Molecular Biology of Diseases

1. Single-gene disorders – extra requirements

**Thalassemia**

In thalassemia the mutation results in reduced rate of synthesis or no synthesis of one of the globin chains that make up hemoglobin. This can cause the formation of abnormal hemoglobin molecules, thus causing anemia (a decrease in number of red blood cells). Thalassemia is a quantitative problem of too few globins synthesized, whereas sickle cell anemia is a qualitative problem of synthesis of an incorrectly functioning globin. Thalassemias usually result in underproduction of normal globin proteins, often through mutations in regulatory genes. The two major forms of the disease, *alpha-* and *beta-* , are prevalent in discrete geographical clusters around the world - probably associated with malarial endemcity in ancient times (heterozygote advantage).

**Galactosemia**

Galactosemia is a rare disorder that affects the body's ability to break down a food sugar called galactose (found in milk and other dairy products). Normally, the body breaks down lactose into galactose and then into glucose. People with galactosemia are missing an enzyme called GATL (*galactose-1-phosphate uridyl transferase*), which normally converts galactose into glucose. Without this enzyme, harmful amounts of galactose build up in the blood. The most common form of the disorder, classic galactosemia, is passed down in an autosomal recessive pattern. A carrier produces less of the GALT enzyme than normal, but is still able to break down glucose and avoid having symptoms of galactosemia. The build-up of galactose in the body can cause several severe symptoms: kidney failure, an enlarged liver, cataracts (clouding of the eye lens), poor growth, and mental retardation. In USA, babies are tested for galactosemia at birth. Using a tiny blood sample taken from the baby's heel, the test checks for low levels of the GALT enzyme. This allows for prompt treatment, which can substantially prevent the serious symptoms of this disorder. For those families with a history of the disorder, a doctor can determine during a woman's pregnancy whether her baby has galactosemia by amniocentesis, or by taking a chorionic villus sampling or CVS. The only way to treat galactosemia is through dietary restrictions. People with the disorder must stay away from foods and drinks containing galactose, including milk, cheese, and dried beans.

**Hemophilia**

Hemophilia is a group of hereditary genetic disorder that impairs the body's ability to control blood clotting (coagulation), which is used to stop bleeding when a blood vessel is broken. **Hemophilia A** (clotting factor VIII deficiency) is the most common form of the disorder, occurring at about 1 in 5,000–10,000 male births. **Hemophilia B** (factor IX deficiency) occurs at about 1 in about 20,000–34,000 male births. Like most recessive X chromosome-linked disorders, hemophilia is more likely to occur in males than females. This is because females have two X chromosomes while males have only one, so the defective gene is guaranteed to manifest in any male who carries it. Female carriers can inherit the defective gene from either their mother or father, or it may be a new mutation. When a blood vessel is injured, a
temporary scab does form, but the missing coagulation factors prevent fibrin formation, which is necessary to maintain the blood clot. Hemophilia acquired the name the royal disease due to the high number of descendants of Queen Victoria afflicted by it.

Marfan syndrome

Marfan syndrome is a genetic disorder of the connective tissue. People with Marfan's tend to be unusually tall, with long limbs and long, thin fingers. It is inherited as a dominant trait. It is carried by a gene called FBN1, which encodes a connective protein called fibrillin-1. This syndrome has a range of expressions, from mild to severe. The most serious complications are defects of the heart valves and aorta. In addition to being a connective protein that forms the structural support for tissues outside the cell, the normal fibrillin-1 protein binds to another protein, TGF-β (transforming growth factor beta). TGF-β has deleterious effects on vascular smooth muscle development and the integrity of the extracellular matrix. Researchers now believe that secondary to mutated fibrillin there is excessive TGF-β at the lungs, heart valves, and aorta, and this weakens the tissues and causes the features of Marfan syndrome.

