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PAX2-Related Disorder

Synonyms: Papillorenal Syndrome, Renal Coloboma Syndrome

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Summary

Clinical characteristics

PAX2-related disorder is an autosomal dominant disorder associated with renal and eye abnormalities. The disorder was originally referred to as renal coloboma syndrome and characterized by renal hypodysplasia and abnormalities of the optic nerve; with improved access to molecular testing, a wider range of phenotypes has been recognized in association with pathogenic variants in *PAX2*. Abnormal renal structure or function is noted in 92% of affected individuals and ophthalmologic abnormalities in 77% of affected individuals. Renal abnormalities can be clinically silent in rare individuals. In most individuals, clinically significant renal insufficiency / renal failure is reported. End-stage renal disease requiring renal transplant is not uncommon. Uric acid nephrolithiasis has been reported. Ophthalmologic abnormalities are typically described as optic nerve coloboma or dysplasia. Iris colobomas have not been reported in any individual with *PAX2*–related disorder. Ophthalmologic abnormalities may significantly impair vision in some individuals, while others have subtle changes only noted after detailed ophthalmologic examination. Additional clinical findings include high-frequency sensorineural hearing loss, soft skin, and ligamentous laxity. *PAX2* pathogenic variants have been identified in multiple sporadic and familial cases of nonsyndromic renal disease including renal hypodysplasia and focal segmental glomerulosclerosis.

Diagnosis/testing

The diagnosis of *PAX2*-related disorder is established in a proband with the characteristic renal and/or eye findings by the identification of a heterozygous pathogenic variant in *PAX2* by molecular genetic testing. Among individuals with apparently nonsyndromic renal hypodysplasia and in families with autosomal dominant isolated focal segmental glomerulosclerosis, pathogenic variants in *PAX2* have been identified in approximately 8% and 4%, respectively.

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Management

Treatment of manifestations: Ongoing treatment of hypertension and/or vesicoureteral reflux; renal replacement therapy (dialysis and/or renal transplantation) for end-stage renal disease; low vision aids for significant visual impairment.

Prevention of secondary complications: Use of protective eyewear to prevent retinal detachment.

Surveillance: Follow up by a nephrologist to monitor renal function and blood pressure and an ophthalmologist to monitor vision, with periodic audiometric evaluations.

Evaluation of relatives at risk: Offer molecular genetic testing if a *PAX2* pathogenic variant has been identified in an affected family member. If no *PAX2* pathogenic variant has been found, perform dilated ophthalmologic examination, renal ultrasound examination, tests of renal function, uric acid levels, and urinalysis; measure blood pressure.

Genetic counseling

PAX2-related disorder is inherited in an autosomal dominant manner. Approximately 65% of probands with a documented *PAX2* pathogenic variant have a negative family history. In such cases, the negative family history may be explained by a *de novo* pathogenic variant, unrecognized symptoms in the parents, or parental germline mosaicism for a *PAX2* pathogenic variant. Both maternal and paternal germline mosaicism, with unaffected parents having more than one affected child with a pathogenic variant, have been reported. Prenatal testing and preimplantation genetic testing are possible if the pathogenic *PAX2* pathogenic variant has been identified in the family.

Diagnosis

Renal coloboma syndrome (or papillorenal syndrome) was the name given to an autosomal dominant condition associated with renal hypodysplasia and abnormalities of the optic nerve and a heterozygous pathogenic variant in *PAX2*. With improved access to molecular genetic testing, more individuals have been identified and it has become clear that multiple phenotypes beyond that of classic renal coloboma syndrome may be associated with pathogenic variants in *PAX2*. The authors feel that the term "*PAX2*-related disorder" best reflects this wide phenotypic variability.

There are no formal diagnostic criteria for *PAX2*-related disorder.

Suggestive Findings

PAX2-related disorder **should be suspected** in individuals with the following clinical findings in the kidneys and/or eyes.

Note: *PAX2* pathogenic variants are more likely to be identified in individuals with both ophthalmologic and renal involvement, but are increasingly recognized in cases with isolated renal findings such as renal hypodysplasia or focal segmental glomerulosclerosis [Barua et al 2014].

