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X-linked cataracts are a rare group and appear as a complication of other disease. Changes in the lens are difficult to visualize and the family history may alert the examiner to the possibility of cataractous changes. This paper is a review of 13 sex-linked conditions with cataract as a possible complication. Cataracts may be present in an occasional case or in some instances in every case. Short abstracts follow of Fabry's disease, glucose 6-dehydrogenase deficiency, myotonic dystrophy, ectodermal hypohidriotic dysplasia, oculocerebral syndrome, keratosis follicularis spinulosa decalvans with cataract, Norrie disease, incontinenti pigmenti, hypoparathyroidism due to a sex-linked recessive trait, pseudohypopara-thyroidism, X-linked cataracts – two pedigrees, X-chromosome-linked sutural cataracts, and congenital X-linked cataracts, dental anomalies and brachymetacarpia.

This information is extremely important to pediatricians and others who examine infants and small children.

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IN REVIEWING cataracts, the number and variety of associated findings are confusing to pediatricians and others who examine infants and children. The search for an inherited condition in which X-linked cataracts alone appear has been unsuccessful so far. This characteristic of X-linkage has long stimulated research. Recently the refinement of chromosome staining by banding techniques has made possible identification of each chromosome. The genetic constitution of each chromosome is being studied as to specific gene placement, and many gene loci have been assigned to the X-chromosome.

The multiple causes of cataract make it difficult at times to be certain of its origin. There are developmental cataracts in premature infants which usually disappear. Recently a study has been made of vascularization of the anterior capsule of the lens as it is related to gestational age. This has a direct bearing on the developmental significance of cataract in the premature infant. These vessels were usually atrophied by the 34th week of gestation.[1] There are types due to infections. There is a group called nutritional or metabolic due to lack of, or failure to absorb, one or more vitamins or food elements. There are cataracts due to varied supply of oxygen, to drug sensitivity or overdose, to prolonged cortisone treatment and to varieties of trauma, including radiation. The lens at times is a sensitive or easily abused tissue.[2,3]

1. *Fabry's disease (Angiokeratoma corporis diffusum)*

The condition may start in early adolescence or childhood, consists of severe extremity pain, general cutaneous vascular lesions (angiokeratomata) and corneal opacities. As the disease progresses spoke-like opacities appear in 50% of the lenses.[4] Hemizygous males are most severely affected. Heterozygous females are less involved, but may show cardiac or renal disease later in life.

The condition is inherited as an X-linked recessive and becomes more severe as the patient grows older. The lipid present intracellularly is ceramide trihexoside acting as a cell poison. The necessary enzyme, ceramide trihexosidase (alpha-galactosidase), is lacking.[5] The use of peripheral nerve-conduction time and biochemical estimation of the enzyme alpha-galactosidase was reported successful in separation of the hemi- and heterozygous states, this delineating the amount of involvement in females.[6] The cataract is secondary to the lack of enzyme.

Information regarding the genetic constitution of the X-chromosome is constantly being increased. A large number of genes have been assigned to the X-chromosome through family studies. The relative position of gene loci is found mainly through detection of new X-chromosome markers, through regional assignment of these markers using translocations, and the establishment of the linear order of genes.

The gene concerned with Fabry's disease controls alpha-galactosidase (α-GAL) and has been confirmed to the long arm of the X-chromosome in the region between bands 22 and 24 (q22-q24).[7] As Fabry's disease is complicated in 50% of cases by cataract, this condition is of special interest in the study and understanding of other X-linked cataracts. All lesions of circulatory system and kidneys are also secondary to the enzyme deficiency.

2. *Glucose-6-phosphate dehydrogenase deficiency (G6PD)*

The symptom complex caused by G6PD deficiency is an X-linked, non-spherocytic hemolytic anemia. The recurrent episodes of this anemia are triggered by a number of drugs, by infection and by at least one food, the fava bean. This illness is inherited as an X-linked dominant deficiency of the enzyme G6PD and has caused cataract as an unusual sign.[8]

The substances usually precipitating this condition are primiquine, naphthalene, antimalarias, sulfas, nitrofurons, antipyretics, analgesics, sulfones, methylene blue, phenyl hydrazone, probenecide, vitamin K, chloramphenicol, chloroquin, naladixic acid and orinase.[3]

The locus of this X-linked dominant gene has been confirmed on the long arm of the X chromosome. This deficiency of G6PD has rarely caused cataract and, when it does so, the cataract is secondary. It is of interest and concern because it has a confirmed locus and its action depends on a single amino-acid substitution.

