Age-Related Macular Degeneration – AMD

Age-related macular degeneration (AMD) is characterized by pathological changes of the retinal pigment epithelium (RPE), progressive degeneration of photoreceptors, thickened Bruch's membrane and choroidal neovascularization. These alterations lead to the loss of sharp, central vision. It is an age-related process and usually develops after a person reaches 50 years.

In Western Europe and USA 30% of people older than 75 years suffer from different types of AMD. 85-90% cases of AMD are dry AMD, which have no treatment. 10-15% cases of AMD are wet AMD, which have number of treatments available (injection into the eye to stop further development) and early diagnosis can save vision.

AMD increased risk assessment enables prevention and early diagnosis of the disease. The early diagnosis is vital to delay progression of disease and vision loss.

Indications for genetic testing:

1. Risk determination of at-risk individuals for early diagnosis and prediction of disease progression
2. Risk assessment of individuals with family history of AMD
3. Genetic counseling

Aniridia

Aniridia is characterized by complete or partial absence of the iris. The symptoms of the disease may include foveal hypoplasia, reduced visual acuity, nystagmus, photophobia, glaucoma, cataract, and optic nerve hypoplasia.

Aniridia can be **isolated** or as a part of the **WAGR** (Wilms tumor, aniridia, genital anomalies and mental retardation) **syndrome**.

The prevalence of aniridia is estimated between 1:50 000-1:100 000.

Isolated aniridia is caused by mutations in the **PAX6 gene** or deletion of a regulatory region controlling PAX6 expression. WAGR syndrome is caused by a deletion of chromosome 11p13, the region harboring the PAX6 and WT1 genes. Isolated aniridia and WAGR syndrome are inherited in an **autosomal dominant** manner.

Indications for genetic testing:

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

Autosomal Dominant Optic Atrophy – ADOA

Autosomal dominant optic atrophy (ADOA) is characterized by progressive bilateral blindness due to the loss of retinal ganglion cells and optic nerve deterioration. The severity of vision loss varies from nearly normal vision to complete blindness. The age of onset is usually between 4 and 6 years, but ADOA rarely causes severe vision impairment in childhood.

Indications for genetic testing:

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

Autosomal Dominant Retinitis Pigmentosa

Retinitis pigmentosa is an inherited **retinal dystrophy** caused by the loss of photoreceptors and characterized by retinal pigment deposits visible on fundus examination. Affected individuals first experience night blindness, followed by reduction of the peripheral visual field and, sometimes, loss of central vision late in the course of the disease which eventually leads to blindness after several decades. Signs and symptoms often first appear in childhood, but severe visual problems do not usually develop until early adulthood. In some cases, RP is characterized by cone-rod dystrophy, in which the decrease in visual acuity predominates over loss of the visual field. RP is usually nonsyndromic but there are also many syndromic forms. The main risk factor is a family history of retinitis pigmentosa.

Indications for genetic testing:

1. Confirmation of clinical diagnosis
2. Testing of individuals in subsequent generations with family history of autosomal dominant retinitis pigmentosa
3. Genetic counseling
4. Prenatal diagnosis for known familial mutation

Autosomal Recessive Retinitis Pigmentosa – AR RP

Retinitis pigmentosa (RP) is an inherited retinal dystrophy caused by the loss of photoreceptors and characterized by retinal pigment deposits visible on fundus examination. Affected individuals first experience night blindness, followed by reduction of the peripheral visual field and, sometimes, loss of central vision late in the course of the disease which eventually leads to blindness after several decades. Signs and symptoms often first appear in childhood, but severe visual problems do not usually develop until early adulthood. In some cases, RP is characterized by cone-rod dystrophy, in which the decrease in visual acuity predominates over loss of the visual field. RP is usually non-syndromic but there are also many syndromic forms. The main risk factor is a family history of retinitis pigmentosa.

Indications for genetic testing:

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

Bardet Biedl Syndrome, McKusick-Kaufman Syndrome, Borjeson-Forssman-Lehmann Syndrome, Alström Syndrome, Albright Hereditary Osteodystrophy

McKusick-Kaufman Syndrome is characterized by postaxial polydactyly, congenital heart disease and hydrometrocolpos in females and genital malformations (hypospadias, cryptorchidism, chordee) in males. Hydrometrocolpos develops in the female fetus as a result of accumulation of secretions in the vagina and uterus due to a congenital obstruction. McKusick-Kaufman Syndrome (MKKS) is inherited in an autosomal recessive manner. MKS is concentrated in the Amish population, where it affects an estimated 1 in 10,000 people. The disease is caused by mutations in **MKKS (BBS6) gene**, which encodes a protein with similarity to members of the chaperonin family. Some mutations in MKKS gene are associated with McKusick-Kaufman Syndrome, most mutations cause one of the forms of Bardet-Biedl Syndrome (BBS). There are also several symptoms of MKS that overlap significantly with BBS.