Kidney

Abnormalities of kidney structure and/or function are the most frequent finding in individuals with *PAX2*-related disorder, noted in 159 (92%) of 173 cases [Bower et al 2012].

- **Hypoplastic kidneys** characterized on ultrasound examination by hypoplasia (small size for age) and hyperechogenicity [Schimmenti et al 1995]. Renal hypoplasia is usually bilateral, although marked variability between kidneys can be observed (e.g., 1 kidney small or absent, 1 of normal size).

- **Renal hypodysplasia,** characterized histologically by reduced number of nephrons, small kidney size, and disorganized renal tissue [Weber et al 2006]. Renal hypodysplasia was the most common renal finding in 114 (65%) of 173 affected individuals [Bower et al 2012].
- **Multicystic dysplastic kidney,** characterized histologically by cystic or dysplastic kidneys exhibiting some degree of disorganization of the kidney architecture. Multicystic dysplastic kidneys are observed in about 6%-10% of affected individuals [Fletcher et al 2005, Bower et al 2012].
- **Oligomeganephronia,** a pathologic finding characterized by fewer-than-normal glomeruli that are enlarged in size [Salomon et al 2001]. Note: Oligomeganephronia is not pathognomonic for *PAX2*-related disorder.
- **Renal insufficiency and end-stage renal disease (ESRD).** Because most data are aggregated from individual case reports and small case series, the exact incidence of Stage 5 chronic kidney disease requiring kidney transplantation is not precisely known. One study reported the mean age at diagnosis of ESRD in *PAX2*-related disorder was 19.5 years (range: birth to 79 years) [Bower et al 2012].
- **Vesicoureteral reflux** was reported in 25 (14%) of 173 affected individuals in a large literature review and case series [Bower et al 2012].
- **Other renal anomalies in the congenital anomalies of the kidney and urinary tract (CAKUT).** Each of the following findings in the CAKUT spectrum has been reported in fewer than five individuals with *PAX2*-related disorder: ureteropelvic junction obstruction; medullary sponge kidney; horseshoe kidney; pyeloureteral duplication; and renal malrotation.
- **Focal segmental glomerulosclerosis (FSGS).** *PAX2* pathogenic variants have been documented in pedigrees with isolated autosomal dominant FSGS [Barua et al 2014, Okumura et al 2014].
- **Uncommon non-CAKUT renal findings.** Uric acid nephrolithiasis (kidney stones) has been reported in several individuals; an intrarenal teratoma was reported in a single individual [Choi et al 2005, Bower et al 2012].

Eye

The primary eye finding is **dysplasia of the optic nerve** that ranges from severe to mild. Abnormalities of the optic nerve have been identified in 125 (72%) of 173 affected individuals [Bower et al 2012].

- The most severe form is characterized by an apparently enlarged disc in which the vessels that normally exit from the center of the disc exit instead from the periphery [Schimmenti et al 2003]. Associated abnormalities may include deep excavation of the optic nerve head with redundant fibroglial tissue.
- A milder form is an optic nerve pit characterized by a relatively localized (or sub-total) excavation of the optic disc.
- The mildest form is the exiting of the retinal vessels from the periphery of the disc without malformation of the disc itself.

Note: (1) Differences exist in the terminology used to designate dysplasia of the optic nerve with abnormal passage of retinal vessels from the periphery of the optic nerve head. Some ophthalmologists refer to this finding as congenital excavation of the optic nerve and others as "optic nerve coloboma." However, the use of the term coloboma can be confusing in this setting because coloboma usually refers to non-closure of the optic fissure during the seventh week of gestation, resulting in typical uveal colobomas (iris and retinal colobomas). The developmental mechanism underlying the optic nerve abnormalities observed in *PAX2*-related disorder is under investigation in animal models: in both mouse and zebrafish, homozygous loss-of-function alleles of *Pax2*/*pax2a* result in failed optic fissure closure [Schimmenti 2009]. (2) Some have described one of the optic nerve findings in this syndrome as "morning glory anomaly," defined as a wide and deeply excavated optic nerve with a central glial tuft and all vessels exiting abnormally at the periphery of the nerve, giving the appearance of a morning glory flower. However, it is debated whether use of the term morning glory anomaly is appropriate to describe

the optic nerve malformation in *PAX2* -related disorder because it may be a misnomer for the dysplasia of the optic nerve typically seen in this syndrome.