3. *Myotonic dystrophy – Type of inheritance uncertain*

Myotonic dystrophy illustrates a disease in which lens changes progressively become more severe as the patient becomes older. The occurrence of lens changes increases from approximately 10% at 15 years of age to nearly 100% at 60 years of age. This disease may be recognized by wasting and weakness of facial and neck muscles and of limbs distally. Other evidence is myotonia to percussion in the thenar eminence, and on the tongue, myopathic changes in EMG, difficulty in relaxing the grip, and family history of similar disease. Neurologic examination of first-degree relatives has shown abnormal findings in 26 of 131 individuals. Slit lamp examination of 96 of these showed four new cases of cataracts and 20 with non-specific

changes in the choroid. Where the parents could be reported in this survey, the mother was the carrier in 34 of 35 cases. The locus of myotonic dystrophy is known to be linked to the secretor locus and the Lutheran blood group locus but no chromosome assignment has yet been made.

This condition awaits further evidence as a possible X-linked gene inherited through the maternal line or as an autosomal dominant under enzyme control of differential fertility.[9]

4. Ectodermal hypohidriotic dysplasia

Characteristic findings in this disease are hypohidrosis, hypodontia and hypotrichosis. Other findings associated are saddle nose, frontal bossing, pouting lips and periorbital pigmentation. Hair color may be lighter than siblings. Also, there may be eczema and, rarely, deafness and mental retardation. Affected infants may be diagnosed at birth by inability to perspire.

The ocular complications secondary to lack of tears are keratitis, photophobia, cataracts and microphthalmia. The tissues involved primarily are the sweat, sebaceous and mucous glands, hair structure and tooth buds.[10]

The inheritance is X-linked recessive and only appears in males. If the mother is the carrier the chance is 1 in 2 for each son to be affected. The patient having a child faces 100% chance that daughters will be carriers, but sons' chances are not increased unless the wife is a carrier.[5]

Exact locus of this condition on the X-chromosome is unknown. The most similar condition with confirmed assignment is ichthyosis.

5. Oculocerebro renal (Lowe's Syndrome)

This condition is present at birth and consists of bilateral cataracts in male babies. It also includes mental defects and hypotonia. The complex array of symptoms is secondary to renal tubular dysfunction and aminoaciduria. Renal tubular acidosis leads to vitamin-D resistant rickets, cataracts and glaucoma. Cataracts are present in 100% of cases.[5] The inherent derangement of energy metabolism is not entirely known. Female carriers may show lenticular opacities. Proteinuria is composed partly of beta globulinuria but total components of aminoaciduria were not identified by 1973.

Lowe syndrome is inherited as an X-linked recessive believed limited to males. Report of one female indicates that there may be more than one mode of inheritance.[10]

This condition has an important relationship to cataract inheritance because cataracts are present in every case.

6. Keratosis follicularis spinulosa decalvans with cataract

This rare congenital condition consists of skin lesions with keratotic plugs of hair follicles, corneal clouding, alopecia and sparseness of the lateral eyebrows and eyelashes. Associated findings have included congenital glaucoma, mental retardation, arachnodactyly, extra digital creases, aminoaciduria and lenticular cataract in one case reported by Adler and Nyhan.[11] In this case aminoaciduria was present with increased amounts of glutamic acid, glycine, lysine and histidine. There were also slight increases in threonine, serine, cystine and tyrosine.

The inheritance is X-linked, appearing only in males and the female carriers occasionally showing much milder abnormalities.

The similarities between this condition and Lowe's syndrome are mental deficiency, aminoaciduria and cataract. These similar findings suggest that the two loci may be related. The study of individual increased

aminoacids showing four increased and four others slightly increased may later give important information regarding a specific locus for cataract.

7. Norrie disease, (Congenital bilateral pseudoglioma of the retina with recessive X-linked inheritance)

This condition consists of dysplasia of the retina in boys blind from birth on an X-linked basis. Both eyes are affected and usually show some microphthalmos, and shallow anterior chamber, dilated pupil and absence of reflex to light. Posterior synechiae, ectropion of the iris pigment fringe, and hypoplastic retina are present. Retinal folds, detached retina and pseudotumor may be observed. The lens is initially clear but may become cataractous. Most patients develop mental retardation and frequently sensorineural deafness.

