

Alport Syndrome

Also known as: hereditary nephritis, hematuria–nephropathy deafness, hereditary deafness and nephropathy

Clinical Characteristics

The characteristics of Alport syndrome include congenital hearing loss, ocular abnormalities, and progressive renal insufficiency. Ocular abnormalities include “flecks” or granulations in the retina, ocular lesions, and anterior lenticonus, in which the central portion of the lens protrudes anteriorly. Renal insufficiency is characterized by microhematuria, proteinuria, and hypertension. Some individuals progress to end-stage renal disease.

Alport Syndrome and Hearing Loss

Bilateral high-frequency sensorineural hearing loss is commonly observed in individuals with Alport syndrome. Rarely congenital, hearing loss is more likely to develop later in life and demonstrate progression. The age of onset and rate of progression is partially dependent on the pattern of inheritance, though variability exists even among members of the same family.

Genetics

The characteristics of Alport syndrome are all due to defects of type IV collagen. Those defects are secondary to a mutation in one of the following genes: *COL4A5* on chromosome X, *COL4A3* on chromosome 2, and *COL4A4* on chromosome 2. About 80% of Alport syndrome is **X-linked**, 15% is **autosomal recessive**, and 5% is **autosomal dominant**. Individuals are affected differently depending on the type of inheritance pattern in which their condition was transmitted. Recurrence risks also vary for each type of pattern. X-linked conditions are often transmitted through carrier mothers. A woman who is a carrier for X-linked Alport syndrome (XLAS) has a 50% chance of passing the disease-causing mutation on to each of her sons. There is also a 50% chance she will pass the mutation on to each of her daughters, who would then also be carriers. An affected male cannot pass the disease-causing mutation on to his sons; he will, however, always pass that mutation on to a daughter, who would then be a carrier. When an individual is affected with autosomal recessive Alport syndrome (ARAS), the parents of that individual must be carriers for the condition. Whenever two carriers for ARAS have a child, there is a 1 in 4 (25%) chance the child will be affected, a 2 in 4 (50%) chance the child will be an unaffected carrier just like their parents, and a 1 in 4 (25%) chance the child will neither be affected nor a carrier. Overall, there is a 75% chance with each pregnancy the child will not have ARAS. An individual affected with autosomal dominant Alport syndrome (ADAS) has a 50% chance with each pregnancy of having an affected child, and a 50% chance of having an unaffected child.

Natural History

The prevalence of Alport syndrome is estimated to be about 1 in 50,000. The natural history of the condition depends upon the type of inheritance by which it is transmitted.

X-Linked

Manifestations are generally more severe in affected males than in affected females. Males tend to have persistent microhematuria, while it may be intermittent in females. All males will develop proteinuria and eventually progress to renal insufficiency and end-stage renal disease. 60% of males reach end-stage renal disease by age 30 years, 90% by 40. In contrast, only about 12% of females develop end-stage renal disease by 30, 30% by 60, and 40% by age 80. Hearing loss is often first detected in males by late childhood or early adolescence. 80-90% of patients have sensorineural hearing loss by the time they are 40. Hearing loss is less frequent and the onset tends to be later in females. Ocular findings are more common in males, but few numbers are available for comparison.

Autosomal Recessive

There are generally no differences in clinical expression between affected males and females. Nearly all individuals have persistent microhematuria, which often progresses to end-stage renal disease by age 30. Heterozygous carriers of a mutation have about a 50% chance of developing microhematuria at some point. Sensorineural hearing loss often develops in adolescence. Ocular findings are similar to those found in XLAS.

Autosomal Dominant

In general, the manifestations of ADAS are less severe than those of XLAS or ARAS. While nearly all affected individuals do have microhematuria which eventually progresses to end-stage renal disease, the progression is slower. Individuals with ADAS tend to develop hearing loss later in life, and ocular findings are much less common. Ocular symptoms generally do not appear.

Individuals with Alport syndrome, regardless of the mode of inheritance, typically have normal intelligence. Life expectancy is usually shortened due to the likelihood of renal failure.

Management

The diagnosis of Alport syndrome is made clinically. Genetic testing is available for confirmation of diagnosis, and carrier testing and prenatal diagnosis if a mutation is identified. Mutations are identified 50-100% of the time, depending on the mode of inheritance and the method of testing.

Management of Alport syndrome requires regular evaluation and surveillance by a nephrologist. Renal transplantation is typically successful, provided a suitable donor is found. Relatives must be considered carefully, especially if there is a positive family history.

Hearing aids are usually the intervention of choice for hearing loss. Annual evaluations by an audiologist are recommended in order to track progression. Ocular findings do not usually require any specific intervention, though regular assessment by an ophthalmologist is still appropriate. Vision is typically normal, needing no treatment. A scheduled appointment with a geneticist and/or genetic counselor is also recommended.

Resources for Families

Statewide Genetics Program

Phone: 608-267-7148

Fax: 608-267-3824

Email: meyeram@dhfs.state.wi.us

Wisconsin First Step Hotline

Phone: 1-800-642-7837 voice/TTY

Website: www.mch-hotlines.org

Wisconsin Office for Deaf and Hard of Hearing

Phone: 1-608-266-3118 voice/TTY

Website: www.dhfs.state.wi.us/sensory

Regional Children and Youth with Special Health Care Needs Centers

Centers in Green Bay, Wausau, Milwaukee, Madison, and Chippewa Falls

Website: http://dfhs.wisconsin.gov/DPH_BFCH/cshcn/index.HTM

WI Chapter of Families for Hands & Voices

Phone: (920) 437-7370

Website: www.handsandvoices.org

Parent-to-Parent of Wisconsin

Phone: 1-888-266-0028

Email: rmathea@shsmh.org

Alport Syndrome Home Page

<http://home.utah.edu/~cla6202/ASHP.htm>

National Organization of Rare Disorders (NORD)

www.rarediseases.org