Retinal findings in addition to optic nerve findings have been described in 23 (13%) of 173 affected individuals. Retinal coloboma (defined as absence of retinal tissue in the nasal ventral portion of the retina resulting from failure of closure of the uveal tract) has been reported in six individuals. Other retinal findings reported include: abnormal retinal pigment epithelium, abnormal retinal vessels, macular anomalies, and chorioretinal degeneration.

Less common associated eye malformations include the following [Sanyanusin et al 1995a, Sanyanusin et al 1995b, Schimmenti et al 1995, Schimmenti et al 1999, Amiel et al 2000, Dureau et al 2001, Schimmenti et al 2003, Bower et al 2012]:

- **Scleral staphyloma,** defined as posterior bulging of the eye wall (sclera), is likely a secondary thinning of neural-crest-derived tissue in the area of the anatomically abnormal optic nerve head. Retinal thinning and myopia may be secondary to enlargement of the globe.
- **Optic nerve cyst,** a cystic dilatation of the optic nerve posterior to the globe, is observed by cranial imaging (e.g., MRI). The cyst likely results from incomplete regression of the primordial optic stalk, followed by accumulation of fluid in its potential space.
- **Macular abnormalities** including macular degeneration, hyperpigmentation of the macula, cystic degeneration of the macula, and papillomacular detachment have been reported in a limited number of affected individuals.
- **Lens abnormalities.** Lens opacity and posterior lens luxation have been reported in one affected individual each. It is not clear whether these findings are coincidental or part of this disorder.

Note: (1) Some individuals with *PAX2*-related disorder may not have vision loss and hence, examination of the fundus through a dilated pupil may be necessary to observe optic nerve abnormalities [Chung et al 2001]. (2) Iris coloboma has not been observed in persons with *PAX2*-related disorder.

Other

A wide range of non-renal and non-ophthalmologic findings including high-frequency sensorineural hearing loss – or more rarely, CNS malformations, developmental delay, hyperuricemia (gout), soft skin, joint laxity, and elevated pancreatic amylase – have been reported in individuals with *PAX2*-related disorder. Each of these findings is reported in a limited number of individuals and a definitive causal connection with *PAX2* variants has not been established.

Establishing the Diagnosis

The diagnosis of *PAX2*-related disorder **is established** in a proband with the characteristic renal and/or eye findings by the identification of a heterozygous pathogenic (or likely pathogenic) variant in *PAX2* on molecular genetic testing (see Table 1).

Note: Per ACMG variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants.

Molecular genetic testing approaches can include **single-gene testing**, **chromosomal microarray analysis (CMA)**, use of a **multigene panel**, and **more comprehensive genomic testing**:

- **Single-gene testing.** Sequence analysis of *PAX2* is performed first and followed by gene-targeted deletion/duplication analysis if no pathogenic variant is found.

- **Chromosomal microarray analysis (CMA)** – if not already performed – may be obtained to detect genome-wide deletions/duplications (including *PAX2*).

  Note: A single case of *PAX2*-related disorder with an apparently balanced *de novo* t(10;13) translocation with a breakpoint at the *PAX2* locus has been reported [Narahara et al 1997]. Because balanced rearrangements may not be detected by CMA, karyotype analysis could be considered in cases with a compelling clinical phenotype and normal *PAX2* sequencing and gene-targeted deletion/duplication analysis.

- **A multigene panel** that includes *PAX2* and other genes of interest (see Differential Diagnosis) may be considered. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

- **More comprehensive genomic testing** (when available) including exome sequencing and genome sequencing may be considered. Such testing may provide or suggest a diagnosis not previously considered (e.g., mutation of a different gene or genes that results in a similar clinical presentation).