Bardet-Biedl Syndrome is characterized by male hypogenitalism, complex female genitourinary malformations, postaxial polydactyly, cone-rod dystrophy, obesity, cognitive impairment, and renal abnormalities. Renal abnormalities are major cause of morbidity and mortality. The first symbol of retinal degeneration is night blindness, which later evolves into a progressive loss of peripheral vision. Patients

with Bardet-Biedl also experience central vision loss during childhood or adolescence. Bardet-Biedl Syndrome is inherited in an autosomal recessive manner. BBS prevalence in Europe is estimated at between 1/125,000 and 1/175,000. BBS is associated with mutations in **18 different genes**, that encode proteins involved in the development and function of primary cilia.

This phenotypic overlap between McKusick-Kaufman Syndrome and Bardet-Biedl Syndrome in infancy may lead to diagnostic errors, and all children who have been diagnosed with McKusick-Kaufman Syndrome in infancy should be reevaluated for retinitis pigmentosa and other signs of Bardet-Biedl Syndrome in later childhood.

Borjeson-Forssman-Lehmann Syndrome is characterised by the association of intellectual deficit with endocrine anomalies, epilepsy, hypogonadism and facial dysmorphism. The main clinical features evolve with age and show considerable variation both within and between families. Newborns have small genitalia and large ears and many infants have generalized hypotonia. Developmental delay is usually evident before the first birthday; the eventual degree of mental handicap is mild to moderate. Truncal obesity emerges in late childhood and gynaecomastia in adolescence. In late adolescence and adult life, the classically described heavy facial appearance emerges. Frequent visual problems have also been associated with syndrome. The pattern of inheritance is X linked. Borjeson-Forssman-Lehmann Syndrome is caused by mutations in the **PHF6 gene**. The differential diagnosis of obesity related syndromes includes the Prader-Willi, Bardet-Biedl, or Wilson-Turner Syndromes.

Alström Syndrome is characterized by cone-rod dystrophy, obesity, progressive sensorineural hearing impairment, dilated cardiomyopathy, the insulin resistance syndrome, developmental delay and progressive hepatic and renal dysfunction. The cone-rod retinal dystrophy usually develops within a few weeks after birth, the first symptoms are nystagmus and extreme photodysphoria or light sensitivity. It is progressive and leads to blindness, usually by the second decade of life. Progressive sensorineural hearing loss presents in the first decade in as many as 70% of individuals. Males may have hypogonadotrophic hypogonadism. Obesity, insulin resistance and hyperinsulinemia are early and consistent features.

In contrast to BBS, Alström Syndrome is characterized by relative preservation of cognitive function and the absence of polydactyly. Approximately 450 cases of Alström Syndrome have been identified worldwide. Alström Syndrome is caused by mutations in the **gene ALMS1** and is inherited in an autosomal recessive manner. Differential diagnosis includes Bardet-Biedl Syndrome, Biemond II Syndrome, Wolfram Syndrome, Cohen Syndrome, sporadic infantile dilated cardiomyopathy, and mitochondrial disorders.

Albright Hereditary Osteodystrophy (AHO) is characterised by a wide range of features including short stature in adulthood, a tendency for obesity and brachydactyly (shortening of the bones in the hands and feet). Other features may include a rounded face, wide neck and small subcutaneous ossifications (hard lumps under the skin). Mental retardation was less frequently described. There are different types of AHO. These are AHO with Pseudo Hypoparathyroidism (PHP) and AHO with Pseudo Pseudo Hypoparathyroidism (PPHP).

PHP is associated with resistance to parathyroid hormone (PTH) and to other hormones (thyroid-stimulation hormone – TSH, in particular). PHP1a is characterized by AHO features, hypoparathyroid manifestations (hypocalcemia, hyperphosphoremia), elevated PTH levels and decreased erythrocyte Gs activity. Individuals with PHP-1b have PTH resistance and normal levels of erythrocyte Gs activity. Classically, patients do not have features of AHO. PHP Ic is characterized by PTH resistance, generalized hormone resistance, features of AHO and normal Gs activity.

