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Commentary

Inherited Metabolic Disorders: A Prospective Study

Esther Dora
Center for Diabetes Research, Isreal.
Corresponding Author : **Esther Dora**, Center for Diabetes Research,Isreal. **Email:** esther.dora@gmail.com

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Most inherited disorders of metabolism (also called inborn errors of metabolism) are caused by mutations in genes that code for enzymes; enzyme deficiency or inactivity leads to accumulation of substrate precursors or metabolites or to deficiencies of the enzyme's products (1-8).Hundreds of disorders exist, and although most inherited disorders of metabolism are extremely rare individually, collectively they are not rare.

Inherited metabolic disorders are typically grouped by the affected substrate, for example:

- Amino acid metabolism disorders
- Carbohydrate metabolism disorders
- Fatty acid metabolism disorders
- Purine and pyrimidine metabolism disorders

Mitochondrial Oxidative Phosphorylation Disorders

Cellular respiration (oxidative phosphorylation) occurs in the mitochondria, where a series of enzymes catalyze the transfer of electrons to molecular oxygen and the generation of energy-storing ATP. Defects involving enzymes used in this process impair cellular respiration, decreasing the ATP:ADP ratio. Mitochondria have their own DNA (mitochondrial DNA [mtDNA]), which is maternally derived. However, mtDNA shares responsibility with nuclear DNA for mitochondrial function. Thus, both mitochondrial and nuclear mutations can cause mitochondrial disorders.

Tissues with a high energy demand (eg, brain, nerves, retina, skeletal and cardiac muscle) are particularly vulnerable to defects in oxidative phosphorylation. The most common clinical manifestations are seizures, hypotonia, ophthalmoplegia, strokelike episodes, muscle weakness, severe constipation, and cardiomyopathy.

Biochemically, there is profound lactic acidosis because the NADH:NAD ratio increases, shifting the equilibrium of the lactate dehydrogenase reaction toward lactate. The increase in the lactate:pyruvate ratio distinguishes oxidative phosphorylation defects from other genetic causes of lactic acidosis, such as pyruvate carboxylase or pyruvate dehydrogenase deficiency, in which the lactate:pyruvate ratio remains normal. A large number of oxidative phosphorylation defects have been described; only the most common ones are outlined here, along with their distinguishing features.

Mitochondrial mutations and variants have also been implicated in a number of diseases of aging (eg, Parkinson disease, Alzheimer disease, diabetes, deafness, cancer).

Causes of Inherited Metabolic Disorders

In most inherited metabolic disorders, a single enzyme is either not produced by the body at all or is produced in a form that doesn't work. The missing enzyme is like an absentee worker on the assembly line. Depending on that enzyme's job, its absence means toxic chemicals may build up, or an essential product may not be produced.

The code or blueprint to produce an enzyme is usually contained on a pair of genes. Most people with inherited metabolic disorders inherit two defective copies of the gene -- one from each parent. Both parents are "carriers" of the bad gene, meaning they carry one defective copy and one normal copy.

In the parents, the normal gene copy compensates for the bad copy. Their enzyme levels are usually adequate, so they may have no symptoms of a genetic metabolic disorder. However, the child who inherits two defective gene copies cannot produce enough effective enzyme and develops the genetic metabolic disorder. This form of genetic transmission is called autosomal recessive inheritance.(21-35).

The original cause of most genetic metabolic disorders is a gene mutation that occurred many, many generations ago. The gene mutation is passed along through the generations, ensuring its preservation.

Each inherited metabolic disorder is quite rare in the general population. Considered all together, inherited metabolic disorders may affect about 1 in 1,000 to 2,500 newborns. In certain ethnic populations, such as Ashkenazi Jews (Jews of central and eastern European ancestry), the rate of inherited metabolic disorders is higher.

Challenge testing is used judiciously to detect symptoms, signs, or measurable biochemical abnormalities not detectable in the normal state. The need for challenge testing has diminished with the availability of highly sensitive metabolite detection methods, but it is still occasionally used. Examples include fasting tests (eg, to provoke hypoglycemia in hepatic forms of GSD); provocative tests (eg, fructose challenge to trigger symptoms in hereditary fructose intolerance, glucagon challenge in hepatic forms of GSD [failure to observe hyperglycemia suggests disease]); and physiologic challenge (eg, exercise stress testing to elicit lactic acid production and other deformities in muscle forms of GSD). Challenge tests are often associated with an element of risk so they must be done under well-controlled conditions with a clear plan for reversing symptoms and signs(36-40).

References

1. Saha K, Jaenisch R. Technical challenges in using human induced pluripotent stem cells to model disease. *Cell Stem Cell.* 2009;5(6):584–595.
2. Park IH. Disease-specific induced pluripotent stem cells. *Cell.* 2008;134(5):877–886.
3. Maehr R, et al. Generation of pluripotent stem cells from patients with type 1 diabetes. *Proc Natl Acad Sci U S A.* 2009;106(37):15768–15773.
4. Dimos JT. Induced pluripotent stem cells generated from patients with ALS can be differentiated into motor neurons. *Science.* 2008;321(5893):1218–1221.
5. Lee G, et al. Modelling pathogenesis and treatment of familial dysautonomia using patient-specific iPSCs. *Nature.* 2009;461(7262):402–406.
6. Ebert AD. Induced pluripotent stem cells from a spinal muscular atrophy patient. *Nature.* 2009;457(7227):277–280.