  For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in *PAX2*-Related Disorder

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
PAX2	Sequence analysis [3]	~95% [4]
	Gene-targeted deletion/duplication analysis [5, 6]	2 intragenic deletions [7] and 6 whole-gene deletions [8]
	Chromosomal microarray analysis (CMA)	6 cases [8]
	Karyotype	Single case [9]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Based on 136/144 probands with pathogenic variants detected by sequence analysis in the *PAX2* locus-specific database
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Gene-targeted methods will detect from single-exon to whole-gene deletions; however, breakpoints of large deletions and/or deletion of adjacent genes may not be determined.
7. Two intragenic *PAX2* deletions have been reported [Heidet et al 2017]. Intragenic *PAX2* deletions were not frequently identified in other case series [Bower et al 2012, Karger et al 2013].
8. Six whole-gene deletions have been reported [Benetti et al 2007, Raca et al 2011, Hoefele et al 2012, Peltekova et al 2014, Heidet et al 2017, Pfundt et al 2017]. Most of these deletions have involved additional genes, and in some cases patients demonstrated clinical findings beyond the typical spectrum of renal coloboma syndrome.
9. A single individual with a *de novo* apparently balanced translocation with breakpoints within *PAX2* has been reported [Narahara et al 1997]. No gene-targeted deletion/duplication analysis was performed.

Clinical Characteristics

Clinical Description

PAX2-related disorder is associated with abnormalities involving the kidneys and/or the eyes. The original *PAX2*-related disorder known as renal coloboma syndrome is characterized by hypodysplastic kidneys and optic nerve abnormalities (most commonly optic nerve dysplasia) with or without optic nerve or retinal coloboma [Sanyanusin et al 1995a, Schimmenti et al 1995, Schimmenti et al 2003].

Variability. The clinical findings vary even within families, with some family members having either renal manifestations or optic nerve abnormalities and others having both. The severity of renal malformations can range within a family from absence of clinical symptoms to severe fetal renal failure.

In some instances a detailed eye examination is necessary to reveal the ocular findings of *PAX2*-related disorder in individuals presenting with characteristic renal findings [Chung et al 2001, Nishimoto et al 2001, Salomon et al 2001] or renal evaluation is needed in individuals with characteristic eye findings [Parsa et al 2001].

A wide range of kidney and eye findings can be found in individuals with *PAX2*-related disorder (see Suggestive Findings).

Renal disease. Renal insufficiency/failure can occur at any age. The age at diagnosis of Stage 5 chronic kidney disease ranges from birth to 79 years.

The natural history of vesicoureteral reflux varies: in some individuals ureteral reimplantation has been required [Schimmenti et al 1995]; in others the reflux has spontaneously resolved [Ford et al 2001].

Eye abnormalities. Impaired visual acuity of one or both eyes is present in 75% of affected individuals; acuity ranges from light perception only to normal. Other findings can include nystagmus, myopia, and strabismus.

The natural history of visual acuity in individuals with *PAX2*-related disorder has not been prospectively studied. In some instances, significant changes in visual acuity have been reported. Visual acuity deteriorated in one person as a result of retinal detachment [Ford et al 2001]. One person reported acute vision loss resulting in a change of visual acuity from 20/80 to light perception only [Schimmenti et al 1995]; however, the cause of vision loss was unexplained as there was no evidence of detachment or macular changes [Schimmenti, unpublished observation].

Other. Less commonly reported findings in affected individuals include high-frequency hearing loss, soft skin, and ligamentous laxity. The age of onset and progression of hearing loss remain unknown and have not been evaluated prospectively. The hearing loss, when present, has been discovered in childhood and is bilateral high-frequency sensorineural hearing loss [Schimmenti et al 1995, Bower et al 2012].

