more frequent than the incidence of aniridia in the general population [25, 30]. In 36% of cases of Wilms tumour and aniridia, the tumour is bilateral; sometimes the second tumour is so small that it may be detected only by contrast enhanced CT [21].

Other findings in patients with both Wilms tumour and aniridia include severe mental retardation (75%), craniofacial dysmorphism (75%) and genitourinary anomalies (66%). Growth retardation is frequent and microcephaly occasional [30]. Long, narrow face, prominent nose, and low-set ears with poor lobulation are characteristic features [30]. Jotterand and co-workers [21], added downslanted palpebral fissures, stubby nose, long and poorly demarcated philtrum and thin upper lip, as well as tracheomalacia and delayed closure of the anterior fontanelle.

WAGR syndrome may be only partially manifested in different combinations. Some authors propose renaming it "AGR triad with an increased risk of Wilms tumour". This triad could also be accompanied by other tumours such as gonadoblastoma [25]. The gonadal dysgenesis, which may be one of the genitourinary abnormalities, is a precancerous state that leads to gonadoblastoma in 30% –50% of patients [25].

There is a high incidence of deletion at 11p13 in patients with WAGR syndrome in all its manifestations [21, 25, 30]. Accordingly, the risk of developing Wilms tumour in aniridic patients with a deletion in 11p13 may be as high as 68% [21]. The WAGR syndrome usually occurs sporadically [21, 28, 30]. Wilms tumour develops in one-third of all patients with sporadic aniridia, most often prior to 3 years of age [30]. There is only one reported case of familial aniridia and Wilms tumour [28].

Other associated syndromes

In 1965 Gillespie [11] reported on two siblings with cerebellar ataxia, partial aniridia, and mental retardation. By 1990 this syndrome had been described in ten patients, several showed cerebellar hypoplasia on brain CT [31, 39]. The disorder is inherited as an autosomal recessive trait [31, 39].

Ring chromosome 6 syndrome (growth and mental retardation, microphthalmia, microcephaly, facial dysmorphism, short neck) was reportedly accompanied by unilateral aniridia and hydrocephalus in two cases [3, 22].

Iris hypoplasia, prominent Schwalbe line and iris adhesions to the Schwalbe line with hypodontia and sometimes mental retardation are seen in the Rieger syndrome [36].

Aniridia with sensorineural deafness (cochlear pattern) has been reported in a father and daughter [6]. The other daughter had only deafness.

Aniridia with absence or hypoplasia of the patella has been described in one family through three successive generations [28, 30]. Chromosomal studies in this family were normal.

Iris hypoplasia was found in 10% of patients with Marfan syndrome, but there are only two reports of "complete" aniridia among them [30, 35]. In one, partial adontia was also described [35].

Zamzam and colleagues [41] reported on a boy with bilateral aniridia, ectopia of the lens, dental anomaly and mental retardation, and Baraitser and Winter [1] on three nonrelated children with iris coloboma, ptosis, hypertelorism, broad nasal bridge, and growth and mental retardation. Chromosomal investigations were not conducted in these cases [1, 35, 41].

Aniridia may be associated with dwarfism, mental deficiency, craniofacial dysostosis, polydactyly and club foot. Nelson and co-workers [30] found aniridia in patients with Smith-Lemli-Opitz syndrome, Biemond syndrome and XXXXY chromosomal pattern.

Genetic achievements

Great progress had been made in the genetic study of aniriddia over the last 5 years. The aniridia gene locus has been discovered and its structure and mode of action determined.

The first steps in this direction were made by Riccardi and co-workers in 1978 [34] who reported the association of the WAGR syndrome with a deletion at band 13 of the short arm of chromosome 11. In 1982 Niikawa [32] suggested that familial isolated aniridia, for which no microscopic chromosomal changes had been discovered up to that time, may also be caused by a single break at 11p13 – an aberration that affects only the probable aniridia locus, but not the neighbouring genes responsible for the other manifestations of WAGR syndrome. The reports of familial isolated aniridia due to an interstitial deletion or a balanced reciprocal translocation at 11p13 that followed this hypothesis [7, 24, 33] allowed the aniridia locus to be assigned to band 11p13.

On the basis of overlapping constitutional deletions found in WAGR patients or in families with isolated aniridia, as well as in mice with the Sey (small eyes) gene (equivalent to the aniridia gene in humans), several maps of the WAGR region on the 11p13 band were made [4, 10, 12]. The sequence of the genes responsible for aniridia, Wilms tumour, decreased somatic growth and genitourinary abnormalities, and acatalasia is well illustrated (Fig. 3) and proves that WAGR may be a contiguous gene syndrome [27].

