Alport Syndrome

Alport syndrome is characterized by renal, cochlear, and ocular involvement. The main manifestation is glomerular nephropathy with hematuria, progressing to end-stage renal disease. Eye abnormalities include anterior lenticonus, maculopathy, corneal endothelial vesicles, and recurrent corneal erosion. The hearing loss develops gradually and is usually detectable during late childhood or early adolescence.

Prevalence of Alport syndrome is estimated at 1/50 000.

Alport syndrome is caused by mutations in COL4A3, COL4A4, and COL4A5 genes. The disease is known to be inherited in an **X-linked**, **autosomal recessive** or **autosomal dominant** pattern.

Indications for genetic testing:

1. Confirmation of clinical diagnosis
2. Carrier testing for at-risk relatives
3. Genetic counseling
4. Prenatal diagnosis for known familial mutation

Aminoglycoside-Induced Deafness

Aminoglycosides are a group of pharmacologic agents that have been shown to have toxic effects to the cochleovestibular system.

Cochlear toxicity can result in sensorineural hearing loss and dysequilibrium. Hearing loss is bilateral and severe to profound, occurring within a few days to weeks after administration of any amount of an aminoglycoside antibiotic such as gentamycin, tobramycin, amikacin, kanamycin, or streptomycin.

Predisposition to **aminoglycoside,** caused by aminoglycoside exposure is known to be associated with pathogenic variants in the **MT-RNR1 gene**. Nonsyndromic mitochondrial hearing loss and deafness is transmitted by maternal inheritance.

Indications for genetic testing:

1. Determination of molecular genetic basis of nonsyndromic sensorineural hearing loss
2. Define etiology of hearing loss after aminoglycoside therapy
3. Detection the carrier status of individuals with family history of maternally-inherited hearing loss with or without aminoglycoside therapy
4. Detection the carrier status of relatives with a known mutation
5. Genetic counseling

Branchiootorenal Syndrome

Branchiootorenal (BOR) syndrome is characterized by malformations of the outer, middle, and inner ear associated with conductive, sensorineural, or mixed hearing impairment, branchial arch anomalies (branchial clefts, fistulae, cysts), and renal abnormalities. Renal malformations may include urinary tree malformation, renal hypoplasia or agenesis, renal dysplasia, renal cysts. In some cases, end-stage renal disease develops later in life.

BOR manifests wide clinical heterogeneity between affected individuals. Estimated prevalence of the disease is 1/40,000.

BOR syndrome is transmitted in an **autosomal dominant** manner.

Indications for genetic testing:

1. Confirmation of clinical diagnosis
2. Genetic counseling
3. Prenatal diagnosis for known familial mutation

Branchiootorenal Syndrome NGS-based test details

NGS-based test covers the entire coding region of EYA1, SIX1, SIX5 genes associated with**branchiootorenal syndrome**.

Testing is available both with **genotyping** service (includes genotyping, electronic copy of the results report) and **diagnostic package** service (includes DNA extraction, detection of genetic variations, confirmation of disease associated variants by Sanger sequencing, biological and clinical interpretation of disease associated variants, the results report by registered mail).

Turnaround Time:
Genotyping service
8 weeks
Diagnostic package service
12 weeks

Specimen Requirements:
2-4 ml of blood with anticoagulant EDTA
Send blood samples at room temperature. Blood samples can be preserved at 2-8°C before shipping. Blood samples are recommended not to freeze and not to store longer than one week.
4 µg DNA in TE, AE or pure sterile water at 100-250 ng/µl
Send DNA samples at room temperature or frozen. To avoid sample loss and contamination, please use 0,5-2,0 ml screw cap tubes, tubes with safe lock lid or wrap the caps of each microtube with parafilm.

The A260/A280 ratio should be 1.8-2.0. DNA sample should be run on an agarose gel as a single band, showing no degradation, alongside with a quantitative DNA marker.

Jervell and Lange-Nielson Syndrome

Jervell and Lange-Nielsen syndrome (JLNS) is characterized by congenital profound bilateral sensorineural hearing loss and prolonged QT interval with ventricular tachyarrhythmias. Cardiac events, which are primarily triggered by stress and exercise, may result in syncope or sudden death. 50% of individuals become symptomatic before age of 3. Iron-deficient anemia and elevated levels of gastrin are also frequent symptoms of JLNS.

JLNS is inherited in an autosomal recessive manner.

An estimated prevalence of disorder is 1.6 to 6 per 1 million. In Norway and Sweden there are a higher prevalence, up to 1:200,000.

Indications for genetic testing:

1. Confirmation of clinical diagnosis
2. Testing of family members of the affected individuals
3. Carrier status detection of known mutation
4. Genetic counseling

Pendred Syndrome

Pendred syndrome is an autosomal recessive condition characterized by bilateral sensorineural hearing impairment, vestibular and cochlear abnormalities, temporal bone abnormalities and goiter. Considerable phenotypic variability is found even within the same family. **Sensorineural hearing loss**is usually congenital, severe to profound and non-progressive. However, hearing loss may be later onset and progressive in some patients.