Prenatal phenotype. Abnormalities including oligohydramnios/anhydramnios, cystic renal dysplasia, multicystic dysplastic kidneys, and renal hypoplasia were reported on prenatal ultrasound in 18 individuals with *PAX2* pathogenic variants [Bower et al 2012]. Seven fetuses with a confirmed *PAX2* pathogenic variant and severe prenatal renal failure (Potter sequence) have been reported [Martinovic-Bouriel et al 2010, Bower et al 2012]. In several instances, parents with mild renal disease had pregnancies where the fetus presented with severe renal disease in utero.

Genotype-Phenotype Correlations

Review of all reported cases to date does not reveal a consistent genotype/phenotype correlation. This is most dramatically illustrated by the tremendous *intrafamilial* variability in the severity of ocular and renal findings. To date, no clear evidence suggests that the location of a pathogenic variant (paired domain, octapeptide domain, partial homeodomain, or transactivation domain) or the type of pathogenic variant (missense variant, nonsense variant, or gene deletion) consistently predicts the clinical phenotype.

Penetrance

Only one individual with a pathogenic variant in *PAX2* in whom renal and ophthalmologic examinations were performed and documented as normal has been reported [Bower et al 2012]. Thus, penetrance appears to be greater than 99%. In individuals with pathogenic variants in *PAX2*, the penetrance of eye malformations is at least 77% [Bower et al 2012]. This should be viewed as a minimum figure, as fully 21% of individuals with *PAX2* pathogenic variants have not had a dilated eye examination to evaluate for subclinical abnormalities of the optic nerve. The penetrance for renal malformations or renal disease is at least 92%. Again, this figure should be viewed as a minimum, as some individuals with pathogenic variants have not had full renal evaluations.

Nomenclature

Terms previously used for renal coloboma (papillorenal syndrome) syndrome:

- Coloboma-ureteral-renal syndrome
- Optic nerve coloboma with renal disease
- Coloboma of the optic nerve with renal disease
- Optic coloboma-vesicoureteral reflux-renal anomalies

Controversy regarding the naming of this syndrome has caused confusion in the field. The condition was named renal coloboma syndrome based on the presence of kidney abnormalities and the optic nerve abnormalities described by the ophthalmologists who identified the original families found to have *PAX2* pathogenic variants [Sanyanusin et al 1995a, Sanyanusin et al 1995b]. In 2001, Parsa et al identified a family with similar optic nerve

and renal abnormalities where no variants in *PAX2* were identified and suggested that the name of the condition be changed to papillorenal syndrome; it is unclear if the two entities are related.

Prevalence

The prevalence of *PAX2*-related disorder is unknown. At the time of the most recent update, 243 affected individuals from 124 different families are recorded in the *PAX2* locus-specific database (www.lovd.nl/PAX2). There is no evidence for a significant founder effect in any population.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *PAX2*.

Differential Diagnosis

Table 2. Disorders to Consider in the Differential Diagnosis of *PAX2*-Related Disorder

Diff Dx Disorder	Gene(s)/ Other	MOI	Clinical Features of DiffDx Disorder		
			Kidney	Eye	Distingishing from *PAX2*-related disorder
CHARGE syndrome [1]	*CHD7* [2]	AD	Occasional finding: renal anomalies incl dysgenesis, horseshoe/ectopic kidney	Unilateral or bilateral coloboma of the iris, retina-choroid, &/or disc w/or w/o microphthalmos	Craniofacial findings incl cleft lip/palate or choanal atresia; may be assoc w/iris coloboma or retinal coloboma
Branchiootorenal syndrome	*EYA1* [3] *SIX1* *SIX5*	AD	Oligomeganephronia, renal malformations ranging from mild renal hypoplasia to bilateral renal agenesis, → ESRD later in life in some	Lacrimal duct aplasia; gustatory lacrimation	Assoc w/outer-ear malformations; may be assoc w/inner-ear abnormalities incl enlarged vestibular aqueduct & severe sensorineural or mixed hearing loss
Cat-eye syndrome (OMIM 115470)	Tetraploid dosage of proximal 22q	AD	Kidney abnormalities	Colobomatous eye defects	Iris coloboma
PAX6 pathogenic variants (See Aniridia.)	*PAX6* [4]	AD	No kidney findings reported	Complete or partial iris hypoplasia usually (not always) w/assoc foveal hypoplasia → ↓ visual acuity & nystagmus presenting in early infancy	Note: No clinical overlap between aniridia & *PAX2*-related disorder; frequently confused as both involve mutation of a PAX gene expressed in the eye
Joubert syndrome and related disorders (JSRD)	>30 genes	AR [5] XL	Renal disease in some	Retinal dystrophy &optic nerve colobomas in some	Incl developmental delay & hepatic & cerebellar defects (not typical of *PAX2*-related disorder); see footnote 6 for clinical features of JSRD.