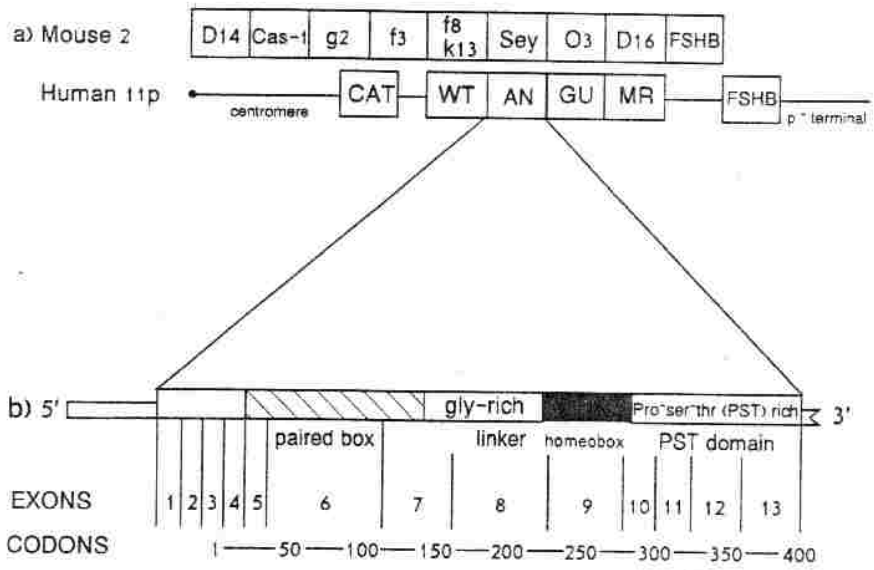

Fig. 3 Scheme of the location of the PAX6 gene on band p13 of chromosome 11. (**a**) Homologous portions of human chromosome 11 and mouse chromosome 2 with nine conserved DNA markers arranged according to the gene order established in humans. In humans the WAGR complex genes region is depicted between the CAT and FSHB genes: *CAT* Catalase gene; deletions cause reduced levels of erythrocyte catalase activity; WAGR region: *WT* Wilms tumour gene, *AN* Aniridia gene; *GU* Deletion-region cause genitourinary malformations; *MR* Deletions-region cause mental retardation; *FSHB* Follicle-stimulat-mone beta-subunit genes. (**b**) Structure of PAX6 (aniridi) with its four domains. The respective exons are indicated a PAX6 gene structure

Following the identification of the aniridia and the Wilms tumour genes it became possible to analyse familial and sporadic aniridia patients for deletions in 11p13 by pulsed field gel electrophoresis and by in situ hybridization. Such an analysis allows determination of the exact extent of the deletions and as a result, can delineate the risk for Wilms tumour development in patients with aniridia [8].

In 1980 after investigating 38 patients from one family with autosomal dominant aniridia, Ferrell and co-workers [9] suggested the existence of another aniridia gene on chromosome 2p. This was not confirmed in later reports. In 1992 Lyons and colleagues [23] examined the same family and postulated that the locus for aniridia had been misassigned and that the aniridia in this family could also be traced to a mutation in the 11p13 region.

Ton et al. [37] in 1991, and Glaser et al. [14] in 1992 isolated a candidate gene for the aniridia locus at 11p13. This gene was later named PAX6, because it proved to be the human homologue of the mouse PAX6 gene causing the small-eye phenotype. It belongs to the mammalian PAX gene family of developmental, protein-producing genes which invariably contain a paired box and a homeobox regions in their DNA sequence. Mutations in these genes that are highly conserved in the evolution are known to cause developmental defects (i.e., PAX3 gene and Waardenburg syndrome type I).

The PAX6 gene is located 700 kb telometrically from the Wilms tumour gene. It spans over 50 kb genomic DNA and codes for a 2.7 kb message [14, 37]. Th dicted polypeptide of 422 amino acids has the str motifs of a transcription factor. It acts as an inducti nal in the development of the ocular structures whe expressed – the neuroretina, the rim portion of the cup (corresponding to the future iris and ciliary bod lens, and the surface ectoderm that will form the and conjunctiva [17, 37].

