AT THE FOREFRONT
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Mitochondrial Diabetes

Overview:
Mitochondrial diabetes can be caused by a single genetic change (sometimes called a "mutation") in the MT-TL1, MT-TK, or MT-TE genes found in the mitochondria. The majority of cases of mitochondrial diabetes are caused by the m. 3243A>G mutation in MT-TL1. If someone has this form of diabetes and also experiences deafness, they may be diagnosed with maternally inherited diabetes and deafness (MIDD). Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) is a condition that can also be caused by a single gene mutation in one of the genes MT-TL1, MT-TK, or MT-TE. There is considerable overlap between MIDD and MELAS, and it is very possible for people to have both conditions.

The MT-TL1, MT-TK, and MT-TE genes contain instructions for building a transfer RNA molecule that guides the assembly of proteins needed for energy production in the mitochondria. A diabetes-causing mutation in MT-TL1 or MT-TK can decrease the amount of insulin that is released by the β cells of the pancreas and/or can impair the ability of insulin-receiving cells to respond properly to insulin.

Presentation:
People with mitochondrial diabetes are often diagnosed with high blood sugars and have symptoms such as increased frequency of urination (polyuria), increased thirst (polydipsia), weight loss, and fatigue. People with mitochondrial diabetes are usually first misdiagnosed with Type 1 or Type 2 diabetes.

Mitochondrial diabetes is a systemic disease. Features that make us suspect mitochondrial diabetes include:

- Strong maternal family history of diabetes suggestive of direct inheritance through three or more generations.
- Multiple organs are affected, especially:
    - Cochlea (sensorineural deafness)
    - Retina (macular pattern dystrophy)
    - Muscle (myopathy, muscle weakness)
    - Heart (heart failure)
    - Brain (seizures, strokes)
    - Kidney (focal segmental glomerulosclerosis)
- Negative autoantibody testing. These tests are usually done around the time of diabetes diagnosis; if positive, they indicate an autoimmune type of diabetes like Type 1 diabetes.
- Persistently detectable C-peptide. This is a test that tells us if your body is still making any insulin on its own.

Treatment:
Elevated blood sugars in people who have mitochondrial diabetes can be treated with insulin. Since mitochondrial diabetes is a multi-system disease, it is important to complete the following on a periodic basis: echocardiogram, kidney function test, diabetes screening (if not diagnosed with diabetes), hearing test, and ophthalmological examination.

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Medications to avoid

- Antibiotics such as tetracyclines and chloramphenicol
- Anti-epileptic drugs such as valproate, phenytoin and phenobarbitone
- Nucleoside analogue reverse transcriptase inhibitors used in the treatment of human immunodeficiency virus (HIV)
- Metformin (particularly in the context of other risk factors for lactic acidosis)

Inheritance:

Mitochondrial genes are maternally inherited. If a patient has a MIDD or MELAS-causing mutation in a mitochondrial gene, we strongly recommend that all maternal relatives receive genetic testing and urine heteroplasmy testing.

Testing negative

Testing negative for the mutation in blood or saliva, or even urine, does not exclude the presence of the mutation in other tissues. Urine heteroplasmy tests are the best way to detect the level of mutated mitochondria.

Why should I consider getting genetic testing?

Getting genetic testing can result in the correct diagnosis of your diabetes, the best treatment plan for you (avoiding harm or useless treatments) and prognosis (being able to understand what to test and monitor). Finally, getting genetic testing can help researchers learn more about diabetes so that improvements in treatment and care can be made for you and future generations.

Research:

Why should I consider joining the University of Chicago Monogenic Diabetes Registry?

- Gain resources and the ability to speak with our research staff and doctors on our team
- Low time commitment to register and fill out our registry survey (roughly 1 hour)
- We have over 4,000 people in the Registry and almost 1,300 with known monogenic diabetes-causing mutations; we are actively recruiting families with mitochondrial diabetes-causing mutations.
- Help us learn more about mitochondrial diabetes and gather more complete family histories, which are extremely important to our research

If you or someone you know is interested in participating in our studies, they can sign up on our website at https://cri-app02.bsd.uchicago.edu/monogenics/registration_2013.aspx.

Additional resources:

https://www.mitoaction.org/
https://www.umdf.org/
https://www.chop.edu/centers-programs/mitochondrial-medicine-program