Table 2. continued from previous page.

Diff Dx Disorder	Gene(s)/ Other	MOI	Clinical Features of DiffDx Disorder		
			Kidney	Eye	Distingishing from *PAX2*-related disorder
Congenital anomalies of the kidney and urinary tract (CAKUT) [7]	>20 genes	AD AR	Renal hypodysplasia / agenesis, vesico-urerteral reflux, cystic dysplasia, ureteropelvic junction obstruction, & other urinary tract abnormalities	None	Anomalies confined to the kidney & renal tract

AD = autosomal dominant; AR = autosomal recessive; DiffDx = differential diagnosis; MOI = mode of inheritance; XL = X-linked
1. Coloboma, *h*eart malformations, *a*tresia choanae, *r*estriction of growth and development, *g*enital abnormalities, *e*ar and hearing defects syndrome
2. An estimated 65%-70% of individuals with CHARGE syndrome have pathogenic variants in or deletions of *CHD7*. Pathogenic variants in *PAX2* were not identified in a small series of persons with CHARGE syndrome [Tellier et al 2000; Schimmenti, unpublished].
3. Sikora et al [2001]
4. Azuma et al [2003]
5. Joubert syndrome is inherited predominantly in an autosomal recessive manner. *OFD1*-related JS is inherited in an X-linked manner.
6. Joubert syndrome is characterized by a distinctive cerebellar and brain stem malformation (the "molar tooth sign" seen on cranial MRI), hypotonia, developmental delays, and either episodic hyperpnea (or apnea) or atypical eye movements, or both. Most children with Joubert syndrome develop truncal ataxia.
7. Renkema et al [2011]

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *PAX2*-related disorder, the following are recommended if they have not already been completed:

- Evaluation of renal structure by renal ultrasound examination
- Measurement of renal function by serum electrolyte concentrations, BUN, and creatinine
- Urinalysis to evaluate for the presence of blood and protein
- Evaluation for vesicoureteral reflux, by voiding cytourethrogram (VCUG)
- Dilated eye examination
- Audiologic assessment (See Deafness and Hereditary Hearing Loss Overview for details of audiologic assessment.)
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

A team approach that includes specialists in ophthalmology, nephrology, audiology, and clinical genetics is recommended.

Management is focused on preventing complications of end-stage renal disease (ESRD) and/or vision loss resulting from retinal detachment.

- Ongoing treatment of hypertension and/or vesicoureteral reflux (if present) may preserve renal function.
- ESRD is treated with renal replacement therapy (i.e., dialysis and/or renal transplantation).
- Low vision experts can assist with adaptive functioning of those with significant vision loss.

Prevention of Secondary Complications

Prevention of retinal detachment in those with congenital optic nerve abnormalities includes close follow up with an ophthalmologist and use of protective eyewear.

Surveillance

No disease-specific guidelines have been developed. The following ongoing evaluations are recommended in all individuals with *PAX2*-related disorder.

