MED12 Related Disorders

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Clinical characteristics:

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-related disorders include the phenotypes of FG syndrome type 1 (FGS1), Lujan syndrome (LS), X-linked Ohdo syndrome (XLOS), Hardikar syndrome (HS), and nonspecific intellectual disability (NSID). FGS1 and LS share the clinical findings of cognitive impairment, hypotonia, and abnormalities of the corpus callosum. FGS1 is further characterized by absolute or relative macrocephaly, tall forehead, downslanted palpebral fissures, small and simple ears, constipation and/or anal anomalies, broad thumbs and halluces, and characteristic behavior. LS is further characterized by large head, tall thin body habitus, long thin face, prominent nasal bridge, high narrow palate, and short philtrum. Carrier females in families with FGS1 and LS are typically unaffected. XLOS is characterized by intellectual disability, blepharophimosis, and facial coarsening. HS has been described in females with cleft lip and/or cleft palate, biliary and liver anomalies, intestinal malrotation, pigmentary retinopathy, and coarctation of the aorta. Developmental and cognitive concerns have not been reported in females with HS. Pathogenic variants in

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have been reported in an increasing number of males and females with NSID, with affected individuals often having clinical features identified in other

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-related disorders.

Diagnosis/testing:

The diagnosis of an

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-related disorder is established in a male by identification of a hemizygous

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pathogenic variant on molecular genetic testing. The diagnosis of an

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-related disorder is established in a female with suggestive findings and a heterozygous pathogenic variant in

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identified by molecular genetic testing.

Management:

Treatment of manifestations:

Early individualized education; physical therapy, occupational therapy, and speech therapy for developmental delays; individualized management of behavior problems; routine management of seizures, strabismus and other ocular anomalies, imperforate anus, chronic constipation, joint contractures, genitourinary anomalies, congenital heart defects, hearing loss, palate anomalies, and dental anomalies; social work support. Treatment of aneurysms, intestinal malrotation, and liver disease in females with HS as recommended by the appropriate specialist.

Surveillance:

At each visit, assess growth, development, behavior concerns, neurologic issues, gastrointestinal functioning, and musculoskeletal manifestations. Annual eye examination with attention to retinal changes for individuals with HS. Annual audiology evaluation. Dental evaluation every six months, particularly for individuals with XLOS and LS. Females with HS should have an annual echocardiogram, carotid ultrasound, gastroenterology evaluation with liver function testing and consideration of clotting studies, serum bile acids, and liver ultrasound based on recommendations of a gastroenterologist; and MRA of the head and neck for aneurysms every two years.

Genetic counseling:

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-related disorders are inherited in an X-linked manner. If the mother of a proband is heterozygous for a pathogenic variant, the chance of transmitting it in each pregnancy is 50%. Males who inherit the pathogenic variant will be affected. Females who inherit a pathogenic variant associated with FGS1, LS, or XLOS will typically be unaffected while females who inherit a pathogenic variant associated with HS will typically be affected. Females who inherit a

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pathogenic variant associated with NSID will be at an increased risk of developing variable clinical features. Males with a

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-related disorder are not known to reproduce. Once the

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pathogenic variant has been identified in an affected family member, heterozygote testing for at-risk female relatives and prenatal and preimplantation genetic testing for

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-related disorders are possible.