Over the last 2 years further evidence has bee vided that aniridia arises from mutations in the gene, regardless of whether its occurrence is fam sporadic [15, 20, 27]. Two types of PAX6 mutati

Table 1 Syndromes and associations with aniridia

1. WAGR syndrome
2. Gillespie syndrome
3. Ring chromosome 6 syndrome
4. Rieger syndrome
5. Aniridia with sensorineural deafness
6. Aniridia with absent patella
7. Aniridia in Marfan syndrome
8. Aniridia, ectopia lentis, abnormal upper incisors and me tardation
9. Iris coloboma, ptosis, hypertelorism and mental retarda
10. Smith-Lemli-Opitz syndrome
11. Biemond syndrome
12. XXXXY syndrome

described: intragenic (most cases of isolated aniridia), and deletions and translocations that affect the whole gene (i.e., WAGR syndrome, some cases of familial isolated aniridia). The common result of all types of mutations is haploid insufficiency for PAX6 leading to a low level of the protein product [27].

Of interest is the report by Glaser et al. [13] who described two different PAX6 mutations segregating in a single family which combined to create a range of ocular phenotypes extending from normal eyes (no mutations) through aniridia and congenital cataracts (mutations at codons 103 and 353, respectively) to anophthalmia (compound heterozygotes to these two mutations). This study demonstrated a correlation between the severity of the phenotype with the level of PAX6 activity and suggests a critical role for PAX6 in controlling migration and differentiation of specific neuronal progenitor cells in the brain.

The considerable variations in the aniridia phenotype raise questions regarding their correlations with the corresponding gene aberrations. Glaser et al. [14], maintained that the clinical similarity sometimes observed within a family and the phenotypic differences among different families are PAX6-determined. In 1992 Martha and colleagues [26] after evaluating all available information on the intragenic mutations identified in PAX6, concluded that there is no correlation between the site and type of the mutation and the corresponding severity of the aniridia. Some authors found a milder phenotype in isolated aniridia compared to that in WAGR syndrome and explained this by the retention of partial function in some intragenic mutations [14]; others did not find such a phenotypic difference [15].

The studies of Gessler et al. [10] in 1989, of a family with isolated aniridia and a balanced translocation in 11p13 but a non-affected PAX6 gene suggested that another gene for aniridia exists on the same band of chromosome 11. No further proof for this hypothesis has been reported. The probable explanation for the phenotype in this family and also in other patients without any structural alterations in the PAX6 gene is that another mutation caused a disruption in the distal regulatory sequences of the PAX6 gene, or the gene expression was silenced after translocation [14, 15].

Aniridia with or without other ocular pathology is probably not the only ophthalmological result of mutations of the PAX6 gene. Hanson et al. [16] in 1994 reported on a family in which one member had iris hypoplasia, while three others had different anterior chamber malformations such as Peters anomaly and Rieger anomaly. All affected members were heterozygous for mutation of the PAX6 gene [15].

The PAX6 gene is also expressed in the brain, mainly in the cerebellum, the pons and the intermediate brain layers which consist of migratory undifferentiated neuroepithelial cells [37]. Some authors connect this finding with the autosomal recessive Gillespie syndrome in which the cerebellum and brainstem are the most severely affected brain structures. They explain this phenotype by the existence of partially defective PAX6 alleles which are clinically manifest only in the homozygous state [14]. The neural expression of the PAX6 gene may be also related to the mental retardation observed in some of the WAGR patients, as no specific locus for mental retardation in the WAGR region of 11p13 has been found. On the other hand, the absence of mental retardation in isolated familial aniridia suggests that multiple gene deficiency interactions may be necessary for its occurrence.

The aniridia trait may be lethal in the homozygous state. Hodgson and Saunders [18] reported on a stillborn fetus with the total absence of eyes, nose and adrenal glands. The parents both had familial aniridia [37].

Severe lethal craniofacial disorders are found also in mice in which both alleles of PAX6 are inactivated [27].

Genetic counselling should be preceded by karyotype studies in all patients with WAGR syndrome or other extra-ocular anomalies associatedd with aniridia. In familial cases of isolated aniridia, linkage analysis using DNA markers in the PAX6 locus should be applied to allow for proper genetic and prenatal diagnosis [26]. The more expensive and time-consuming PAX6 mutation analysis should be restricted to sporadic cases of isolated aniridia or WAGR syndrome in which there is no cytogenetic evidence for chromosomal aberrations.