- Follow up by a nephrologist to monitor renal function and blood pressure
- Follow up by an ophthalmologist to monitor vision. Any change in vision could indicate a retinal detachment and should be treated as a medical emergency.
- Audiometric evaluation with periodic follow up

Agents/Circumstances to Avoid

Avoid the following:

- Use of medications known to affect renal function (requires consultation with a specialist in nephrology)
- Contact sports

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic at-risk relatives of an affected individual by molecular genetic testing of the *PAX2* pathogenic variant in the family in order to identify as early as possible those who would benefit from prompt initiation of treatment and preventive measures.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

It is important that a female with *PAX2*-related disorder have a thorough renal evaluation prior to becoming pregnant. Individuals with clinical renal disease should consult with appropriate professionals including nephrologists and maternal-fetal medicine specialists to establish a plan for medical management during pregnancy.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

PAX2-related disorder is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Approximately 35% of individuals with *PAX2*-related disorder have a recognized clinically affected parent [Bower et al 2012]. Because tremendous variability in the severity of ocular and renal findings is observed within families, parents may be more or less severely affected than their offspring.
- Approximately 65% of probands with *PAX2*-related disorder represent simplex cases (i.e., a single occurrence in a family). Molecular testing in 23 (41%) of 56 simplex cases confirmed the *de novo* origin for the pathogenic variant, while parental testing was not performed in the remaining 33 cases [Bower et al 2012].
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* pathogenic variant include molecular genetic testing for the *PAX2* pathogenic variant identified in the proband.
- If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent and/or neither parent has clinical findings consistent with a diagnosis of *PAX2*-related disorder, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent. Both maternal and paternal germline mosaicism have been reported in *PAX2*-related disorder [Amiel et al 2000, Cheong et al 2007].
- Note: If the parent is the individual in whom the pathogenic variant first occurred, the parent may have somatic mosaicism for the variant and may be mildly/minimally affected.

  Ophthalmologic abnormalities consistent with *PAX2*-related disorder have been reported in a parent without a *PAX2* pathogenic variant who had two children with a *PAX2* pathogenic variant. It was hypothesized that this parent had somatic (and germline) mosaicism, but the pathogenic variant was absent in the tissues analyzed (leukocytes, fibroblasts, oral mucosa) [Bower et al 2012].

Sibs of a proband. The risk to the sibs of the proband depends on the status of the proband's parents:

- If a parent of the proband is affected, the risk to the sibs is 50%.
- If the parents of a proband with *PAX2*-related disorder have been tested for the pathogenic variant identified in the proband and:
  - A parent of the proband has the *PAX2* pathogenic variant, the risk to the sibs of inheriting the variant is 50%. Because of intrafamilial clinical variability, it is not possible to predict the phenotype in sibs who have inherited a pathogenic variant.
  - If the *PAX2* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the risk to sibs is slightly greater than that of the general population because of the possibility of parental germline mosaicism. Germline mosaicism, in which parents who test negative for the familial *PAX2* pathogenic variant have more than one affected child, has been documented in two families [Bower et al 2012].

Offspring of a proband. Each child of an individual with *PAX2*-related disorder has a 50% chance of inheriting the *PAX2* pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent is affected and/or has a *PAX2* pathogenic variant, the parent's family members are at risk.

Related Genetic Counseling Issues

See Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Testing of at-risk asymptomatic individuals. It is appropriate to consider molecular genetic testing of at-risk asymptomatic family members in order to guide vision and renal management (see Management, Surveillance). Molecular genetic testing can only be used for testing at-risk relatives if a *PAX2* pathogenic variant has been identified in an affected family member. Because early detection of at-risk individuals affects medical management, testing of individuals during childhood who have no symptoms is beneficial. It is appropriate to provide education and genetic counseling for at-risk individuals younger than age 18 years and their parents prior to genetic testing.

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with an autosomal dominant condition has the pathogenic variant identified in the proband or clinical evidence of the disorder, the pathogenic variant is likely *de novo*. However, non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

Prenatal Testing and Preimplantation Genetic Testing

Molecular genetic testing. Once the *PAX2* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Prenatal fetal ultrasound examination of an at-risk pregnancy or known affected pregnancy may be used during the later stages of pregnancy to detect renal malformations and assess amniotic fluid volume, as findings could affect the well-being of the newborn or warrant further evaluation after birth.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **International Children's Anophthalmia Network (ICAN)**
  Phone: 800-580-ican
  Email: info@anophthalmia.org
  www.anophthalmia.org