The inheritance is X-linked recessive. Combined with mental retardation and deafness, it has positive distinguishing marks from the chromosome anomaly Trisomy-13.[5]

As there is a known locus for congenital mental retardation and also one for retinoschisis, both X-linked, this disease with cataract may become more important in location of X-linkage.

8. Incontinenti pigmenti

This condition consists of irregular skin pigmentation in flecks, whorls or a spidery pattern. First lesions at birth or during infancy may be bullae which are replaced by pigmentation. The pigmentation slowly fades but may last into the third decade. It appears almost exclusively in girls and is probably transmitted as an X-linked dominant.[5] In addition to cutaneous changes, there are multiple ectodermal and mesodermal changes consisting of abnormalities of the eyes, hair and teeth. Epilepsy, mental deficiency and cardiac anomalies have been associated. Bilateral congenital cataracts have appeared.[12]

The inheritance has been considered X-linked dominant and is lethal in the male.

The conditions with a confirmed X-chromosome locus suggestive of this disease are ichthyosis and congenital mental deficiency.

9. Hypoparathyroidism due to a sex-linked recessive trait

The clinical condition of hypoparathyroidism has several causes among which is familial hypoparathyroidism as a sex-linked trait. The condition is limited to males and consists of symptoms associated with low blood calcium, high phosphorus, convulsions, absence of rickets, absence of renal and intestinal complications, and absence of brachydactyly, dwarfing, or subcutaneous calcium deposits. Cataracts occur in long-standing untreated disease. They characteristically appear as bilateral slowly developing, small discrete lamellar opacities often associated with multicolored crystal-like structures within the lens. They are best observed by means of slit lamp and rarely interfere with vision.[3]

The report by Peden[13] gives in detail a summary of this condition and of the 10 acceptable cases reported up to 1960. Of these, all were under one year of age, and seven were under seven weeks of age. The disease is practically always present in the early weeks and if it has a later onset must be suspected as a non-sex-linked congenital aberration accompanied by other anomalies, especially an association with Addison's disease.

The first of Peden's two cases had bilateral cataracts at 4½ months of age, was alive at three years, mentally and physically retarded and was not talking.

In her review of the 10 acceptable cases, including her two, there was one child with cataract. This rare condition, of which only 58 cases were reported up to 1960, has very few cataracts and will require further study.

X-linked disease with cataract

10. Pseudohypoparathyroidism

This condition has cataracts similar to hypoparathyroidism and is considered X-linked dominant in inheritance. Patients have the dyschrondroplastic changes and ectopic calcifications and ossifications of hypoparathyroidism, but gland secretion of parathormone and serum levels of calcium and phosphorus are normal. Mental retardation is common and blue sclerae and esotropia have been described.[3] The defect appears in the end organ response to secretion. Normal parathyroid secretion does not evoke an increase in intracellular cyclic AMP, and urinary cyclic AMP excretion is deficient.[10]

The disorder has been recognized as X-linked dominant but some females appear to be more severely affected than males and further classification of familial incidence may appear.[14]

11. X-linked cataract (2 pedigrees)

Two pedigrees of X-linked cataracts are to be considered. The first includes three generations; the disease is confined to males, with minor signs in carrier females. The males have congenital zonular cataract and the females have posterior suture line cataracts.

The first pedigree was first reported in 1937 by Walsh and Wegman[5] and has been reviewed and completed for another 30 years by Gragg.[15] The males had congenital microcornea and zonular cataracts which increased in size after birth. The females showed posterior suture line cataracts which did not interfere with vision. Recent follow-up of the family showed a third generation similarly affected. The kindred was from the inbred tri-racial isolate of Southern Maryland, known as the Wesorts.

The first pedigree from 1937 as modified in 1971 is shown in Figure 1.

