MAN1B1-CDG

MAN1B1 mutations cause a recessively inherited form of intellectual disability. MAN1B1-CDG is one of the 26 diseases of the protein N-glycosylation.

What is MAN1B1-CDG?

Rafiq and colleagues were the first to associate MAN1B1 mutations with a syndromic form of intellectual disability. MAN1B1 (MIM:604346) encodes mannosyl-oligosaccharide alpha-1, 2-mannosidase, a Golgi protein involved in the maturation and secretory pathway of N-glycans. Importantly, great clinical variability has been seen among affected siblings.

What are CDG?

Congenital Disorders of Glycosylation (CDG) are a rapidly growing group of monogenic metabolic diseases, which counts over 130 different types.

When to suspect MAN1B1-CDG?

MAN1B1-CDG should be considered in the presence of intellectual disability, particularly associated with facial dysmorphism (e.g. prominent eyes, bulbous nose tip, tent-shaped mouth with thin upper lip, and large ears).”

Causes

As the wide majority of CDG, MAN1B1-CDG is an autosomal recessive disorder. Reported mutations include nonsense, missense, splice site and deletions. The p.R324C mutation has been the most commonly found with 10 diagnosed patients so far.

Diagnosis

Biochemical features, include a type 2 serum transferrin isoelectric focusing pattern. Mass spectrometry analysis of serum transferrin exhibits a build-up of hybrid N-glycans. The diagnosis is confirmed by mutation analysis. Contact us if you wish to connect with a CDG diagnosis laboratory.

Major signs and symptoms

Neurologic

Intellectual Disability (Ranging From Mild to Severe) Global Developmental Disability (Including Delayed Speech and Psychomotor Milestones) Epilepsy Ataxia Hypotonia Sensory Processing Disorder

Behaviour

Aggressiveness (Both Verbal and Physical) Inappropriate Sexual Behaviour Overeating Autism Tics Anxiety

Dysmorphism (Variable)

Hypertelorism Flat Oval Face Down-Slanting Palpebral Fissure Low Frontal Hairline Curved Eyebrows With Lateral Thinning Prominent Bulbous Nose Tip Thin Upper Lip Tent Shaped Mouth Large Ears

Skeletal

Long Thin Fingers Hypermobility of the Joints Scoliosis Pectus Excavatum Macrocephaly Dolichocephaly Clindactyly

Other Symptoms / Signs

Skin Laxity Overweight (Mainly Truncal Obesity) Asthma Cardiac Defects Hyperglicemia Mild Coagulation Abnormalities Mild Increase of Serum Transaminases Inverted Nipples Strabismus Syndactyly Inability to Regulate Body Temperature (1 patient) Inability to Process Monosaccharides and Disaccharides (1 patient)

Prevalence

It has been diagnosed in 35 patients from 22 different families worldwide (for 12 patients nationality is unavailable). Additionally, 2 Australian patients have been diagnosed, but not reported in literature. (9 Pakistani 6 Turkish 3 Iranian 2 Belgian 2 Portuguese 1 Emirati)

Clinical Management

Scoliosis and pectus excavatum can be surgically corrected. Sleep disturbances have been improved with clonidine intake. Inability to regulate body temperature can lead to episodes of overheating, which may be controlled by keeping the patient in a cool environment and increasing liquid intake. Additionally, panadol can help decrease body temperature.

It is highly recommended that MAN1B1-CDG patients are followed by a multi-disciplinary team of health professionals. These patients might benefit from speech, physical, occupational and psychological therapy. Additionally, nutritional advice and follow-up should be given to these patients.

Prognosis

Motor skills have been reported to improve with age, whereas intellectual disability seems to be stable and non-progressive overtime. Epileptic seizures may only manifest later in childhood (5 – 10 yrs). Features, such as hypotonia and macrocephaly have also been reported to spontaneously improve. Overweight may lead to rapid bone maturation and premature puberty. Some patients acquire speech and become independent in their daily hygiene (including toilet trained), whilst others remain non-verbal and highly dependent for their daily care.

References