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Defining the phenotype of PGAP3-congenital disorder of glycosylation; a review of 65 cases

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Abstract

Biallelic pathogenic variants in *PGAP3* cause a rare glycosylphosphatidyl-inositol biogenesis disorder, PGAP3-CDG. This multisystem condition presents with a predominantly neurological phenotype, including developmental delay, intellectual disability, seizures, and hyperphosphatemia. Here, we summarized the phenotype of sixty-five individuals including six unreported individuals from our CDG natural history study with a confirmed PGAP3-CDG diagnosis. Common additional features found in this disorder included brain malformations, behavioral abnormalities, cleft palate, and characteristic facial features. This report aims to review the genetic and metabolic findings and characterize the disease's phenotype while highlighting the necessary clinical approach to improve the management of this rare CDG.

Keywords

PGAP3; glycosylphosphatidylinositol anchor biogenesis defects; GPI-anchor; alkaline phosphatase; psychomotor developmental delay

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INTRODUCTION

PGAP3 gene (Post-GPI attachment to proteins phospholipase 3), is located on chromosome 17q12 and encodes the glycosylphosphatidylinositol (GPI)-specific phospholipase in the Golgi apparatus. Post-GPI attachment to proteins phospholipase 3 deficiency was previously named hyperphosphatasia with mental retardation syndrome 4 (HPMRS4), (recently changed to hyperphosphatasia with impaired intellectual development syndrome 4 (OMIM 615716)) results from biallelic pathogenic variants in *PGAP3*. This rare subtype of glycosylphosphatidyl-inositol biogenesis disorders (GPIBD) is classified under congenital disorders of glycosylation (PGAP3-CDG) [1].

Most patients with PGAP3-CDG manifest signs and symptoms at birth or in the first years of life. The typical symptoms are often neurological and include hypotonia, ataxia, severe developmental delay, intellectual disability (ID), distinctive facial features, and seizures with onset between the first days of life to a few years of age. In some patients, seizures are treatable with anti-epileptic drugs (AED), but in many, epilepsy is difficult to treat. Autistic behavior and sleep disturbances are very common in PGAP3-CDG. Brain imaging may show structural abnormalities of the brain. And typically, patients show an elevation of alkaline phosphatase (ALP) in the blood [2].

To date, fifty-nine individuals with a confirmed PGAP3-CDG diagnosis have been reported. In this study, we describe an additional six individuals with PGAP3-CDG, in addition to a detailed review of previously reported individuals aiming to characterize the phenotypic spectrum of PGAP3-CDG and direct the clinical management of this rare CDG.

MATERIALS AND METHOD

We evaluated six patients with confirmed pathogenic *PGAP3* variants from the 208 enrolled CDG patients followed by the Frontiers of Congenital Disorders of Glycosylation Consortium (FCDGC) natural history study (institutional review board [IRB]: 19–005187; [NCT04199000](#)). Prospective data, as well as retrospective data were available for frequent patients' follow-ups are part of standard care at each site.

We also reviewed all publications on patients diagnosed with PGAP3-CDG with confirmed pathogenic variants, focusing on their clinical, genetic, and metabolic characteristics by using PubMed database search from the date of the first clinical description until May 2023 using the following terms: hyperphosphatasia with mental retardation syndrome 4 (HPMRS4), hyperphosphatasia with impaired intellectual development syndrome 4, Mabry syndrome, PGAP3, and PGAP3-CDG.

RESULTS

This review included sixty-five molecularly confirmed PGAP3-CDG patients (26 males and 39 females). Data from 59 patients were collected from previously published articles (n=13) including case cohorts (n=6) [3,4,5,6,7,8], and case reports (n=7) [9,10,11,12,13,14,15]. Data for the so far unreported, additional six patients were collected from the shared natural history database.

The median age was 7 years whereas the youngest and oldest patients were 2 and 25 years old, respectively. All patients shared the common phenotype of severe psychomotor developmental delay, with a characteristic high serum alkaline phosphatase (ALP) level, in addition to multi-system involvement and severity as detailed below.

Systems involvement in PGAP3-CDG

Development—All reported patients including our cohort had a global developmental delay with two or more affected developmental domain milestones. The three major delayed developmental domains are: cognition, reported in 95% (n=62); motor function, in 96% (n=63); and speech, in 93% of patients (n=61), 53 patients were reported as nonverbal while only eight patients used limited verbal communication. No data was available for 4 patients.

