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THE BOGGS CENTER ON DEVELOPMENTAL DISABILITIES
New Jersey's University Center for Excellence in Developmental Disabilities Education, Research, and Service
New Jersey's Leadership Education in Neurodevelopmental and Related Disabilities Program

Identification of Genetic Conditions Associated with Neurodevelopmental Disabilities (NDDs) Among Consanguineous Couples

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Background on Consanguinity, Expanded Carrier Screening, and Neurodevelopmental Disabilities (NDDs)

- Consanguinity is a term used to describe reproductive unions between couples who share at least one common ancestor.
- Consanguineous couples, depending on the degree of relationship, have an increased risk for offspring affected by autosomal recessive (AR) conditions (Teeuw et al., 2010).
- Expanded carrier screening (ECS) can detect mutations in hundreds of genes associated with recessive genetic conditions all in the same panel, regardless of ancestry and geographic origin (Edwards et al., 2015).
- As defined by the DSM-5, the term NDD encompasses intellectual disability (ID), global developmental delay, and autism spectrum disorder.
- In individuals with a diagnosed NDD with consanguineous parents, about 50% of cases are attributable to inherited recessive genetic variants (Boonsawat et al., 2022).
- Since NDDs can be a major concern of couples who wish to have children, we wondered how many consanguineous carrier couples detected by ECS panels were at risk for a genetic condition associated with NDD.

Materials, Methods, and Subjects

- A retrospective chart review was conducted on genetics records from January 1, 2012, to October 10, 2022, at Rutgers-Robert Wood Johnson Medical School in New Brunswick, New Jersey.
- This study included couples who reported being in a consanguineous union.
- ECS was offered to all consanguineous couples who presented for genetics consultation, and testing was performed during their visit.

Results

- A total of 96 couples seen for genetic counseling between January 1, 2012, to October 10, 2022, were identified to be consanguineous. 14 of these couples had previously completed ECS, leaving a total of 82 patients who were offered ECS.
- Of the 82 consanguineous couples, 68 elected to proceed with ECS after genetic counseling.
- Of the 68 consanguineous couples who underwent expanded carrier screening, we found 9 carrier couples in which both partners were heterozygous carriers for the same variant (13.2%).
- These nine conditions and their association with NDD are described in Table 1. Three out of nine of these conditions (33.3%) (Leber Congenital Amaurosis, Congenital Disorders of Glycosylation, and MCAD Deficiency) are known to be associated with NDDs.

