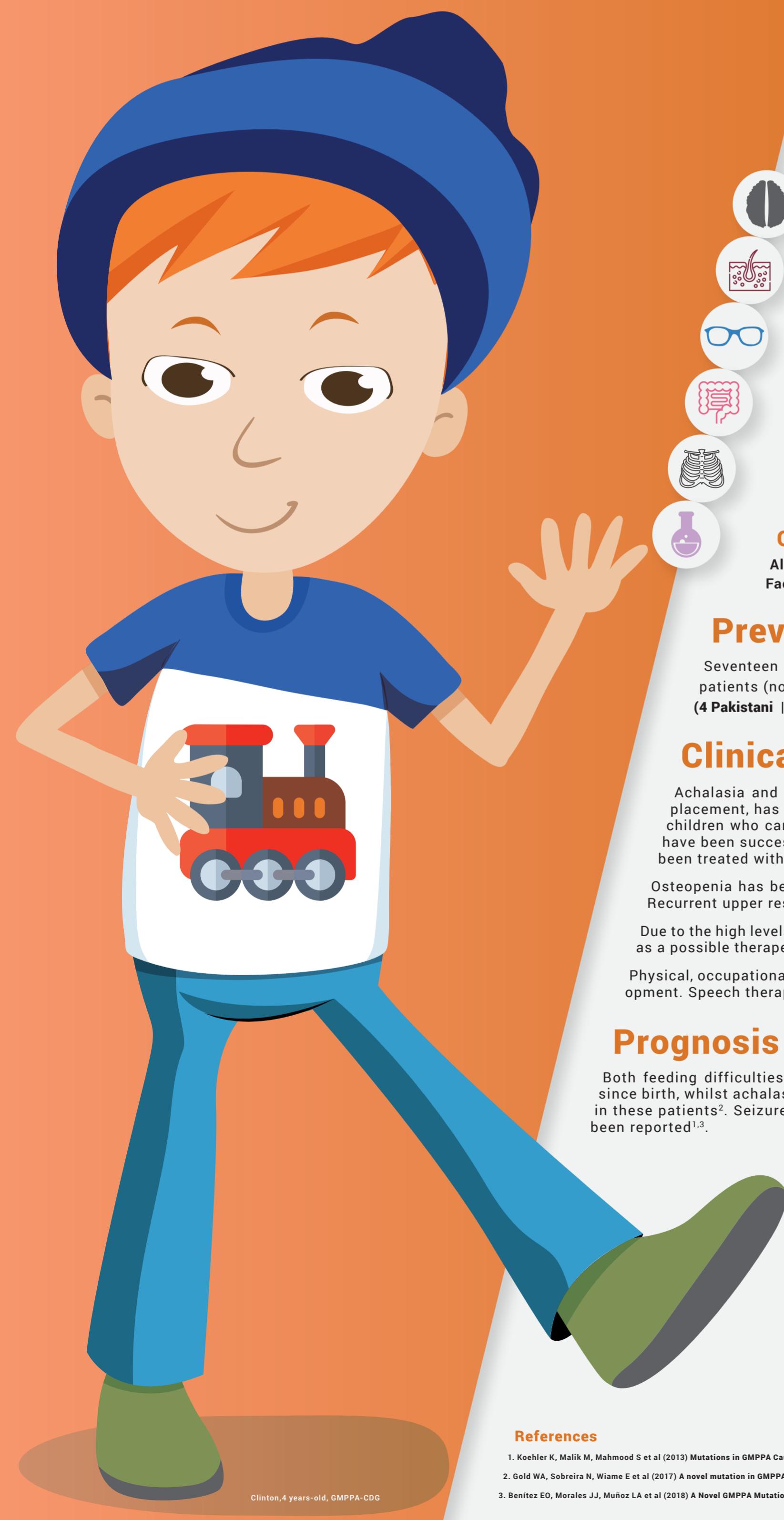


GMPPA-CDG

GMPPA mutations cause an alacrima, achalasia and mental retardation syndrome. It's one of the 5 CDG caused by defects in nucleotide-sugar synthesis.



What is GMPPA-CDG?

