

# You May Be Your Patient's Best Hope for Diagnosing a Rare, Yet Treatable, Disease<sup>1-3</sup>

*Early-onset bilateral cataracts are a hallmark symptom in ~85% of these patients<sup>4</sup>*



**BEHIND THE BLUR**  
Early-Onset Bilateral Cataracts

# Diagnosing Cerebrotendinous Xanthomatosis (CTX) can be challenging<sup>3</sup>

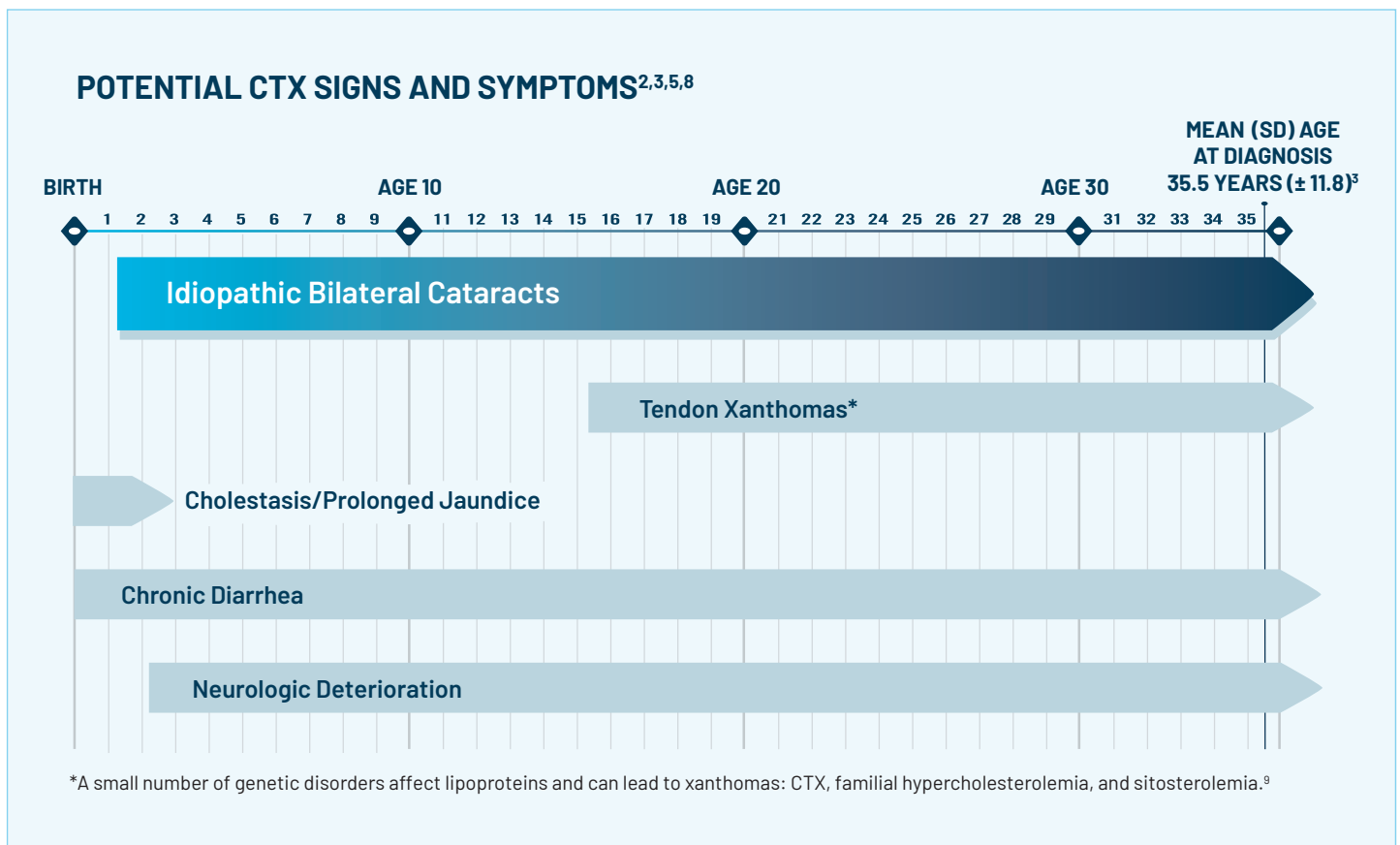
CTX diagnosis typically occurs 20–25 years after onset of signs and symptoms<sup>3</sup>