Neurological manifestation—Neurological involvement was a consistent finding in all patients. Hypotonia was present in 90% of patients (n=59). Ataxic and unsteady gait was described in 27% of patients (n=18) including our cohort. Microcephaly was reported in 38% (n=25) while macrocephaly was noted in five patients. Nearly half of the patients had seizures (n=32). Different seizure subtypes included generalized tonic-clonic, myoclonic, absence, partial, and atypical febrile seizures. Seizures were medically controlled in eight patients and only two patients failed to respond to multiple AEDs including one newly reported 16-year-old patient. Different AEDs have been used to control the seizure either as monotherapy or as multiple therapies including sodium valproate, levetiracetam, diazepam, pregabalin, clonazepam, lamotrigine, and phenobarbital. Ketogenic diet was trialed on one patient who had refractory seizures. (Supplementary material 1)

Brain magnetic resonance imaging (MRI) abnormalities—Different structural brain malformations were detected by brain MRIs performed on 31 patients. The most common finding was corpus callosum hypoplasia, detected in 54% of patients (n=17), followed by cerebellar vermis hypoplasia or atrophy in five patients, brain atrophy in four, and hypoplastic cerebellum in three patients. Other rare brain MRI findings included delayed myelination, cerebroventricular hemorrhage, Dandy-Walker malformation, cortical dysplasia, small internal capsule, Rathke cyst, and ventriculomegaly with frontoparietal atrophy.

Craniofacial manifestation—Almost all patients showed distinctive facial features such as arched eyebrows, hypertelorism, broad nasal bridge and tip, short and bulbous nose, long palpebral fissures, long philtrum, thin and wide upper lip, large fleshy earlobes, low set ears, and abnormal dentation. Cleft palate was stated in 61% of patients (n=40). Figure 1 illustrates the commonly reported facial features of PGAP3-CDG.

Behavioral abnormalities—About 44% of patients manifested with one or a combination of two behavioral symptoms. Autism was the most commonly stated abnormality, reported in 29% of patients (n=19), followed by hyperactivity, in 18% (n=12), and sleep disturbance in 12% (n=8). Less reported behavioral issues included bruxism, hypersomnolence, aggression, obsessive-compulsive behavior, and involuntary midline hand movement.

Other less common involved systems include cardiovascular, gastrointestinal, ophthalmological, skeleton, and hearing—Cardiovascular and gastrointestinal involvement are not commonly reported in patients with PGAP3-CDG with a rate of 12% for each (n=8).

Structural cardiac defects were found only in eight patients including atrial septal defect, ventricular septal defect, or concentric ventricular hypertrophy. The main reported gastrointestinal manifestations were failure to thrive, reported in 35% (n=23), followed by dysphagia, gastroesophageal reflux, esophagitis, constipation, or intestinal malrotation.

The ophthalmological manifestation was documented in only 20% of patients, (n=13) where the most common abnormality was megalocornea, stated in seven patients. Other less reported eye phenotypes include nystagmus, microphthalmia, poor vision, and optic disc abnormality.

Short stature was stated in 40% of patients (n=26). Skeletal deformities are rarely noted including plagiocephaly, scoliosis, pectus excavatum, clinodactyly camptodactyly of 5th finger, hip dysplasia, pes equinovarus, and coxa valga. Sensorineural hearing loss was documented in 20% of patients (n=13). There was no reported brachytelephalangy in PGAP3-CDG patients.

Pyridoxine (vitamin B6) therapy and ketogenic diet—Pyridoxine therapy was initiated in only four patients including three from our cohort. The ketogenic diet was trialed on two of our patients. Supplementary material 1.

PGAP3 variants—Twenty-four different pathogenic variants were reported in *PGAP3*. Homozygous variants were detected in 78% of reported patients who are born to consanguineous families. The most commonly observed variants more than once were His284Tyr, followed by Met135fs. Figure 2 lists all previously reported *PGAP3* variants. There was no genotype/phenotype found in this review.

Disease course and outcome—A total of 7 patients were above 14 years of age (three were >18 years of age). All had static conditions. Their main phenotype included ID, speech delay, behavioral abnormalities, and seizures [3,4,6]. Based on our data we have knowledge of one patient who succumbed to aspiration pneumonia at 18 months of age.

DISCUSSION:

The *PGAP3* gene encodes a glycosylphosphatidylinositol (GPI)-specific phospholipase that is expressed in the Golgi apparatus. The enzyme is involved in fatty acid GPI remodeling which is critical for a proper association between GPI-anchored proteins and lipid rafts [16]. Mutations in *PGAP3* results in a rare autosomal recessive CDG subtype; PGAP3-CDG or previously called Mabry syndrome/ HPMRS4. In this review, we describe the genetic, biochemical and phenotypic spectrum of 65 patients with PGAP3-CDG.