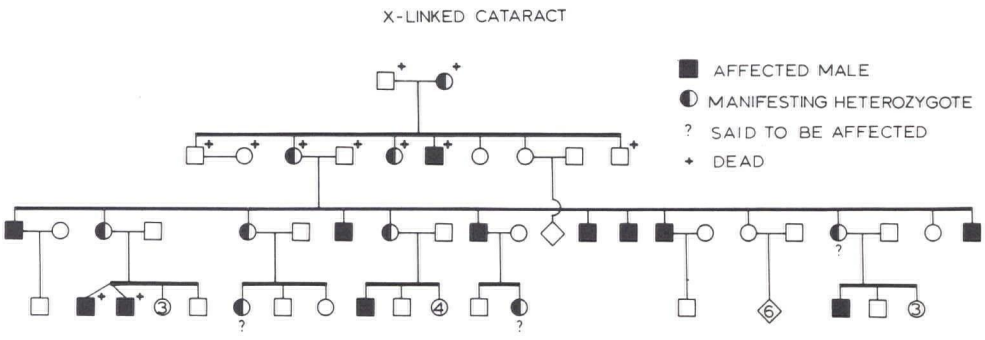

Figure 1
Pedigree showing affected males in three generations related through carrier females. (Courtesy of Walch, F. and Wegman, M. *Bull, Johns Hopkins Hosp.* 61:125, 1937 and Hussels, I. and Gragg, G.W., *Birth Defects,* 7:164-5, 1971.

The second pedigree, Figure 2, reported in 1971 by Hussells showed two identically affected brothers and the carrier state in the mother.

The first boy, born in 1967, was diagnosed at two months of age as microcornea and congenital cataract when it was noted he could not focus nor regard his hands. He was treated by unilateral cataract extraction at four months of age and at this age he developed hepatosplenomegaly and positive cultures for cytomegolic virus. By nine months of age his physical examination was normal and a second cataract extraction was performed. At two years his examination was normal except for vision.

The second boy was born in 1969, the mother's second child, and he was noted to have bilateral cataracts at birth. The examination for cytomegalic virus was negative. At 12 and 19 days the cataracts were removed. At eight months of age he was doing well with bilateral contact lenses but had a definite microphthalmus.

It is very unlikely that the first child had cataract from cytomegalovirus. In infants whose first sign of disease is apparent some time after birth, clinical manifestations are more varied[10] than the severe disease present from intra-uterine infections. This child had hepatosplenomegaly at four months. If his eye condition had been due to intra-uterine cytomegalic viral infection, his general condition should have been much worse. The prognosis in such infections is grave and mortality high.

The type of X-linked cataract reported by Fraccaro and others[16] is probably the same as reported by Hussels. By linkage studies, Fraccaro concluded that the X_g blood group locus is within mappable distance of the cataract locus. The pedigree of Fraccaro's family is shown in Figure 3.

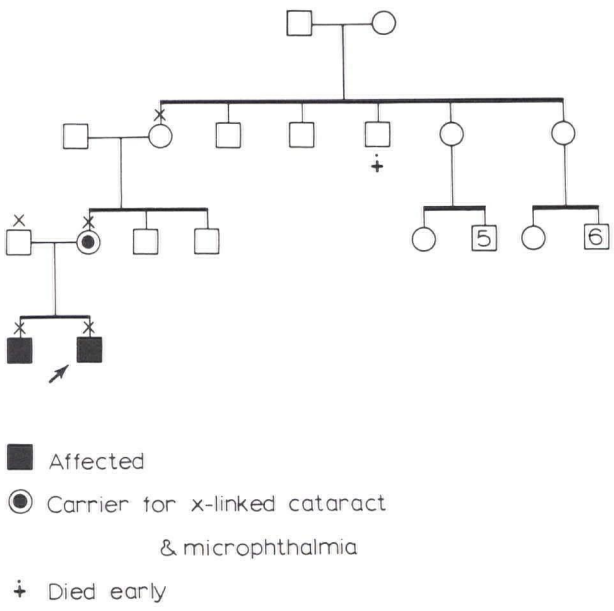

Figure 2

Pedigree showing two identically affected male sibs and their mother exhibiting carrier state. (Hussels, I: X-linked cataract: Two pedigrees. *Birth Defects* 7:164-5, 1971.)