- **Kidney Foundation of Canada**
  Canada
  Phone: 514-369-4806; 800-361-7494
  Email: info@kidney.ca
  www.kidney.ca

- **National Eye Institute**
  Phone: 301-496-5248
  Email: 2020@nei.nih.gov

Low Vision

- **National Kidney Foundation**
  Phone: 855-NKF-CARES; 855-653-2273
  Email: nkfcares@kidney.org
  kidney.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. PAX2-Related Disorder: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
PAX2	10q24.31	Paired box protein Pax-2	PAX2	PAX2

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for PAX2-Related Disorder (View All in OMIM)

120330	PAPILLORENAL SYNDROME; PAPRS
167409	PAIRED BOX GENE 2; PAX2

Molecular Pathogenesis

The pattern of abnormalities in *PAX2*-related disorder is consistent with the known expression pattern of *PAX2* during embryonic development. Porteous et al [2000] and Torban et al [2000] have demonstrated in mouse models and tissue culture that normal biallelic *PAX2* expression is needed to prevent programmed cell death.

Gene structure. *PAX2* contains 12 coding exons. Alternative splicing of this gene results in multiple transcript variants. The longest transcript variant, NM_003990.3, has 11 exons. None of the known transcripts contains all 12 coding exons. See Table A, **Gene** for a detailed summary of gene and protein information.

Pathogenic variants. See Table A, **Locus Specific**. To date, nearly 90 different pathogenic variants have been reported in the *PAX2* coding exons and adjoining intronic sequences [Bower et al 2012].

Frameshift variants are the most common type; nonsense and missense variants, splice site changes, and in-frame duplications have also been reported. Pathogenic variants tend to cluster in the paired domain (exons 2-4), the homeodomain (exon 7), and the 5' portion of the transactivation domain (exon 8). A limited number of missense variants have been reported in exons 9-12, but the pathogenicity of these variants is not clearly established. A small number of genomic deletions and rearrangements have been reported. Partial-gene deletions are not a common pathogenic mechanism [Karger et al 2013].

The most common recurring pathogenic variant, c.76dupG (previously called c.619insG), is a duplication of a G residue in a stretch of seven Gs and has been reported in more than 25 independent families.

Table 3. *PAX2* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change (Alias [1])	Predicted Protein Change	Reference Sequences
c.76dupG (c.619insG)	p.Val26GlyfsTer28	NM_003987.3 NP_003978.2

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Variant designation that does not conform to current naming conventions

Normal gene product. NM_003990.3 encodes a PAX-2 isoform of 431 amino acids (NP_003981.2). Paired box protein PAX-2 is a DNA-binding protein characterized by an N-terminal paired domain, a bipartite helix-loop-helix domain, a small octapeptide domain, a truncated homeodomain, and a proline/serine/threonine-rich C-terminal domain. Multiple isoforms, by alternative splicing of exons 6, 10, and 12, are known to exist.

Abnormal gene product. Review of ExAC (exac.broadinstitute.org) indicates that PAX2 is relatively intolerant of loss of function or missense alleles. The majority of *PAX2* pathogenic variants are expected to result either in the loss of expression from one allele or in expression of a significantly truncated protein.

To date, all clearly pathogenic in-frame variants (missense, in-frame deletions, and in-frame duplications) are located in the paired domain (exons 2-4). It is not known if these pathogenic variants exert their effect by reducing the binding to normal DNA targets or by allowing binding to abnormal DNA targets. Six missense variants have been reported outside of the paired domain. Each of these variants has been reported in a single individual and the evidence for pathogenicity is not as strong as with other *PAX2* variants.

Chapter Notes

Revision History

- 8 February 2018 (ha) Comprehensive update posted live
- 20 November 2014 (me) Comprehensive update posted live
- 12 July 2012 (me) Comprehensive update posted live
- 8 June 2007 (me) Review posted live
- 8 December 2006 (las) Original submission

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National Society of Genetic Counselors. Position statement on genetic testing of minors for adult-onset conditions. Available online. 2018. Accessed 6-21-22.

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