PGAP3 has a critical role in brain morphogenesis and oligodendrocytes formation and function which explains the predominant and significant neurological involvement in

PGAP3 deficiency [13]. All patients had major neurological involvement with high ALP (65/65).

PGAP3 is involved in the later step of GPI-anchor synthesis and defects in PGAP3 leads to GPI anchored proteins instability including Alkaline phosphatase (ALP). As result, hyperphosphatemia is observed in PGAP3-CDG and some other GPIBDs [1]. Thus, it is considered a useful marker for biochemical diagnosis of some GPIBDs.

Other GPI-anchored proteins (GPI-APs) like CD59, CD55 and urokinase plasminogen activator receptor can be measured in individuals affected with PGAP3 deficiency. Reduced cell surface levels of GPI-APs in patients' blood granulocytes was noted in PGAP3-CDG [3]

The most common features observed across PGAP3-CDG patients are developmental delay, (ID), hypotonia, seizures, and distinctive dysmorphic features. The frequency of phenotypic features in all patients with PGAP3-CDG is shown in Figure 3. The main presenting phenotype is often noticed either at birth with congenital craniofacial abnormalities or during the first or second year of life with failure to acquire major developmental milestones mainly the motor and language skills, with or without seizures. Behavioral abnormalities, autism spectrum disorders, and sleep disturbance are recognizable phenotypes of GPIBDs including PGAP3-CDG [17]. Significant behavioral involvement was found in our review, autism and sleeping difficulties were the main reported behavioral phenotype.

The most common neuroimaging abnormalities reported are hypoplastic corpus callosum, and cerebellar and, *or* cerebral atrophy. Neuroimaging data were missing in 50% of previous reports. The pathomechanism of the neurostructural abnormalities has been shown in a knockdown *Pgap3* zebrafish which also may contribute to the craniofacial dysmorphism as a sequence of early fetal brain dysmorphogenesis [13].

In comparison to other CDGs, multisystem involvement was not well illustrated in GPIBD. Data on the multisystem involvement in PGAP3-CDG may be underestimated due to the scarce data available from previous reports. PGAP3-CDG shares the other GPIBDs' main phenotype including global developmental delay, hypotonia, seizures, and facial dysmorphism. Brachytelephalangy which is a notable skeletal anomaly in GPIBDs was not reported in PGAP3-CDG patients.

From reviewing previous reports including our cohort, PGAP3-CDG was found to present with at least one or more extra-neurological involvement including cardiac anomalies, gastrointestinal abnormalities, eye dysmorphology, hearing loss, or skeletal defects and short stature. Deafness can contribute to the failure of acquiring language skills in PGAP3-CDG which is significantly affected in PGAP3-CDG.

Although the cause of the seizure in GPIBD is not well understood, patients with hyperphosphatemia secondary to defects in GPI-anchored tissue nonspecific alkaline phosphatase manifest with seizures that might be refractory to conventional AED therapy [18]. ALP is a key enzyme for dephosphorylation of pyridoxal 5- phosphate to pyridoxal (the active form of pyridoxine). Pyridoxine (B6) can cross the blood-brain barrier and transported to the brain in the absence of effective ALP in GPIBDs [19]. Furthermore, oral

B6 supplements are hypothesized to enhance the g-aminobutyric acid (GABA) synthesis which is depleted in GPIBDs [20,21]. There are few reports in the literature about the benefits of pyridoxine (B6) supplementation in managing untreatable seizures in GPIBDs [18, 20, 21, 22]. Treatment with a 200 mg daily B6 supplement in a child with PGAP3-CDG improved his seizures frequency and sleep pattern [10]. In our cohort, three patients were supplemented with daily 50 mg of B6, and two of them did not manifest seizures yet.

Ketogenic diet has been shown improvement in some patients with GPIBDs [23]. The exact mechanism of ketogenic diet effectiveness in controlling seizures is debated. Many theoretical hypotheses have been proposed [24]. In GPIBDs, restoring the depleted GABA in the brain by the high ketone bodies enhances the inhibitory neurotransmission [25]. Few patients with PIGA-CDG have been managed with ketogenic diet which showed either termination or a significant reduction in seizures frequency [26]. In our cohort, two patients were trialed on ketogenic diet, it was indicated for refractory seizures in a 16-year-old male. However, the diet did not affect his clinical seizures, but his ALP levels showed a significant decline while he was on the ketogenic diet. In another 2-year-old female who did not manifest seizures, a trial of ketogenic diet showed subjective improvement in her motor function and ataxic movement with a reduction of her ALP levels during the therapy (Figure 3). This observatory result suggests that dietary alterations might improve the GPI-anchoring of ALP and could be considered in PGAP3-CDG and GPIBDs. Further studies on the ketogenic diet effect on GPIBDs are required.