- CTX is a rare, genetic lipid storage disorder<sup>3</sup>
  - Excess bile acid precursors, such as cholestanol, accumulate in areas such as the lens of the eye, brain, and tendons<sup>3,5,6</sup>
  - Cataract morphology is often described as posterior subcapsular with fleck deposits<sup>6</sup>

## Early-onset bilateral cataracts are a hallmark CTX symptom that may appear as early as childhood<sup>3</sup>

Yet mean age at CTX diagnosis is 35.5 years ( $\pm 11.8$  years)<sup>3</sup>

Other CTX signs and symptoms are either nonspecific or most often occur after the first decade of life<sup>2,3,5,7,8</sup>



# Early-onset bilateral cataracts may be an important marker for identifying CTX in patients<sup>10</sup>

Up to a 500-fold higher CTX prevalence than in the general population<sup>10,\*</sup>

~2 of every 100 patients with early-onset bilateral cataracts were diagnosed with CTX<sup>10,\*</sup>

\*Findings from a 26-site CTX prevalence study in a patient population diagnosed with early-onset idiopathic bilateral cataracts<sup>10</sup>



## BEHIND THE BLUR

### Early-Onset Bilateral Cataracts

A no-cost to patient genetic test is available to identify up to 66 causes of early-onset bilateral cataracts<sup>11</sup>

#### Genes included on the Early-Onset Bilateral Cataracts Genetic Panel\*

<i>ABHD12</i>	<i>ADAMTSL4</i>	<i>ALDH18A1</i>	<i>BCOR</i>	<i>BEST1</i>	<i>BFSP1</i>	<i>BFSP2</i>	<i>CHMP4B</i>
<i>COL11A1</i>	<i>COL18A1</i>	<i>COL2A1</i>	<i>COL4A1</i>	<i>CRYAA</i>	<i>CRYAB</i>	<i>CRYBA1</i>	<i>CRYBA2</i>
<i>CRYBA4</i>	<i>CRYBB1</i>	<i>CRYBB2</i>	<i>CRYGC</i>	<i>CRYGD</i>	<i>CRYGS</i>	<b><i>CYP27A1</i></b>	<i>DYNC1H1</i>
<i>EPHA2</i>	<i>ERCC2</i>	<i>FAM126A</i>	<i>FOXE3</i>	<i>FTL</i>	<i>FYC01</i>	<i>FZD4</i>	<i>GALE</i>
<i>GALK1</i>	<i>GALT</i>	<i>GCNT2</i>	<i>GJA3</i>	<i>GJA8</i>	<i>GLA</i>	<i>HSF4</i>	<i>LEMD2</i>
<i>LIM2</i>	<i>LONP1</i>	<i>MAF</i>	<i>MIP</i>	<i>MIR184</i>	<i>MYH9</i>	<i>NACC1</i>	<i>NDP</i>
<i>NF2</i>	<i>NHS</i>	<i>OPA3</i>	<i>PAX6</i>	<i>PITX3</i>	<i>P3H2</i>	<i>RAB3GAP1</i>	<i>RDH11</i>
<i>RECQL4</i>	<i>SC5D</i>	<i>SIL1</i>	<i>SLC16A12</i>	<i>TFAP2A</i>	<i>TGM3</i>	<i>UNC45B</i>	<i>VIM</i>
<i>WRN</i>	<i>XYLT2</i>						

**CTX is treatable. If positive for pathogenic mutations in CYP27A1, then refer patient for CTX management**

- Specialties that manage CTX include neurologists and metabolic geneticists

\*For a complete list of the defect/disorder/syndrome for all 66 genes, please refer to the accompanying insert.

# Behind the Blur

No-cost to patient genetic testing program for early-onset bilateral cataracts



## PROGRAM OVERVIEW

In partnership with PreventionGenetics, Retrophin offers a no-cost genetic testing program for qualifying patients to help identify the genetic cause of early-onset, often bilateral, cataracts through a 66-gene panel.

If you have a patient you suspect to have a genetic form of cataracts, they may be eligible for the no-cost genetic test.