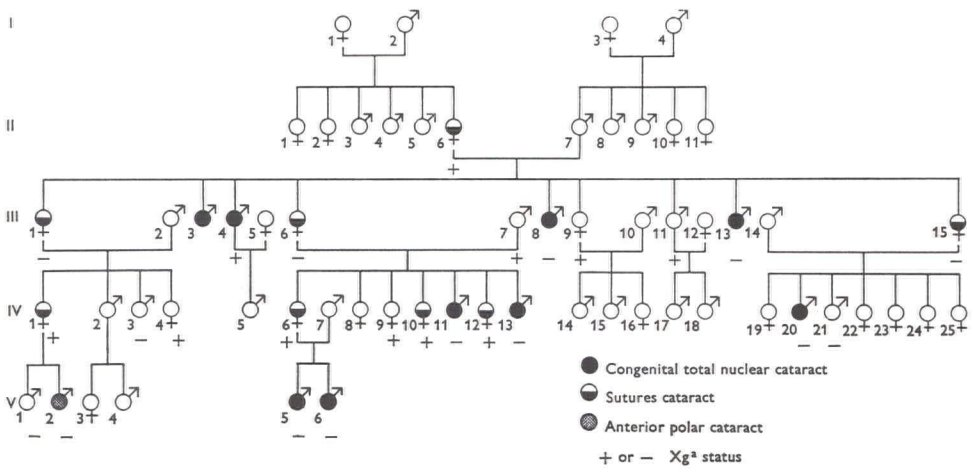

Figure 3

The pedigree of the family described in this report. (Fraccaro, M., Marone, G., Manfredine, V. and Sanger, R.: X-linked Cataract. *Ann. Hum. Genet.* Lond. 31:45, 1967)

12. X-chromosome-linked sutural cataracts

A kindred of three generations is reported by Krill and others[17] showing cataracts in three generations. They observed eight affected men and eight carrier women with posterior sutural cataracts. X-linked inheritance was demonstrated. Only one of the eight males had any complication, ie, mental deficiency. Among the fourteen possible carriers there was only one with a severe cataract, and she had no offspring. This kindred shown in Figure 4 best supports the existence of a true cataract locus.

13. Congenital X-linked cataract, dental anomalies and brachymetacarpia

Nance[18] and associates reported on congenital X-linked cataracts with microcornea, supernumerary incisors, anteverted pinnae and shortened fourth metacarpals. The disease was limited to males. The carrier females had minor defects. The kindred of six generations illustrates a condition of severe cataract accompanied by relatively minor other defects. Eleven family members were examined as thoroughly as possible for type of cataract, nystagmus, vision, color vision, diameter of cornea, extra teeth, wide spaced incisors, narrow distal edge of incisors, serum calcium and phosphorus, alkaline phosphates, G6PD deficiency, Xg^ablood group, antiverted pinnae, and short fourth metacarpal.

In the three patients with cataract who could be examined, the alkaline phosphatases were increased. All three were blood group Xg^a, all had anteverted pinnae and short fourth metacarpals. Color vision was normal in two affected men and not tested in three because of poor vision, but it was normal in the three carriers and the three relatives available for testing.[18] Color vision is important because there are two loci for this already confirmed on the X chromosome. This kindred was studied in detail as seen from the illustration (Figure 5) and is important for showing all seven members tested as being in blood group Xg^a. These seven tested were three men with cataract, three carriers, and one normal brother, number 10 in Figure 5. This information further suggests that the cataract locus may be near the X_g locus.

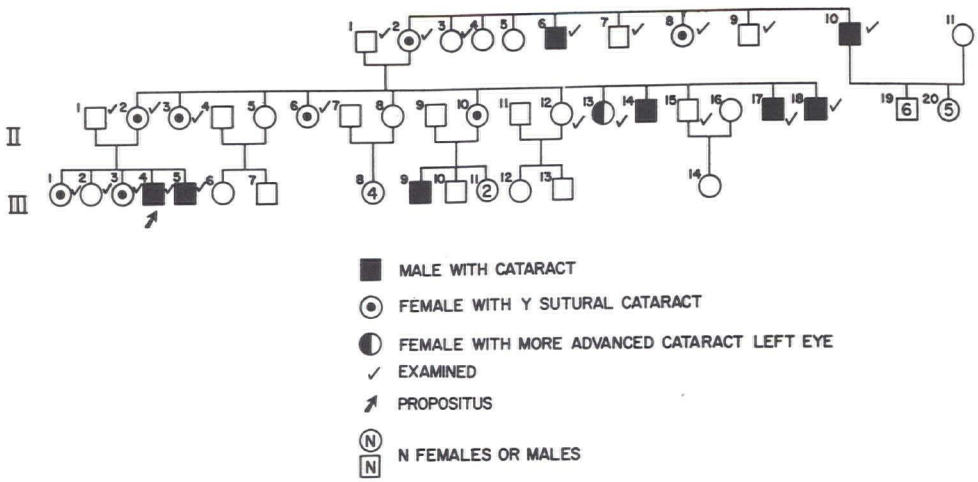

Figure 4

Pedigree of family with X-linked sutural cataract. (Krill, Woodbury and Bowman, *Amer. J. of Ophthalmology,* p. 868, Nov, 1969)

