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### Diseases due to Abnormalities in Lysosomes, Peroxisomes and Mitochondria

Lysosome storage diseases include several genetically inherited conditions that lead to metabolic abnormalities. These organelles that are found in virtually all animal cells are capable of metabolizing biomolecules of various types (Suzuki, Kunihiko and Marie T. Vanier).

Lysosomes have more than 60 enzymes contained within them. A particular manifestation of lysosomes storage disorder depends on and classified by the abnormally accumulated materials. Gaucher's disease, for example, is caused by a mutation in the GBA gene that leads to abnormal functioning of a beta-glucocerebrosidase enzyme that dissolves glucocerebroside into sugar. In individuals with Gaucher's disease, the activity of the GBA gene is greatly reduced (Suzuki, Kunihiko and Marie T. Vanier). The lack of enzyme normally stored within lysosomes leads to a dangerous build-up of glucocerebroside to toxic levels. There are several types of Gaucher's disease distinguished by the severity and time of onset of the symptoms.

In the general population, Gaucher's disease occurs in 1 in 50,000 to 100,000 individuals. Type 1 of the disease is more common among Ashkenazi Jews with a frequency of occurrence being 1 in 500 people than in the general population (Suzuki, Kunihiko and Marie T. Vanier). The disease is inherited following an autosomal recessive pattern.

Symptoms of Gaucher's disease vary depending on the type. For type 1 of the disease, easy bruising is common due to low levels of blood platelets; anaemia is also frequent. In type 2 symptoms begin to show after 3 months of age and include brain damage, spasticity, seizures,

enlarged liver and spleen (Suzuki, Kunihiro and Marie T. Vanier). The third type is known as chronic neuropathic Gaucher's disease and characterized by the slow onset of symptoms related to brain involvement and skeletal abnormalities. For people with type 1 and type 3, Gaucher's disease enzyme replacement therapy has been proved as the main means of treatment.

Peroxisomes are subcellular organelles that contain enzymes crucial for metabolic processes. These organelles are rather flexible and can be assembled rapidly reacting to metabolic needs. Peroxisomes are involved in metabolizing of fatty acids, clearing of glyoxylate, and catabolism of purines. Within the organelles, there are approximately 50 enzymes which are essential for proper metabolic functions (Delille, Hannah K., et al.). There are several peroxisomes disorders including Zellweger spectrum disorder. The Zellweger spectrum disorder includes several conditions with overlapping symptoms and signs that in the past were considered to represent non-related conditions. Infants with Zellweger syndrome are severely impaired in most cases making no developmental progress.

The syndrome is caused by a mutation in 12 genes all responsible for providing instructions for making peroxin proteins which are essential for proper peroxisome functioning (Delille, Hannah K., et al.). These mutations prevent organelles in question from forming and functioning normally (Steinberg, Steven, et al.). Because mutations in genes affect the formation of peroxisomes, the syndrome is characterized as peroxisome biogenesis disorder. Estimates indicate that Zellweger spectrum disorder affects 1 in 50,000 people ("Zellweger Spectrum Disorder"). The condition affecting peroxisomes is inherited if both copies of a gene have a mutation. Thus, the condition has an autosomal recessive pattern of inheritance.

Individuals affected by Zellweger syndrome show first signs of condition early in life. Symptoms that manifest early include poor appetite, seizures, hepatic dysfunction and cyst in the

liver (Delille, Hannah K., et al.). Individuals with less severe phenotypes of Zellweger syndrome spectrum are often suffering from retinal dystrophy and developmental delay accompanied by hypotonia and loss of hearing. Treatment of Zellweger syndrome disorder is symptom-based. Mitochondrial disorders result from dysfunctions or abnormalities that occur in a mitochondrial respiratory chain. These disorders can be caused by mutations that occur either within nuclear or mitochondrial DNA (mDNA) (Chinnery, P. F.). Leigh syndrome is a mitochondrial disorder characterized by severe neurological conditions. Progressive loss of both mental and movement abilities are typical for this syndrome and in most cases result in death after two or three years after the onset (Chinnery, P. F.). Respiratory failure is a prevalent cause of death. In rare cases, individuals may not develop serious symptoms until adulthood or have a slowly progressing disease.

Leigh syndrome occurs in 1 in 40,000 individuals with condition reported to be more common in some populations. In Quebec region of Canada frequency of Leigh syndrome is estimated to be 1 in 2,000 people. The population of the Faroe Islands is also reported to have a higher frequency of Leigh syndrome in comparison to the general population and is approximately 1 in 1,700 individuals.

Genetic mutations that can result in Leigh syndrome occurs in nuclear DNA and mDNA alike. Mutations in genes of mitochondrial DNA affect the process of oxidative phosphorylation needed for cellular energy production. Mutations associated with Leigh syndrome disrupt production of proteins that make up the protein complexes that carry out the oxidative phosphorylation process. Mutation of the MT-ATP6 gene found in mitochondrial DNA is the most common cause of Leigh syndrome associated with a mutation in mDNA.

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