HGNC APPROVED GENE SYMBOL	PHENOTYPE/DEFECT/DISORDER/SYNDROME	HGNC APPROVED GENE SYMBOL	PHENOTYPE/DEFECT/DISORDER/SYNDROME
<b>ABHD12</b>	Polyneuropathy, hearing loss, ataxia, retinitis pigmentosa, and cataract		Retinal arteries, tortuosity of {Hemorrhage, intracerebral, susceptibility to}
<b>ADAMTSL4</b>	Ectopia lentis et pupillae Ectopia lentis, isolated, autosomal recessive	<b>COL4A1</b>	Angiopathy, hereditary, with nephropathy, aneurysms, and muscle cramps Brain small vessel disease with or without ocular anomalies Microangiopathy and leukoencephalopathy, pontine, autosomal dominant
<b>ALDH18A1</b>	Cutis laxa, autosomal dominant 3 Cutis laxa, autosomal recessive, type IIIA Spastic paraplegia 9A, autosomal dominant Spastic paraplegia 9B, autosomal recessive	<b>CRYAA</b>	Cataract 9, multiple types
<b>BCOR</b>	Microphthalmia, syndromic 2	<b>CRYAB</b>	Cardiomyopathy, dilated, III Cataract 16, multiple types Myopathy, myofibrillar, 2 Myopathy, myofibrillar, fatal infantile hypertonic, alpha-B crystallin-related
<b>BEST1</b>	Bestrophinopathy, autosomal recessive Macular dystrophy, vitelliform Microcornea, rod-cone dystrophy, cataract, and posterior staphyloma Retinitis pigmentosa-50 Retinitis pigmentosa, concentric Vitreoretinchoroidopathy	<b>CRYBA1</b>	Cataract 10, multiple types
<b>BFSP1</b>	Cataract 33, multiple types	<b>CRYBA2</b>	Cataract 42
<b>BFSP2</b>	Cataract 12, multiple types	<b>CRYBA4</b>	Cataract 23
<b>CHMP4B</b>	Cataract 31, multiple types	<b>CRYBB1</b>	Cataract 17, multiple types
<b>COL11A1</b>	Deafness, autosomal dominant 37 {Lumbar disc herniation, susceptibility to} Fibrochondrogenesis 1 Marshall syndrome Stickler syndrome, type II	<b>CRYBB2</b>	Cataract 3, multiple types
<b>COL18A1</b>	Glaucoma, primary closed-angle Knobloch syndrome, type 1	<b>CRYGC</b>	Cataract 2, multiple types
<b>COL2A1</b>	Epiphyseal dysplasia, multiple, with myopia and deafness Achondrogenesis, type II or hypochondrogenesis Avascular necrosis of the femoral head Czech dysplasia Kniest dysplasia Legg-Calve-Perthes disease Osteoarthritis with mild chondrodysplasia Platyspondylic skeletal dysplasia, Torrance type SED congenita SMED Strudwick type Spondyloepiphyseal dysplasia, Stanescu type Spondyloperipheral dysplasia Stickler syndrome, type I, nonsyndromic ocular Stickler syndrome, type I Vitreoretinopathy with phalangeal epiphyseal dysplasia	<b>CRYGD</b>	Cataract 4, multiple types
		<b>CRYGS</b>	Cataract 20, multiple types
		<b>CYP27A1</b>	<b>Cerebrotendinous xanthomatosis</b>
		<b>DYNC1H1</b>	Charcot-Marie-Tooth disease, axonal, type 20 Mental retardation, autosomal dominant 13 Spinal muscular atrophy, lower extremity-predominant 1, AD
		<b>EPHA2</b>	Cataract 6, multiple types
		<b>ERCC2</b>	Cerebrooculofacioskeletal syndrome 2 Trichothiodystrophy 1, photosensitive Xeroderma pigmentosum, group D
		<b>FAM126A</b>	Leukodystrophy, hypomyelinating, 5
		<b>FOXE3</b>	{Aortic aneurysm, familial thoracic 11, susceptibility to} Anterior segment dysgenesis 2, multiple subtypes Cataract 34, multiple types