The first patients were described in 2013 by Koehler and collaborators¹. Several clinical features overlap with the manifestations observed in triple A syndrome patients. However, GMPPA-CDG patients do not exhibit adrenal insufficiency. GMPPA (MIM:615495) encodes a GMPPB homologous protein, the mannose-1-phosphate guanylyltransferase alpha. This protein has been suggested to act as a regulatory subunit of GMPPB, allowing allosteric feedback inhibition of GMPPB by GDP-mannose. Interestingly, only homozygous mutations were observed in all reported patients^{1,2,3}.

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 GMPPA-CDG?

GMPPA-CDG should be considered in the presence of clinical manifestations with a great resemblance to triple A syndrome, characterised by gastrointestinal defects (including achalasia), intellectual disability, alacrima and different degrees of involvement of other organs. However, none of the reported GMPPA-CDG patients have adrenal gland insufficiency. Alacrima, which is a very noticeable clinical sign, and feeding difficulties have been mentioned as the first clinical manifestations prompting further medical evaluation. Increased GDP-mannose levels are a distinctive feature¹.

Causes

As the wide majority of CDG, GMPPA-CDG is an autosomal recessive disorder.

Diagnosis

Biochemical diagnosis of this condition is complicated as both serum transferrin, apoCIII glycosylation profiles and enzymatic activity are normal in these patients¹. Thus, the presence of normal glycosylation patterns, high GDP-mannose levels and clinical manifestations resembling triple A syndrome without adrenal failure should prompt mutation analysis to confirm the diagnosis. Contact us if you wish to connect with a CDG diagnosis laboratory: sindromecdg@gmail.com.

Major signs and symptoms

Neurologic

Intellectual Disability (Mild to Severe) | Gait Abnormalities (Ataxia or Spasticity) | Absent or Nasal Speech | Sensorineural Hearing Impairment | Constant Writing Movements and Stereotypies | Seizures | Microcephaly

Dermatological

Hyperkeratosis | Hyperhidrosis

Ophthalmological

Ptosis | Nystagmus | Strabismus | Anisocoria

Gastrointestinal

Achalasia | Chronic Constipation | Inflammatory Bowel Disease | Absent Saliva Leading to Xerostomia | Dysphagia | Vomiting | Gastroesophageal Reflux | Esophageal Stenosis

Skeletal

Osteopenia | Delayed Bone Mineralization | Clinodactyly | Scoliosis | Short stature

Other Symptoms / Signs

Alacrima | Postural Hypotension | Congenital Diaphragmatic Hernia | Recurrent Infections | Facial Dysmorphisms | Delayed Motor Milestones | Hirsutism

Prevalence

Seventeen patients, from 11 unrelated families have been reported in the literature. Additionally, 3 USA patients (not reported in literature) have also been diagnosed with GMPPA-CDG.
(4 Pakistani | 3 Arabic | 2 Lebanese | 2 Palestinian | 2 Mexican | 1 Turkish, Kosovan, Dominican and Moroccan).

Clinical Management

Achalasia and strabismus have both been corrected through surgery^{1,2,3}. Tube feeding, namely by gastrostomy placement, has shown positive results in solving aspiration and gastroesophageal reflux complications. Also, for children who can feed orally, pureed foods may be a good approach². Additional gastrointestinal manifestations have been successfully treated, including a duodenal perforation by laparotomy. Inflammatory bowel disease has been treated with prednisolone, azathioprine, and salazopyrin².

Osteopenia has been treated with Zoledronate, whilst seizures seem to respond to therapy with anticonvulsants². Recurrent upper respiratory tract infections have improved in a patient after tonsillectomy and adenoidectomy².

Due to the high levels of GDP-mannose found in GMPPA-CDG patients' cells, a mannose-depleted diet has been proposed as a possible therapeutic strategy¹, but to the best of our knowledge this strategy has not yet been tried in any patient.

Physical, occupational and speech therapy may have beneficial effects, particularly if started early in the patient's development. Speech therapy may play an even more relevant role, since delayed and nasal speech are common problems.

Prognosis

Both feeding difficulties and neurologic manifestations are usually progressive¹. Alacrima is most frequently present since birth, whilst achalasia usually develops during the first 2 years of life¹. Microcephaly also appears to be progressive in these patients². Seizures have been described to have their onset in late childhood². Patients reaching adulthood have been reported^{1,3}.



CDG & Allies – PPAIN
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www.researchcdg.com

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