Week 6: Metabolic Pathways

1. **Diagram and discuss the metabolic pathway for Tay-Sachs and Sandhoff Disease.**

(a) Describe the phenotype, diagnosis and prognosis and look at the frequency of occurrence in various populations.

Phenotype: Tay-Sachs is the classical phenotype of disease continuum based on the amount of residual β-hexosaminidase A (HEX A) enzyme activity (Toro, Shirvan, & Tifft, 2020). It is characterized by progressive weakness, loss of motor skills beginning between ages three and six months, decreased visual attentiveness, and increased or exaggerated startle response with a cherry-red spot observable on the retina followed by developmental plateau and loss of skills after eight to ten months. Seizures are common by 12 months with further deterioration in the second year of life and death occurring between ages two and three years with some survival to five to seven years (Toro et al., 2020).

HEXB gene is referred to as Sandhoff disease, which is pretty close to TSD, but distinguished by Hepatosplenomegaly, skeletal abnormalities, deficiency of both HEX A & HEX B enzyme activity (Toro et al., 2020).

Diagnosis: Since the disease continuum is based on the amount of residual HEX A enzyme activity, then the molecular characteristics and impact are influenced by pathogenic variants. The disorder is typically divided into acute infantile, subacute juvenile, and late-onset disorders, with unique phenotypes common to each subset (Toro et al., 2020).

HEX A enzymatic activity, or specifically lack of activity, testing is done in the serum, white blood cells, or other tissues in the presence of normal or elevated activity of the β-hexosaminidase B (HEX B) enzyme to establish the diagnosis.

Individuals with acute infantile TSD have none or extremely low HEX A enzymatic activity, while individuals with subacute juvenile or late-onset TSD have some minimal residual HEX A enzymatic activity (Toro et al., 2020).

Prognosis: as previously mentioned, the likely cause is due to disruption of the activity of an enzyme due to disruptions in the HEXA gene, disrupting a subunit of the enzyme responsible for the buildup of the molecule GM2 ganglioside within cells, leading to the destruction of nerve cells and spinal cord. Death often occurs in early childhood (Fernandes Filho & Shapiro, 2004).

Prevalence: TSD is very rare in the general population (Fernandes Filho & Shapiro, 2004). Early incidence of TSD was estimated at 1:3,600 (Toro et al., 2020). However, carrier rate for TSD is approximately 1:30 among Jewish Americans of Ashkenazi extraction (Toro et al., 2020). Due to genetic counseling the incidence of TSD in the Ashkenazi Jewish population of North America has been reduced by greater than 90% (Toro et al., 2020).

Other populations, such as French-Canadian communities of Quebec, the Old Order Amish community in Pennsylvania, and the Cajun population of Louisiana are at higher due to genetic isolation as well (Fernandes Filho & Shapiro, 2004).

Points: [/]

Feedback:

(b) Indicate the biochemical basis for the disease (i.e, the pathway).

Tay-Sachs is a neurodegenerative disease resulting from mutations of the HEXA gene encoding the alpha subunit of beta-hexosaminidase, producing a destructive ganglioside accumulation in lysosomes, principally in neurons with the severity of the disease generally correlating with the level of residual Hex A activity (Gravel, Triggs-Raine, & Mahuran, 1991).

Points: [/]

Feedback:

(c) What is known about the gene/s and proteins involved – chromosomal location, structure of the gene and size, mutations known, protein structure and function.

Lysosomal hexosaminidase occurs in two principal forms, Hex A and Hex B. Hex A is made up of one α and one β sub-unit, while Hex B is made up of two β subunits (Gravel et al., 1991). The α-subunit is encoded by the HEXA gene on chromosome 15 and the βsubunit by the HEXB gene on chromosome 5 (Gravel et al., 1991).

HEXA and HEXB be have similar organizational structure; they are split into 14 exons spanning about 35 kb and 50 kb, respectively, and all but the first splice junction are located at identical positions in the aligned sequence (Gravel et al., 1991).

A variety of different HEXA mutations can ultimately cause the disease. TSD was one of the first genetic disorders with widespread screening and ended up being one of the first disorders in which prevalence of compound heterozygosity (condition of having two or more heterogeneous recessive alleles at a particular locus) was demonstrated.

Most Tay-Sachs mutations probably do not directly affect protein functional elements (e.g., the active site). Instead, they cause incorrect folding (disrupting function) or disable intracellular transport (Chelbi & Ait-Kadi, 2000)

Points: [/]

Feedback:

(d) Any gene therapies?

Research is ongoing to develop enzyme replacement therapy for Tay-Sachs disease, but has not proven successful in people with Tay-Sachs disease (*Tay Sachs Disease*, 2017). The inability to find a way for the replacement enzyme to cross the blood-brain barrier, a protective networks of blood vessels and cells that allow some materials to enter the brain, while keeping other materials out is among the major problems with enzyme replacement therapy (*Tay Sachs Disease*, 2017).

There are some gene therapies also being studied. In these studies the defective gene present in a patient is replaced with a normal gene to enable the production of active enzyme, likely leading to a cure if successful. However, there are still technical difficulties to resolve before gene therapy can succeed (*Tay Sachs Disease*, 2017).

