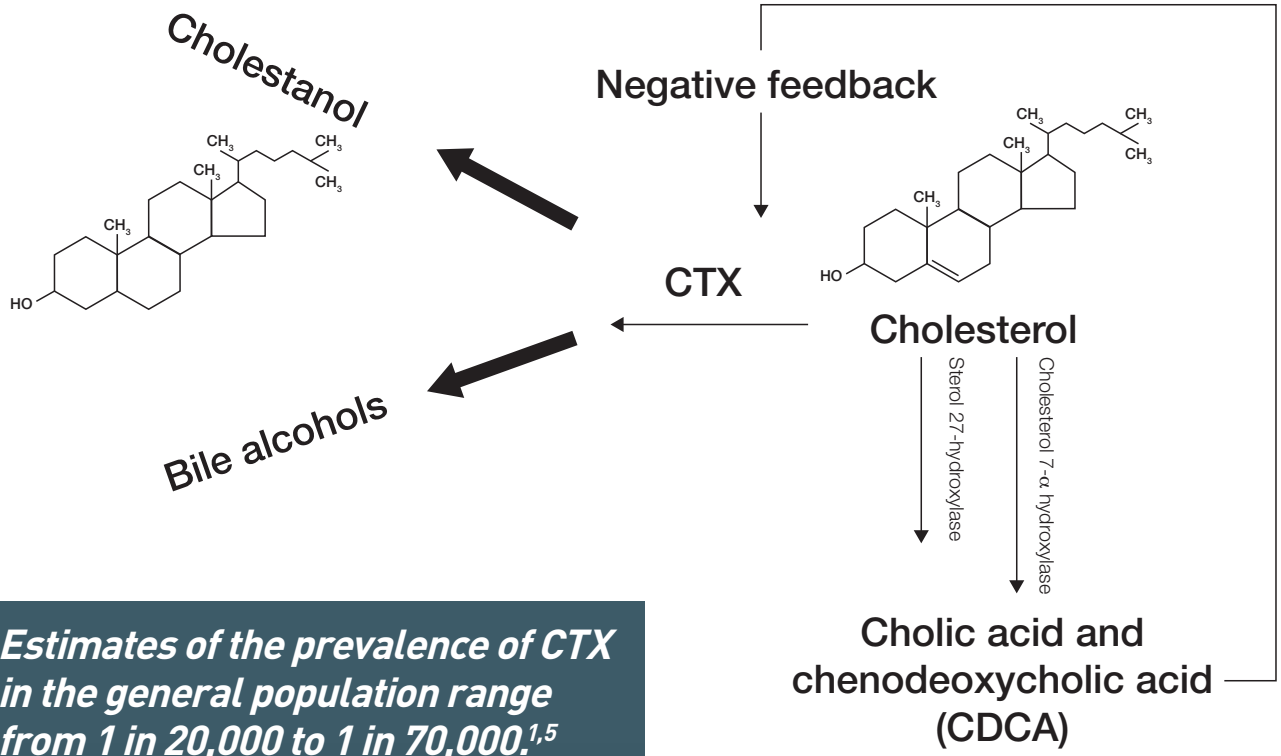
CEREBROTENDINOUS XANTHOMATOSIS (CTX)

CTX is a rare, autosomal recessive lipid storage disease[1-3]

CTX is caused by mutations of the *CYP27A1* gene, which result in deficiency of sterol-27-hydroxylase.[2,4,5] This enzyme deficiency disrupts the conversion of cholesterol to bile acids.[2,5] This produces a decrease in chenodeoxycholic acid (CDCA) thereby disrupting the feedback regulation on the rate-limiting enzyme, cholesterol 7-alpha-hydroxylase, in bile acid synthesis.[4,6,7] This results in an accumulation of cholestanol in the central nervous system (CNS), muscle, blood vessels, eyes, and tendons, and an increase in urinary excretion of bile alcohols.[2,5,6]

In CTX, sterol-27-hydroxylase deficiency disrupts cholesterol breakdown[2,6]



Estimates of the prevalence of CTX in the general population range from 1 in 20,000 to 1 in 70,000.[1,5]