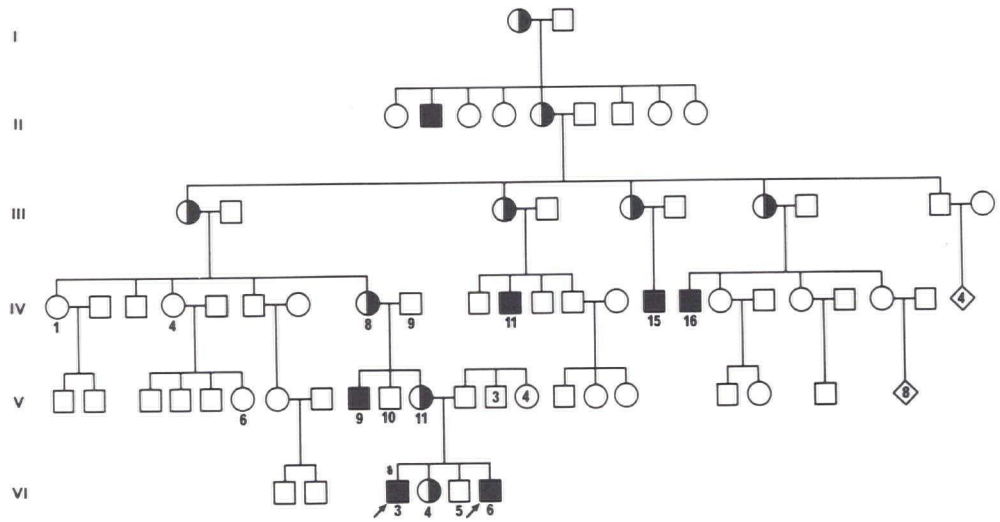

Figure 5

Pedigree of family with X-linked cataracts and dental anomalies. All numbered subjects were examined professionally. (Nance, W. E., Warburg, M., Bixer, D. and Helveston, E. M.: *Birth Defects, Original Articles,* Vol. X, No. 4, 1974, p. 286)

Summary

The subjects reviewed have two characteristics in common: 1) they all have had reported one or more cases with cataracts; and 2) all have been familial. All have been on a Mendelian basis.

The first two conditions, Fabry's disease and G6PD deficiency, both have been associated with cataracts, the first with 50% incidence, the latter with at least one case. However, they are the only two conditions

with confirmed loci on the X-chromosome. The conditon of myotonia congenita has a very high incidence of cataract, from 15% to 100% , depending on patient's age, but there is some question about X-linkage. It is included because 34 of 35 cases were inherited through the mother. As its locus is provisionally linked to the secretor and the Lutheran blood group, the three loci may finally be confirmed together.

Lowe's syndrome is clearly X-linked and has a very high incidence of cataract. Its exact etiology as to specific kidney tubule dysfunction or amino acid loss may help to identify a specific locus.

Other conditions which are sex-linked and occasionally have had cataracts are ectodermal hypohidriotic dysplasia, keratosis follicularis spinulosa decalvans with cataract, Norrie's disease, incontinenti pigmenti, hypoparathyroidism and pseudohypoparathyroidism. These are inherited on a Mendelian basis, and most of the female carriers have had minor signs. Cataracts are such a minimal part of the diseases represented that exact origin of the cataracts is unknown. They appear to be independent occurrences, especially as the lens is sensitive to so many toxins and physical pressures.[2,3]

The last three subjects reviewed give great promise that there is a single X-linked locus for cataracts.

Cataracts are a distinctive and alarming sign. This special group must be understood by pediatricians and others who examine newborn and young children. The family history may contain primary information necessary for diagnosis. The limitation of a disease to one sex may be paramount information. Thirteen X-linked conditions with cataract are described.

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