Points: [/]

Feedback:

2. **Diagram and discuss the metabolic pathway for Lesch-Nyhan Syndrome.**

(a) Describe the phenotype, diagnosis and prognosis and look at the frequency of occurrence in various populations.

Phenotype: Lesch-Nyhan syndrome (LNS) is at the most severe end of in the spectrum of *HPRT1* disorders, with motor dysfunction resembling severe cerebral palsy, intellectual disability, and self-injurious behavior (Jinnah, 2020). It is caused by a deficiency of the enzyme hypoxanthine-guanine phosphoribosyltransferase (HGPRT). The HGPRT deficiency causes a build-up of uric acid in all body fluids. The combination of increased synthesis and decreased utilization of purines leads to high levels of uric acid production leading to varying degrees of neurologic and/or behavioral problems (Jinnah, 2020).

Diagnosis: the diagnosis is established in a male families genetic history with suggestive clinical and laboratory findings and a hemizygous pathogenic variant in *HPRT1* identified by molecular genetic testing and/or low HGprt enzyme activity identified on biochemical testing (Jinnah, 2020).

Prognosis: The prognosis for individuals with LNS is poor. Death is usually due to renal failure in the first or second decade of life (Page, Barshop, Yu, & Nyhan, 1995). Less sever forms of HGPRT deficiency have better prognoses. There is no standard treatment for

LNS, but some symptoms can be managed temporarily.

Prevalence: the prevalence of LNS is approximately 1:380,000. The prevalence of the milder phenotypes (HND and HRH) is not well studied, but they appear to be less common than LNS (Jinnah, 2020). HPRT1 disorders occur in all populations that have been studied, and with relatively equal frequency (Jinnah, 2020).

Points: [/]

Feedback:

(b) Indicate the biochemical basis for the disease (i.e, the pathway).

LNS disrupts the metabolism of the raw material of genes, specifically purines, which are essential part of DNA and RNA. The body can either make purines (de novo synthesis) or recycle them (the resalvage pathway) (Nyhan, 1973).

The product of the normal gene is the enzyme hypoxanthine-guanine phosphoribosyltransferase, which speeds up the recycling of purines from broken down DNA and RNA. Different types of mutations affect this gene, and the result is a very low level of the enzyme (Nyhan, 1973).

Low level of the enzyme results in failure to salvage the purines leading to accumulation of uric acid that normally would have been recycled into purines. The excess uric acid forms painful deposits in the skin (gout) and in the kidney and bladder (urate stones). Other physical manifestations occur due to neurological breakdown, such as unrestrained biting of fingers and tongues, mental retardation and severe muscle weakness (Nyhan, 1973).

Because a lack of HGPRT causes the body to poorly utilize vitamin B12, some males may develop megaloblatic anemia. (Nyhan, 1973).

Points: [/]

Feedback:

(c) What is known about the gene/s and proteins involved – chromosomal location, structure of the gene and size, mutations known, protein structure and function.

The mutation is inherited in an X-linked fashion (location: Xq26.2-q26.3 according to OMIM). Females who inherit one copy of the mutation are not affected because they have two copies of the X chromosome (XX). Males are severely affected because they

only have one X chromosome (XY), and therefore their only copy of the HPRT1 gene is mutated (Nyhan, 1973).

HPRT1 genes contain 9 exons, with a wide variety of mutations possible as previously mentioned. Deletions, insertions, single-base substitutions, and frame-shift mutations all can lead to decreased activity (Nyhan, 1973). Essentially many types mutations in the HPRT1 gene can disrupt the function of the enzyme.

Points: [/]

Feedback:

(d) Any gene therapies?

There are no current gene therapies for Lesh-Nyhan syndromes, though many specific drug therapies can be used on a paitent specific basis (*Lesch-Nyhan*, 2018). Treatment may even require the coordinated efforts of a team of specialists.

Some individuals with Lesch-Nyhan syndrome have been reported to benefit from behavior modification techniques designed to reduce self-mutilating behaviors, but real success is unusual (*Lesch-Nyhan*, 2018).

The drug allopurinol is used to control the excessive amounts of uric acid associated with Lesch-Nyhan syndrome and control symptoms associated with excessive amounts of uric acid. However, this treatment has no effect on the neurological or behavioral symptoms associated with this disorder (*Lesch-Nyhan*, 2018).

No sustained treatment or drug therapy has proven uniformly effective for the treatment of the neurological problems associated with Lesch-Nyhan syndrome. Baclofen or benzodiazepines have been used to treat spasticity. Diazepam may be useful (*Lesch-Nyhan*, 2018).

Points: [/]

Feedback:

Week 8: Mapping and Genome Organization

1. **A synthesis of the Huntington's Disease story**:

(a) Describe in detail the phenotype of this disorder.

Points: [/]

Feedback:

(b) Describe in detail the chromosomal location of Huntington's Disease (HD) and how the location of this gene was worked. Give a detailed description of the process of positional cloning

Points: [/]

Feedback:

(c) Describe in detail what is known about the structure and function of the HD gene.

Points: [/]

Feedback:

(d) Develop the status of treatments and gene therapies. Be detailed here as well.

Points: [/]

Feedback:

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