Table 1. Consanguineous Carrier Couples Identified on ECS & Association with NDD

Genetic Condition	Condition Overview	Associated with NDD (Yes/No)	Type of NDD
Familial Mediterranean Fever	Familial Mediterranean fever (FMF) is an autoinflammatory genetic disorder that is characterized by recurrent episodes of fever and inflammation (chest, abdomen, joints), leading to painful attacks early during childhood.	No	N/A
Leber Congenital Amaurosis	Leber Congenital Amaurosis (LCA) comprises a group of early-onset childhood retinal dystrophies characterized by vision loss, nystagmus, and severe retinal dysfunction.	Yes	Delayed development and intellectual disability have been reported in people with the features of LCA
Oculocutaneous Albinism, Type IV	Oculocutaneous albinism is a group of conditions that affect coloring (pigmentation) of the skin, hair, and eyes. In type 4, the skin is usually a creamy white color and hair may be light yellow, blond, or light brown. People with this condition usually have vision problems such as reduced sharpness; rapid, involuntary eye movements (nystagmus); and increased sensitivity to light (photophobia).	No	N/A
Hereditary Hemochromatosis	Hereditary hemochromatosis is a disorder that causes the body to absorb too much iron from the diet. Early symptoms of hereditary hemochromatosis may include extreme tiredness (fatigue), joint pain, abdominal pain, and weight loss. As the condition worsens, affected individuals may develop arthritis, liver disease (cirrhosis) or liver cancer, diabetes, heart abnormalities, or skin discoloration.	No	N/A
Congenital Disorders of Glycosylation – PMM2	Individuals with PMM2-CDG typically develop signs and symptoms of the condition during infancy. Affected infants may have weak muscle tone (hypotonia), retracted (inverted) nipples, an abnormal distribution of fat, eyes that do not look in the same direction (strabismus), developmental delay, and a failure to gain weight and grow at the expected rate (failure to thrive). Infants with PMM2-CDG also frequently have an underdeveloped cerebellum, which is the part of the brain that coordinates movement.	Yes	Most affected children exhibit intellectual disability, ranging from moderate to severe. Stroke-like episodes can cause regression in a child's previous mental capabilities. Additionally, most affected children exhibit global developmental delays.
Congenital Adrenal Hyperplasia due to 21-Alpha-Hydroxylase Deficiency (CYP21A2)	Classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency affects the adrenal glands which are responsible for producing specific hormones. There are two types of classic 21-OHD CAH, the salt-wasting form and the simple-virilizing form. Symptoms include abnormal development of the external sex organs in females (ambiguous genitalia), early puberty, and short stature. The salt-wasting form also may include the inability to retain salt and water. This can lead to dehydration, low blood pressure, and a life-threatening adrenal crisis.	No	N/A
Sulfate transporter-related osteochondrodysplasias (SLC26A2)	The sulfate transporter-related osteochondrodysplasias (STROs) are a group of inherited diseases characterized by short stature and short limbs, spine and joint abnormalities, and early-onset osteoarthritis. Signs and symptoms of the STROs vary in severity, ranging from mild bone abnormalities with joint pain to lethal conditions.	No	N/A
Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency	Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency is a condition that prevents the body from converting certain fats to energy, particularly during periods without food (fasting). Signs and symptoms of MCAD deficiency typically appear during infancy or early childhood and can include vomiting, lack of energy (lethargy), and low blood sugar (hypoglycemia).	Yes	Individuals with MCAD deficiency who have suffered the effects of an uncontrolled metabolic decompensation are at risk of developmental and neurologic disabilities, including aphasia and attention-deficit disorder.
Cystic Fibrosis	Cystic fibrosis is characterized by abnormalities affecting certain glands of the body, especially those that produce mucus. Saliva and sweat glands may also be affected. In cystic fibrosis, these secretions become abnormally thick and can clog up vital areas of the body causing inflammation, obstruction and infection. Common symptoms include breathing (respiratory) abnormalities including a persistent cough, shortness of breath and lung infections; obstruction of the pancreas, which prevents digestive enzymes from reaching the intestines to help break down food and may result in poor growth and poor nutrition; and obstruction of the intestines. Cystic fibrosis is slowly progressive and often causes chronic lung damage, which eventually results in life-threatening complications.	No	N/A

Discussion

- Only three consanguineous couples who underwent ECS were identified to be at risk for a genetic condition known to be associated with NDD.
- It is likely that these carrier statistics are underestimates given that these panels generally contain limited numbers of genes and thus are less effective for the detection of the often (extremely) rare AR diseases consanguineous couples may be at risk for.
- Consanguinity should still be considered as a risk factor for NDD.
- Clinical exome sequencing to assess for carrier status is currently available on the market. While ECS panels are limited to detecting carrier status for the specific genes or variants included in the panel, exome-based preconception carrier screening allows for analysis of all genes associated with disease.
- Exome-based preconception carrier testing could potentially increase the diagnostic yield of carrier status for recessive causes of NDDs in consanguineous couples.
- The implementation of this technology will be important to identify additional recessive causes of NDD in consanguineous populations either prior to pregnancy or during pregnancy.

Significance to NJ LEND

- Although rare, consanguinity is present in New Jersey, most commonly in families from North Africa, the Middle East, and South Asia.
- Understanding the risk between NDD and consanguinity can provide these families with the education to make informed reproductive decisions about their current pregnancy, gain foresight into neonatal management, and/or use this knowledge in future pregnancies.
- Additionally, knowing that a child could be at risk for NDD can enable families to seek out early assessment & intervention so their child can reach the highest developmental potential. This information can also reduce/eliminate the long diagnostic odyssey that families endure when trying to find a cause or specific diagnosis for their child's symptoms.
- Rarely is the association between rare recessive genetic variants present in consanguineous populations and the association with NDDs discussed outside of the genetics community. With consanguinity being a known risk factor for autosomal recessive causes of NDDs, non-genetics clinicians/providers should routinely screen for it, as this is inconsistently done and refer to a genetics provider who can order appropriate genetic testing.