Achondroplasia

Achondroplasia dwarfism occurs as a sporadic mutation in approximately 85% of cases (associated with advanced paternal age) or may be inherited in an autosomal dominant genetic disorder. However, the mutation can also be completely spontaneous even when neither of the parents of the child is affected with the gene. If both parents of a child have Achondroplasia, and both parents pass on the mutant gene, then it is very unlikely that the homozygous child will live past a few months of its life. The disorder itself is caused by a change in the DNA for fibroblast growth factor receptor 3 which causes an abnormality of cartilage formation. Achondroplastic dwarfs have short stature, with an average adult height of 131 cm for males and 123 cm for females. The prevalence is approximately 1 in 25,000. In normal circumstances, FGFR3 (fibroblast growth factor receptor 3) has a negative regulatory effect on bone growth. In Achondroplasia, the mutated form of the receptor is constitutively active and this leads to severely shortened bones. More than 99% of achondroplasia is caused by two different mutations in the FGFR3. In about 98% of cases, a G to A point mutation at nucleotide 1138 of the FGFR3 gene causes a glycine to arginine substitution. About 1% of cases are caused by a G to C point mutation at nucleotide 1138. At present, there is no known treatment for achondroplasia even though now that the cause of the mutation in the growth factor receptor has been found, therapies and diagnostic methodologies are likely to be looked into and developed.

Albinism

Albinism is a congenital disorder characterized by the complete or partial absence of pigment in the skin, hair and eyes due to absence or defect of an enzyme involved in the production of melanin. Albinism results from inheritance of recessive gene alleles and is known to affect all vertebrates, including humans. Albinism is associated with a number of vision defects, such as excessive sensitivity to light (photophobia), involuntary eye movement (nystagmus). Lack of skin pigmentation makes the organism more susceptible to sunburn and skin cancers. There are two different forms of albinism; a partial lack of the melanin is known as hypomelanism and the total absence of melanin is known as amelanism. The tyrosinase-related albinism results from a genetic defect in an enzyme called tyrosinase. This enzyme helps the body to change the amino acid tyrosine into pigment. P gene albinism results from a genetic defect in the P protein that helps the tyrosinase enzyme to function.
Tay–Sachs disease

Tay–Sachs disease (TSD) is an autosomal recessive genetic disorder. In its most common variant, known as infantile Tay–Sachs disease, it causes a relentless deterioration of mental and physical abilities that commences around six months of age and usually results in death by the age of four. TSD is caused by a genetic defect in a single gene with one defective copy of that gene inherited from each parent. The disease occurs when harmful quantities of gangliosides (a molecule is composed of glycosphingolipid and one or more sialic acids) accumulate in the nerve cells of the brain, eventually leading to the premature death of those cells. There is currently no cure or treatment. Tay–Sachs disease is rare. There is an increased prevalence of TSD in the Eastern European Jewish (Ashkenazi) population. TSD is caused by a genetic mutation on the HEXA gene on chromosome 15. French Canadians of southeastern Quebec have a carrier frequency similar to Ashkenazi Jews, but they carry a different mutation. A more recent theory of heterozygote advantage proposes that Tay–Sachs, and the other lipid storage diseases that are prevalent in Ashkenazi Jews, reflect genes that enhance dendrite growth and promote higher intelligence when present in carrier form.

Color blindness

Color blindness is most often of genetic nature, but may also occur because of some eye, nerve, or brain damage, or exposure to certain chemicals. Color blindness is usually classed as a mild disability, but there are some studies which conclude that color blind individuals are better at penetrating certain color camouflages and it has been suggested that this may be the evolutionary explanation for the surprisingly high frequency of congenital red–green color blindness. The human retina contains two kinds of light cells: the rod cells (active in low light) and the cone cells (active in normal daylight). Normally, there are three kinds of cones, each containing a different pigment, which are activated when the pigments absorb light. The spectral sensitivities of the cones differ; one is maximally sensitive to short wavelengths, one to medium wavelengths, and the third to long wavelengths, with their peak sensitivities in the blue, yellowish-green, and yellow regions of the spectrum, respectively. The absorption spectra of all three systems cover the visible spectrum. These receptors are often called S cones, M cones, and L cones, for short, medium, and long wavelength; but they are also often referred to as blue cones, green cones, and red cones, respectively. Although these receptors are often referred to as "blue, green, and red" receptors, this terminology is not very accurate, especially as the "red" receptor actually has its peak sensitivity in the yellow region. The genes involved in color vision are on the X chromosome making color blindness more common in males than in females.