References

1. Baraitser M, Winter RM (1988) Iris coloboma, ptosis, hypertelorism, and mental retardation: a new syndrome. J Med Genet 25:41–43
2. Barrata G (1818) Observazioni pratiche sulle principal malattie dochi orchi. Milano. Tomo 2, p 349
3. Brusa P, Toricelli O (1953) Nefroblastoma de Wilms' ed affezioni renali congenite nella casistica dell' I.P.P.A.I. de Milano. Minerva Paediat 5:457–458

3a. Chitayat D, Hahm SYE, Iqbal MA, Nitowsky HM (1987) Ring chromosome 6: report of a patient and a literature review. Am J Med Genet 26: 145–151

4. Compton DA, Weil MM, Jones C, Riccardi LC, Strong LC, Saunders GF (1988) Long range physical map of the Wilms's tumor – aniridia region on human chromosome 11. Cell 55:827–836

5. Cohen SM, Nelson LB (1988) Aniridia with congenital ptosis and glaucoma: a family study. Ann Ophthalmol 20: 53–57
6. Courtney-Harris RG, Phil MM (1990) Aniridia and deafness: an inherited disorder. J Laryngol Otol 104:419–420
7. Davis LM, Everest AM, Simola KOJ, Shows TB (1989) Long-range restriction map around 11p13 aniridia locus. Somat Cell Mol Genet 15:505–615