HGNC APPROVED GENE SYMBOL	PHENOTYPE/DEFECT/DISORDER/SYNDROME
<i>FTL</i>	Hyperferritinemia-cataract syndrome L-ferritin deficiency, dominant and recessive Neurodegeneration with brain iron accumulation 3
<i>FYC01</i>	Cataract 18, autosomal recessive
<i>FZD4</i>	Exudative vitreoretinopathy 1 Retinopathy of prematurity
<i>GALE</i>	Galactose epimerase deficiency
<i>GALK1</i>	Galactokinase deficiency with cataracts
<i>GALT</i>	Galactosemia
<i>GCNT2</i>	[Blood group, ii] Adult i phenotype without cataract Cataract 13 with adult i phenotype
<i>GJA3</i>	Cataract 14, multiple types
<i>GJA8</i>	Cataract 1, multiple types
<i>GLA</i>	Fabry disease Fabry disease, cardiac variant
<i>HSF4</i>	Cataract 5, multiple types
<i>LEMD2</i>	Cataract 46, juvenile-onset
<i>LIM2</i>	Cataract 19, multiple types
<i>LONP1</i>	CODAS syndrome
<i>MAF</i>	Ayme-Gripp syndrome Cataract 21, multiple types
<i>MIP</i>	Cataract 15, multiple types
<i>MIR184</i>	EDICT syndrome
<i>MYH9</i>	Deafness, autosomal dominant 17 Macrothrombocytopenia and granulocyte inclusions with or without nephritis or sensorineural hearing loss
<i>NACC1</i>	Neurodevelopmental disorder with epilepsy, cataracts, feeding difficulties, and delayed brain myelination
<i>NDP</i>	Exudative vitreoretinopathy 2, X-linked Norrie disease
<i>NF2</i>	Meningioma, NF2-related, somatic Neurofibromatosis, type 2 Schwannomatosis, somatic
<i>NHS</i>	Cataract 40, X-linked Nance-Horan syndrome

Source: PreventionGenetics

HGNC APPROVED GENE SYMBOL	PHENOTYPE/DEFECT/DISORDER/SYNDROME
<i>OPA3</i>	3-methylglutaconic aciduria, type III Optic atrophy 3 with cataract
<i>PAX6</i>	Coloboma of optic nerve Coloboma, ocular Morning glory disc anomaly Aniridia Anterior segment dysgenesis 5, multiple subtypes Cataract with late-onset corneal dystrophy Foveal hypoplasia 1 Keratitis Optic nerve hypoplasia
<i>PITX3</i>	Anterior segment dysgenesis 1, multiple subtypes Cataract 11, multiple types Cataract 11, syndromic, autosomal recessive
<i>P3H2</i>	Myopia, high, with cataract and vitreoretinal degeneration
<i>RAB3GAP1</i>	Warburg micro syndrome 1
<i>RDH11</i>	Retinal dystrophy, juvenile cataracts, and short stature syndrome
<i>RECQL4</i>	Baller-Gerold syndrome RAPADILINO syndrome Rothmund-Thomson syndrome, type 2
<i>SC5D</i>	Lathosterolosis
<i>SIL1</i>	Marinesco-Sjogren syndrome
<i>SLC16A12</i>	Cataract 47, juvenile, with microcornea
<i>TFAP2A</i>	Branchiooculofacial syndrome
<i>TGM3</i>	Uncombable hair syndrome 2
<i>UNC45B</i>	Cataract 43
<i>VIM</i>	Cataract 30, pulverulent
<i>WRN</i>	Werner syndrome
<i>XYLT2</i>	{Pseudoxanthoma elasticum, modifier of severity of} Spondyloocular syndrome

For complete program details, please contact your Retrophin Clinical Account Manager or visit [www.BehindTheBlur.com](http://www.BehindTheBlur.com).

# You may be the key to diagnosing CTX earlier

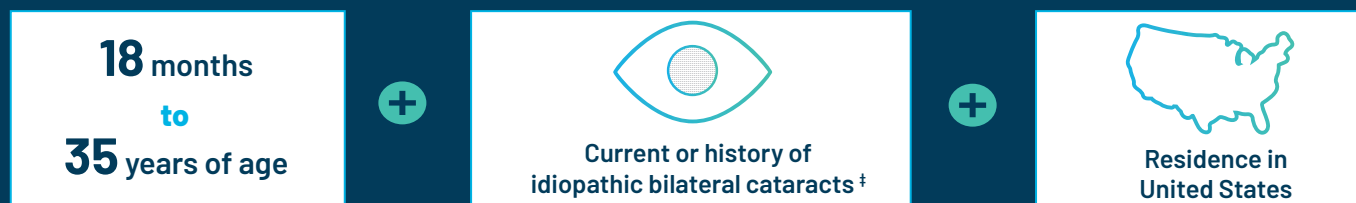
Know the cause of early-onset bilateral cataracts so patients with CTX can be treated sooner<sup>3,10</sup>