Color vision deficiencies can be classified as acquired or inherited. There are three types of inherited or congenital color vision deficiencies: monochromacy, dichromacy, and anomalous trichromacy.

(a) Monochromacy, also known as total color blindness is the lack of ability to distinguish colors; caused by cone defect or absence. Monochromacy occurs when two or all three of the cone pigments are missing.

(b) Dichromacy is a moderately severe color vision defect in which one of the three basic color mechanisms is absent or not functioning (partial color blindness). It is hereditary and, in the case of Protaopia or Deuteranopia, sex-linked, affecting predominantly males. Dichromacy occurs when one of the cone pigments is missing. (b1) Protaopia is a severe type of color vision deficiency caused by the complete absence of red retinal photoreceptors.
It is a form of dichromatism in which red appears dark. It is hereditary, sex-linked, and present in 1% of males. (b2) Deuteranopia is a color vision deficiency in which the green retinal photoreceptors are absent, moderately affecting red–green hue discrimination. It is a form of dichromatism in which there are only two cone pigments present. It is likewise hereditary and sex-linked. (b3) Tritanopia is a very rare color vision disturbance in which there are only two cone pigments present and a total absence of blue retinal receptors.

(c) Anomalous tricromacy is a common type of inherited color vision deficiency, occurring when one of the three cone pigments is altered in its spectral sensitivity. This results in an impairment, rather than loss, of trichromacy (normal three-dimensional color vision).

**Evolutionary arguments** Any recessive genetic characteristic that persists at a level as high as 5% is generally regarded as possibly having some advantage over the long term. At one time the U.S. Army found that color blind people could spot "camouflage" colors that fooled those with normal color vision. People with deuteranomaly have been shown that these individuals can spot differences between shades of khaki that look identical to those with normal vision. It was hypothesized that deuteranomaly may have once provided an evolutionary benefit. For example, it may have helped them spot potential food items in complicated environments such as grass or foliage. Another possible advantage might result from the presence of a tetrachromatic female. Owing to X-chromosome inactivation, females who are heterozygous for anomalous trichromacy ought to have at least four types of cone in their retinas. It is possible that this affords them an extra dimension of color vision.

**Genetics** Color blindness can be inherited. It is most commonly inherited from mutations on the X chromosome but the mapping of the human genome has shown there are many causative mutations – mutations capable of causing color blindness originate from at least 19 different chromosomes and 56 different genes. Color blindness always pertains to the cone photoreceptors in retinas, as the cones are capable of detecting the color frequencies of light. About 8 percent of males, but only 0.5 percent of females, are color blind in some way or another, whether it is one color, a color combination, or another mutation. The two genes associated with red-green color vision defects are OPNILW (opsin 1 long wave), encoding the red pigment and OPN1MW (opsin 1 middle wave), encoding the green pigments. Approximately 75% of all red-green color vision defects (100% of protans and about 65% of deutans) can be diagnosed by molecular genetic testing for these genes; such testing is available on a research basis only.

**Normal color vision** Variation in the red and green pigment gene clusters observed in individuals with normal color vision. The gene cluster on the X-chromosome consists of one red pigment gene 5’ of one or more green pigment genes. The number of green pigment genes varies from one to six with a mean of two among Caucasians. Squares represent the six exons of the red and green pigment genes. The red and green pigment genes are approximately 15 and 13 kb in length, respectively, and the intergenic region is approximately 25 kb in length. Only the red gene and the immediately adjacent green pigment gene are expressed in photoreceptors and, therefore, influence the color vision phenotype. Therefore, the green-red hybrid gene that occupies the third position in the bottom cluster would not cause deutan color vision deficiency.

**Intergenic recombinations** Changes in gene number and formation of red-green hybrid genes Intergenic recombination results in changes in the number of green pigment genes, including their deletion, as observed in deuteranopes. Typical gene clusters associated with red-green color vision defects. The common red-green color vision defects are caused either by deletions of the gene (e.g., B6) or by formation of red/green...
hybrid genes (e.g., A1, A2, A3, B4, B5). Homologous but unequal recombinations that occur in the intergenic region result in deletions; those that occur within the red and green pigment genes form hybrid genes encoding chimerical photopigments.