Patients with pseudopseudohypoparathyroidism (PPHP) have physical findings of AHO with Gs deficiency but without hormone resistance.

Condition characterized by AHO features and decreased Gs activity is caused by heterozygous inactivating mutations of the **GNAS gene**. GNAS encodes the alpha subunit of the stimulatory G protein (Gs). Resistance to hormones is determined by the parental origin of the mutation, a functional maternal GNAS allele has a predominant role in preventing hormone resistance.

PHP with AHO features is inherited in an autosomal dominant manner.

Indications for genetic testing:
1. Confirmation of clinical diagnosis
2. Carrier testing for at-risk family members
3. Genetic counseling
4. Prenatal diagnosis for known familial mutation

Choroideremia is an X-linked recessive chorioretinal dystrophy that mainly affects males. Symptoms evolve from night blindness to peripheral visual field loss, eventually leading to all sight loss by middle age. The vision loss is caused by degeneration of the retinal pigment epithelium, choriocapillaris, and the photoreceptor of the eye. Carrier females are generally asymptomatic, small areas of chorioretinal atrophy can be observed with fundus examination. These changes may cause night blindness and visual field loss after the second decade.

The prevalence of choroideremia is estimated between 1:50 000-1:100 000.

Choroideremia is caused by mutations in the **CHM gene**, mutation spectrum includes deletions, duplications, translocations, insertions, nonsense, splice-site, frameshift and missense mutations.

Cone-Rod Dystrophy

Cone-rod dystrophy (CRD) is an inherited progressive disease characterized by the loss of the cone and rod photoreceptor cells, responsible for both central and color vision. The prevalence of CRD is estimated at 1 in 40,000.

The symptoms of CRD include decreased visual acuity followed by loss of peripheral vision, loss of color vision, sensitivity to bright lights and decreased sensitivity in the central visual field.

The pattern of inheritance might be autosomal dominant, autosomal recessive and X-linked inheritance.

Leber Congenital Amaurosis – LCA

Leber congenital amaurosis (LCA) is an early-onset and severe retinal dystrophy leading to congenital blindness. It is diagnosed by a severely reduced or absent electroretinogram (ERG) before one year of age. Shortly after birth, patients usually manifest poor fixation, nystagmus, photophobia, and amaurotic pupils. Later, in most patients, a large variety of retinal changes appear, including salt-and-pepper pigmentation, attenuated vessels, and atrophy of the retinal pigment epithelium (RPE). LCA is mostly inherited as an autosomal recessive disorder.

Indications for genetic testing:
1. Confirmation of clinical diagnosis
2. Prediction of disease progression
3. Carrier testing for at-risk family members
4. Genetic counseling
5. Prenatal diagnosis for known familial mutation

Leber Congenital Amaurosis – LCA

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Indications for genetic testing:
1. Confirmation of clinical diagnosis
2. Prediction of disease progression
3. Carrier testing for at-risk family members
4. Genetic counseling
5. Prenatal diagnosis for known familial mutation

Oculocutaneous Albinism, Ocular Albinism, Hermansky-Pudlak Syndrome, Chediak-Higashi Syndrome

Albinism is a group of congenital disorders of melanin production characterized by variable hypopigmentation and vision defects, including impaired visual acuity, nystagmus, strabismus, astigmatism, and photophobia. The complete or partial absence of pigment may affect the eyes, skin and hair (**oculocutaneous albinism**) or only the eyes (**ocular albinism**).

Additionally, there are also syndromic forms of albinism such as **Hermansky-Pudlak syndrome** and**Chediak-Higashi syndrome**.

The prevalence of all known forms of albinism is estimated to be 1:17 000 newborns.

Oculocutaneous albinism (OCA) is divided into seven types, which are caused by mutations in the respective genes: OCA1 (TYR), OCA2 (OCA2), OCA3 (TYRP1), OCA4 (SLC45A2), OCA5 (chromosome 4q24), OCA6 (SLC24A5), and OCA7 (C10orf11). All forms of OCA are inherited autosomal recessively.

Ocular albinism is caused by mutations in the GPR143 gene and is inherited in an X-linked manner.