- Earlier diagnosis and treatment of CTX can potentially lead to better outcomes<sup>3,10</sup>

## Retrophin offers a no-cost Early-Onset Bilateral Cataracts Genetic Panel for qualified patients<sup>11, \*</sup>

- Retrophin, Inc. has partnered with PreventionGenetics, a College of American Pathologists-accredited laboratory†
- Flexibility of different genetic test samples: 1) Saliva, 2) Buccal swab, or 3) Blood
- Get results in ~3 weeks

### To qualify, patients must meet all of the following criteria:



To order the no-cost to patient Early-Onset Bilateral Cataracts Genetic Panel, or for complete program details, please contact your Retrophin Clinical Account Manager or visit [www.BehindTheBlur.com](http://www.BehindTheBlur.com).

\*Program may be cancelled or changed at any time.

†Note that Retrophin, Inc. cites the above-named external testing resource for information purposes only, and does not endorse or guarantee in any way the services or advice provided by them.

‡Not known to be due to infectious causes, trauma, etc.

#### REFERENCES

1. Raymond GV, Schiffmann R. Cerebrotendinous xanthomatosis: The rare “treatable” disease you never consider. *Neurology*. 2019;92(2):61-62. doi:10.1212/WNL.00000000000067212.
2. Lorincz MT, Rainier S, Thomas D, Fink JK. Cerebrotendinous xanthomatosis: possible higher prevalence than previously recognized. *Arch Neurol*. 2005;62(9):1459-1463. doi:10.1001/archneur.62.9.1459
3. Mignarri A, Gallus GN, Dotti MT, Federico A. A suspicion index for early diagnosis and treatment of cerebrotendinous xanthomatosis. *J Inherit Metab Dis*. 2014;37(3):421-429. doi:10.1007/s10545-013-9674-3
4. Gallus GN, Dotti MT, Federico A. Clinical and molecular diagnosis of cerebrotendinous xanthomatosis with a review of the mutations in the *CYP27A1* gene. *Neurol Sci*. 2006;27(2):143-149. doi:10.1007/s10072-006-0618-7
5. Verrips A, van Engelen BG, Wevers RA, et al. Presence of diarrhea and absence of tendon xanthomas in patients with cerebrotendinous xanthomatosis. *Arch Neurol*. 2000;57(4):520-524. doi:10.1001/archneur.57.4.520
6. Khan AO, Aldahmesh MA, Mohamed JY, Alkuraya FS. Juvenile cataract morphology in 3 siblings not yet diagnosed with cerebrotendinous xanthomatosis. *Ophthalmology*. 2013;120(5):956-960. doi:10.1016/j.ophtha.2012.10.032
7. Farpour H, Mahloudji M. Familial cerebrotendinous xanthomatosis. Report of a new family and review of the literature. *Arch Neurol*. 1975;32(4):223-225. doi:10.1001/archneur.1975.00490460039003
8. Clayton PT, Verrips A, Sistermans E, Mann A, Mieli-Vergani G, Wevers R. Mutations in the sterol 27-hydroxylase gene (*CYP27A*) cause hepatitis of infancy as well as cerebrotendinous xanthomatosis. *J Inherit Metab Dis*. 2002;25(6):501-513. doi:10.1023/a:1021211520034
9. Federico A, Dotti MT, Gallus GN. Cerebrotendinous xanthomatosis. In: Pagon RA, Adam MP, Ardinger HH, et al, eds. *GeneReviews*<sup>®</sup> [Internet]. Seattle, WA: University of Washington, Seattle. 1993-2016. Updated April 14, 2016. Accessed March 15, 2017. <http://www.ncbi.nlm.nih.gov/books/NBK1409/>
10. Freedman SF, Brennand C, Chiang J, et al. Prevalence of cerebrotendinous xanthomatosis among patients diagnosed with acquired juvenile-onset idiopathic bilateral cataracts. *JAMA Ophthalmol*. 2019;137(11):1312-1316. doi:10.1001/jamaophthalmol.2019.3639
11. PreventionGenetics Panel. Data on file. September 2020.

No actual patients are shown.



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