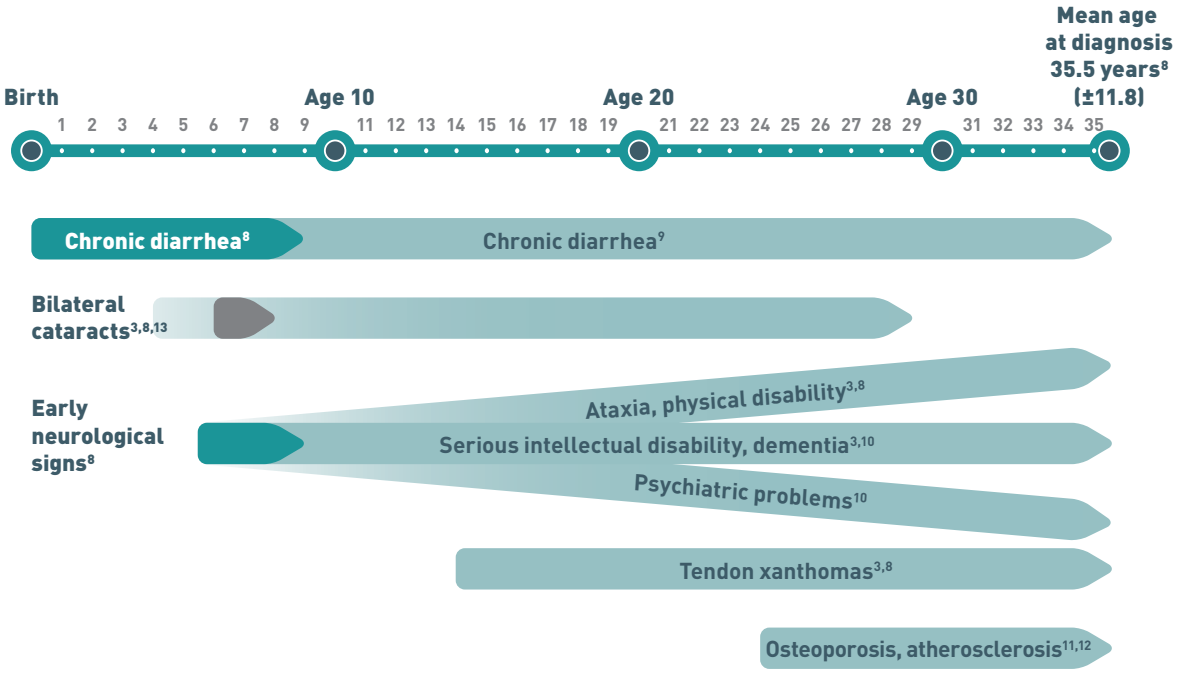
CTX is characterized by a distinct array of hallmark manifestations, though not all occur in every patient[3,8]

Hallmark manifestations have variable onset and severity, which contributes to delayed diagnosis and underdiagnosis.[8] The hallmark manifestations of CTX include infant-onset chronic diarrhea, juvenile-onset bilateral cataracts, tendon xanthomas (particularly of the Achilles tendon), and progressive neurological deterioration.[3,8,9]

Neurological symptoms may include cognitive impairment with learning difficulties that can progress to dementia, spasticity, ataxia, epilepsy, Parkinsonism, and polyneuropathy.[10] Psychiatric manifestations, including personality, affective, and psychotic disorders may also occur, either early in the course of the disease or late, complicating the other neurologic disturbances.[10] Other, later-onset manifestations of CTX may include premature osteoporosis and atherosclerosis.[11,12]

Retrophin

Early diagnosis of CTX can prevent serious physical and intellectual disability[8]



A published suspicion index can help diagnose CTX patients as early as possible[8]

Indicators	Family history	Systemic	Neurological
Very strong	**Sibling with CTX**	**Tendon xanthomas**	
Strong	Consanguineous parents	Juvenile cataract	Ataxia and/or spastic paraparesis
		Childhood-onset chronic diarrhea	Magnetic resonance imaging (MRI) evidence of dentate nuclei signal alterations
		Prolonged unexplained neonatal jaundice or cholestasis	Intellectual disability and/or psychiatric disturbances
Moderate		Early osteoporosis	Epilepsy
			Parkinsonism
			Polyneuropathy

The primary biochemical test used to diagnose CTX is a blood test for cholestanol. A definitive diagnosis can only be made with molecular analysis of the CYP27A1 gene.[14]

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Retrophin

CTX010