Pendred syndrome, as well as **nonsyndromic hearing loss and deafness** (DFNB4) show similar phenotypic spectrum. DFNB4 is characterized by nonsyndromic sensorineural hearing loss, vestibular dysfunction, enlarged vestibular aqueduct but normal thyroid function.

Indications for genetic testing:

1. Confirmation of clinical diagnosis
2. Carrier status detection of known mutation
3. Genetic counseling

Sensorineural Hearing Loss

Hereditary sensorineural hearing loss (SNHL) includes syndromic and non-syndromic forms. The syndromic forms of SNHL include Usher syndrome, Pendred syndrome, Waardenburg syndrome, Jervell and Lange-Nielsen syndromes, etc. Most cases of SNHL are nonsyndromic. SNHL can follow a pattern of autosomal dominant, autosomal recessive, x-linked recessive, or mitochondrial inheritance.

Indications for genetic testing:

1. Confirmation of clinical diagnosis
2. Determination of molecular genetic basis both of nonsyndromic and/or syndromic SNHL
3. Distinguish different forms of nonsyndromic hearing loss and deafness
4. Define etiology of hearing loss after aminoglycoside therapy
5. Detection the carrier status of individuals with family history of maternally-inherited hearing loss with or without aminoglycoside therapy
6. Detection the carrier status of relatives with a known mutation
7. Genetic counseling
8. Prenatal diagnosis

Stickler Syndrome

Stickler syndrome is a group of hereditary conditions affecting connective tissue. Stickler syndrome is characterized by ocular findings, distinctive facial abnormalities, hearing loss, skeletal abnormalities, and joint problems.

Eye findings may include high myopia, cataract, vitreoretinal or chorioretinal degeneration, and retinal detachment. Hearing loss can be both conductive and sensorineural. Affected individuals have a characteristic flattened facial appearance caused by midfacial underdevelopment and cleft palate.

Stickler syndrome is inherited in an autosomal dominant or autosomal recessive manner. Stickler syndrome affects approximately 7,500 to 9,000 newborns.

Indications for genetic testing:

1. Confirmation of clinical diagnosis
2. Carrier testing for at-risk family members
3. Genetic counseling

Treacher Collins Syndrome

Treacher Collins syndrome (TCS) is a congenital disorder characterized by craniofacial deformities, external ear abnormalities, and eye anomalies. The most characteristic features of TCS are micrognathia, conductive hearing loss, coloboma of the lower eyelid, and absence of the lower eyelashes. Less common signs include cleft palate and unilateral or bilateral choanal stenosis or atresia.

TCS affects an estimated 1 in 50,000 people. The disorder has an autosomal dominant pattern of inheritance. Approximately 1% of TCS is inherited in an autosomal recessive manner.

Indications for genetic testing:

1. Confirmation of clinical diagnosis
2. Carrier testing for at-risk family members
3. Genetic counseling

Waardenburg Syndrome

Waardenburg syndrome (WS) is a group of genetic conditions characterized by sensorineural hearing loss and pigmentary abnormalities of the iris, hair, and skin, along with dystopia canthorum. Hearing loss is congenital, typically non-progressive, either unilateral or bilateral, and sensorineural.

The classic sign of hair pigmentation anomaly with WS is white forelock appearing typically in the teen years. Ocular pigmentary manifestations may include complete or segmental heterochromia or hypoplastic or brilliant blue irides.

Waardenburg syndrome affects an estimated 1 in 20,000-40,000 people.

Four types of WS can be distinguished by physical characteristics and genetic cause. Types I and III are inherited in an autosomal dominant manner, types II and IV are autosomal recessive.

Indications for genetic testing:

1. Confirmation of clinical diagnosis
2. Carrier testing for at-risk relatives
3. Genetic counseling

Zellweger Spectrum Disorders

Zellweger spectrum of peroxisome biogenesis disorders comprises **Zellweger syndrome**,**neonatal adrenoleukodystrophy** (NALD), and infantile **Refsum disease**. These three diseases have overlapping clinical phenotypes. Zellweger syndrome is considered to be the most severe form, NALD intermediate, and infantile Refsum disease the least severe.

Onset of manifestations is usually in the newborn period or later in childhood and includes hypotonia, seizures, distinctive craniofacial features (flattened facies, large anterior fontanelle, widely split sutures, and broad nasal bridge), feeding difficulties, and liver dysfunction. Older children experience sensorineural hearing loss, retinal dystrophy and developmental delays. Affected individuals may also have skeletal abnormalities, adrenal insufficiency, episodes of hemorrhage and intracranial bleeding, and coagulopathy.

The Zellweger spectrum disorders are inherited in an **autosomal recessive** manner. The Zellweger spectrum disorders are estimated to occur in 1 in 50,000 individuals.

Indications for genetic testing:

1. Confirmation of clinical diagnosis
2. Carrier status detection of known mutation
3. Prenatal diagnosis for known familial mutation
4. Genetic counseling