8. Drechsler M, Meijers-Heijboer EJ, Schneider S, Schurich B, Grond-Ginsbach C, Tarirerdian G, Kantner F, Blankenagel A, Kaps D, Schroeder-Kurth T, Royer-Pokora B (1994) Molecular analysis of aniridia patients for deletions involving the Wilms tumor gene. Hum Genet 94:331–338
9. Ferrell E, Chakarvarti A, Hittner HM, Riccardi V (1980) Autosomal dominant aniridia: probable linkage to acid phosphatage-1 locus on chromosome 2. Proc Natl Acad Sci USA 77:1580–1583
10. Gessler M, Thomas GH, Coullin P, Junien C, McGillivray BL, Hayden MM, Jaschek G, Bruns GA (1989) A deletion map of the WAGR region on chromosome 11. Am J Hum Genet 44: 486–495
11. Gillespie FD (1965) Aniridia, cerebellar ataxia and oligophrenia in siblings. Arch Ophthal 73: 338–341
12. Glaser T, Lane J, Housman D (1990) A mouse model of aniridia – Wilms' tumor deletion syndrome. Science 250: 823–827
13. Glaser T, Jepeal L, Edwards JG, Young SR, Favor J, Mass RL (1994) PAX6 gene dosage effect in a family with congenital cataracts, aniridia, anophthalmia and central nervous system defects. Nature Genetics 7: 463–471
14. Glaser T, Walton DS, Maas RL (1992) Genomic structure, evolutionary conservation and aniridia mutations in the human PAX6 gene. Nature Genetics 2: 232–239
15. Hanson IM, Seawright A, Hardman K, Hodgson S, Zaletayev D, Fekete G, Van Heyningen V (1993) PAX6 mutations in aniridia. Hum Mol Genet 2: 915–920
16. Hanson IM, Fletcher JM, Jordan T, Brown A, Taylor D, Adams R, Punnet H, Van Heyningen V (1994) Mutations at the PAX6 locus are found in heterogeneous anterior segment malformations including Peters' anomaly. Nature Genetics 6:168–173
17. Harley RD (1975) Pediatric Ophthalmology. WB Saunders, Philadelphia: p 278
18. Hodgson SV, Saunders KE (1980) A probable case of the homozygous condition of the aniridia gene. J Med Genet 6:478–480
19. Johns KJ, O'Day DM (1991) Posterior chamber intraocular lenses after extracapsular cataract extraction in patients with aniridia. Ophthalmology 98: 1698–1702
20. Jordan T, Hanson I, Zaletayev D, Hodgson S, Prosser J, Seawright A, Hastie N, Van Heyningen V (1992) The human PAX6 gene is mutated in two patients with aniridia. Nature Genetics 1:328–332
21. Jotterand V, Boisjoly H, Harnois C, Bigonesse P, Laframboise R, Gagne R, St. Pierre A (1990) 11p13 deletion, Wilms' tumor and aniridia: unusual genetic, non-ocular and ocular features of three cases. Br J Ophthalmol 74: 568–570
22. Levin H, Ritch R, Bara R, Barathur R, Dunn MW, Teekhagzaenee C, Margolis S (1986) Aniridia, congenital glaucoma, and hydrocephalus in a male infant with ring chromosome 6. Am J Med Genet 25:281–287
23. Lyons LA, Martha A, Mintz-Hittner HA, Saunders GF, Ferrel RE (1992) Resolution of the two loci for autosomal dominant aniridia, AN1 and AN2, to a single locus in chromosome 11p13. Genomics 13:925–930
24. Mannens M, Bleeker-Wagemakers EM, Bliek J, Hoovers J, Mandjes I, Van Tol S, Frants RR, Heyting C, Westerveld A, Slater RM (1989) Autosomal dominant aniridia linked to the chromosome 11p13 markers catalase and D11S151 in a large Dutch family. Cytogenet Cell Genet 52:32–36
25. Martinez-Mora J, Andi L, Toran N, Isnar R, Castelui A, Iribinae MP, Egozcue J (1989) Ambiguous genitalia, gonadoblastoma, aniridia, and mental retardation with deletion of chromosome 11. J Urol 142:1298–1300
26. Martha AD, Ferrell RE, Saunders GF (1993) Dinucleotide repeat polymorphism in the human aniridia (PAX6) gene. Hum Mol Genet 2:1982
27. Martha AD, Ferrell RE, Mintz-Hittner H, Lyons L, Saunders GF (1994) Paired box mutations in familial and sporadic aniridia predicts truncated aniridia proteins. Am J Hum Genet 54: 801–811
28. Mets MB, Cross HE (1990) Aniridia. In: Buyse ML (ed) Birth defects encyclopedia. Vol 1. Center for births defect information services inc., Dover, MA. pp 144–145
29. Michel G, Capodano AM, Perrimond H (1989) Leucemie aigue lymphoblastique et aniridie congenitale: une association fortuite? Arch Fr Pediatr 46: 121–122
30. Nelson LB, Spaeth G, Nowinski TS, Margo CE, Jackson L (1984) Aniridia. A review. Surv Ophthalmol 28: 621–642
31. Nevin MC, Lim JHK (1990) Syndrome of partial aniridia, cerebellar ataxia, and mental retardation – Gillespie syndrome. Am J Med Genet 35:468–469
32. Niikawa N, Fukushima Y, Taniguchi N, Iizuka S, Kajii T (1982) Chromosome abnormalities involving II p13 and low erythrocyte catalase activity. Hum Genet 60:373–375
33. Pettenati MJ, Weaver RG, Burton BK (1989) Translocation of t(5;11)(q13.1;p13) associated with familial isolated aniridia. Am J Med Genet 34:230–232
34. Riccardi VM, Sujansky E, Smith AC, Francke U (1978) Chromosomal imbalance in the aniridia-Wilms' tumor association: II p interstitial deletions. Pediatrics 61:604–610
35. Sachdev MS, Sood NN, Kumar H, Ghose S (1986) Bilateral aniridia with Marfan's syndrome and dental anomalies – a new association. Jpn J Ophthalmol 30:360–366
36. Smith DW (1982) Recognizable patterns of human malformation. WB Saunders, Philadelphia: p 445
37. Ton CCT, Hirvonen H, Miwa H, Weil MM, Monaghan P, Jordan T, Van Heyningen V, Hastie ND, Maijers – Heijboer H, Drechsler M, Royer-Pokora B, Collins F, Swaroop A, Strong L, Saunders GF (1991) Positional cloning and characterization of a paired box – and homeobox-containing gene from the aniridia region. Cell 67: 1059–1074
38. Wiggins RE, Tomey KF (1992) The results of glaucoma surgery in aniridia. Arch Ophthalmol 110:502–505
39. Wittig EO, Moreira CA, Freire-Maia N, Vianna-Morgante AM (1988) Partial aniridia, cerebellar ataxia, and mental deficiency (Gillespie syndrome) in two brothers. Am J Med Genet 30: 703–708
40. Yamamoto Y, Hayasaka S, Setogawa T (1988) Family with aniridia, microcornea, and spontaneously resorbed cataract. Arch Ophthalmol 106: 502–504
41. Zamzam A, Sheriff SMM, Phillips CI (1988) Aniridia, ectopia lentis, abnormal upper incisors, and mental retardation – an autosomal recessive syndrome. Jpn J Ophthalmol 32:375–378