Mutations in HPS1 (HPS1), AP3B1 (HPS2), HPS3 (HPS3), HPS4 (HPS4), HPS5 (HPS5), HPS6 (HPS6), DTNBP1 (HPS7), BLOC1S3 (HPS8), and BLOC1S6 (HPS9) genes are known to cause different types of **Hermansky-Pudlak syndrome** (HPS). HPS is inherited in an autosomal recessive manner and characterized by OCA, bleeding disorders, pulmonary fibrosis, and granulomatous colitis.

The LYST gene is know to be associated with **Chediak-Higashi syndrome** (CHS). CHS is inherited in an autosomal recessive manner and characterized by partial OCA, immunodeficiency, peripheral neuropathy, and bleeding tendency.
Indications for genetic testing:

Stargardt Disease

Autosomal recessive **Stargardt disease** is a juvenile-onset macular dystrophy associated with rapid central visual impairment, progressive bilateral atrophy of the foveal retinal pigment epithelium, and the frequent appearance of yellowish flecks around the macula and/or in the central and near-peripheral areas of the retina.

Indications for genetic testing:

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

Vitelliform Macular Dystrophy – VMD

Vitelliform macular dystrophy is an autosomal dominant disorder associated with a vitelliform “egg yolk” lesion that results from abnormal accumulation of lipofuscin in the retinal pigment epithelium (RPE). Lesions are usually bilateral, but can be unilateral. In the early stages, accumulation of lipofuscin-like material in the RPE is observed but acuity remains excellent. Later, the affected area becomes deeply and irregularly pigmented, and as the disorder is progressive, it eventually leads to vision loss. Some cases exhibit multiple extramacular lesions, hemorrhaging, or macular holes. Vitelliform macular dystrophy generally reveals itself in childhood or sometimes later during the teenage years. Severity of vision loss and age of onset exhibit inter- and intra-familial variability.

Indications for genetic testing:

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

X-Linked Retinitis Pigmentosa – XLRP

Retinitis pigmentosa (RP) is an inherited retinal dystrophy caused by the loss of photoreceptors and characterized by retinal pigment deposits visible on fundus examination. Affected individuals first experience night blindness, followed by reduction of the peripheral visual field and, sometimes, loss of central vision late in the course of the disease and eventually leading to blindness after several decades. Signs and symptoms often first appear in childhood, but severe visual problems do not usually develop until early adulthood. In some cases, RP is characterized by cone-rod dystrophy, in which the decrease in visual acuity predominates over the visual field loss. RP is usually nonsyndromic but there are also many syndromic forms. The main risk factor is a family history of retinitis pigmentosa.

Indications for genetic testing:

1. Confirmation of clinical diagnosis
2. Determination of female carriers
3. Genetic counseling

Genetic testing for x-linked retinitis pigmentosa is preferred in the male patients/ families with nonsyndromic retinitis pigmentosa and with family history of x-linked retinitis pigmentosa.

X-Linked Retinoschisis

X-linked retinoschisis is characterized by the abnormal schisis (splitting) of the retina’s neurosensory layers resulting in reduced visual acuity in affected men. Carrier females generally remain asymptomatic. Usually the condition is diagnosed in the first decade of life. It manifests with poor vision and reading difficulties. Other

symptoms include night blindness, strabismus and nystagmus. In about half of the cases, peripheral vision is also affected in people with X-linked retinoschisis. Visual acuity remains stable until forties or fifties, when a significant deterioration in visual acuity occurs. In severe cases, vitreous hemorrhage and retinal detachment, which may lead to impaired vision or blindness, can be seen.

The prevalence of X-linked retinoschisis is estimated to range between 1:5,000-1:25,000 males worldwide.

The disease is caused by mutations on the **RS1 gene**, mutation spectrum reveals missense, nonsense, and splice site mutations, deletions, and insertions.

Indications for genetic testing:

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

Exome Sequencing

Exome sequencing includes the sequencing of the protein **coding regions** and their flanking**intronic regions** in ~20,000 genes of the human genome. The coding region represents 1-2% of the human **genome** but contain approximately 85% of disease-causing mutations. Exome sequencing can be an efficient tool for clinicians to confirm patients' diagnosis of complicated conditions not covered by conventional testing approaches.

Indications for genetic testing:

1. Confirmation of clinical diagnosis
2. Diagnosis of patients with genetic disorders for which diagnostic panels are not available
3. Identification of novel genes responsible for diseases
4. Genetic counseling