Unfortunately, there are gaps in the published literature about details of clinical management, including seizure treatment and, or the use of ketogenic diet. One of the major limitations of our study is the source of retrieved data was based on the high-level clinical descriptions from published case cohorts and case series. The ongoing natural history study on CDG patients: [ClinicalTrials.gov \(NCT03173300\)](https://clinicaltrials.gov/ct2/show/study/NCT03173300) will provide a richer data set for this group of metabolic disorders.

In conclusion, PGAP3-CDG is considered a multisystem CDG with major neurological involvement and high ALP levels. Early recognition of the disease in individuals with ID and/or seizures by screening ALP levels or use of broad genetic testing as a first-tier diagnostic evaluation can help in directing those patients' symptomatic management. Care can include seizure reduction by supplementing B6 and/or trying a ketogenic diet which has shown positive effects in the ALP levels, improving motor function, and controlling the seizures in GPIBDs. In addition, early enrollment in rehabilitation centers enhances patients' development and independency. Management of this rare disease is still only supportive and symptomatic but targeted therapies for several GPIBDs are on the horizon [27].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviation

PGAP3	Post-GPI attachment to proteins 3
GPI	glycophosphatidylinositol
GPIBD	GPI biogenesis disorders
GPI-APs	glycophosphatidylinositol anchored proteins
CDG	Congenital disorder of glycosylation
HPMRS4	hyperphosphatasia with mental retardation syndrome 4
ALP	alkaline phosphatase
ID	intellectual disability
AED	anti-epileptic drugs
GABA	g-aminobutyric acid

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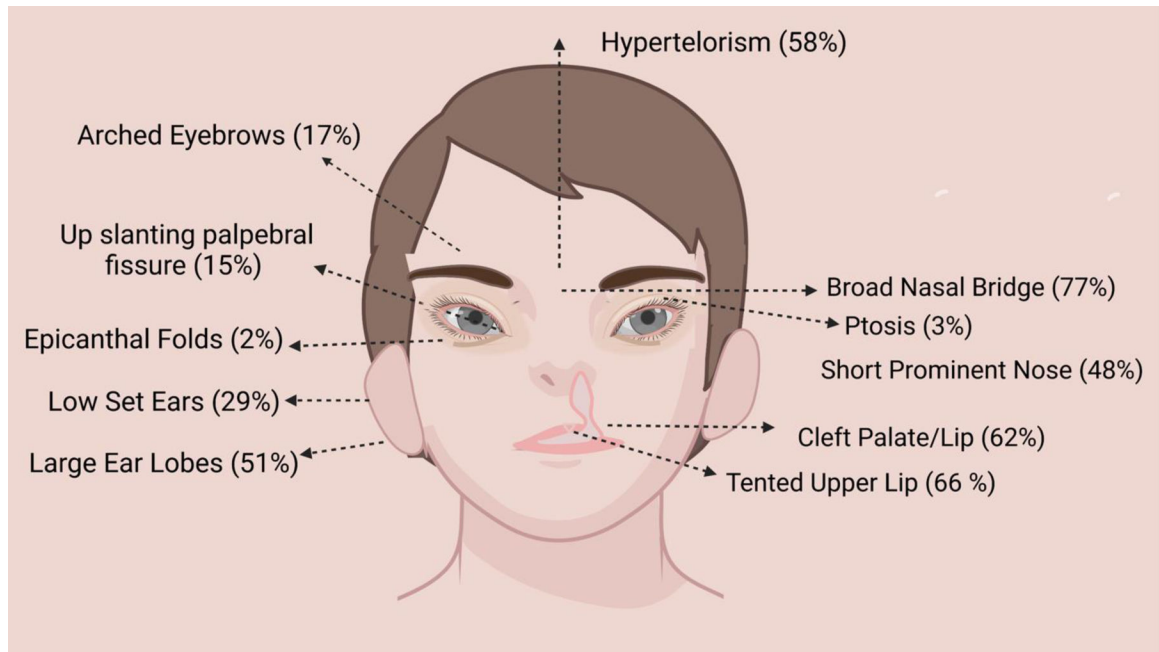


Fig.1.
Commonly reported facial features in PGAP3-CDG

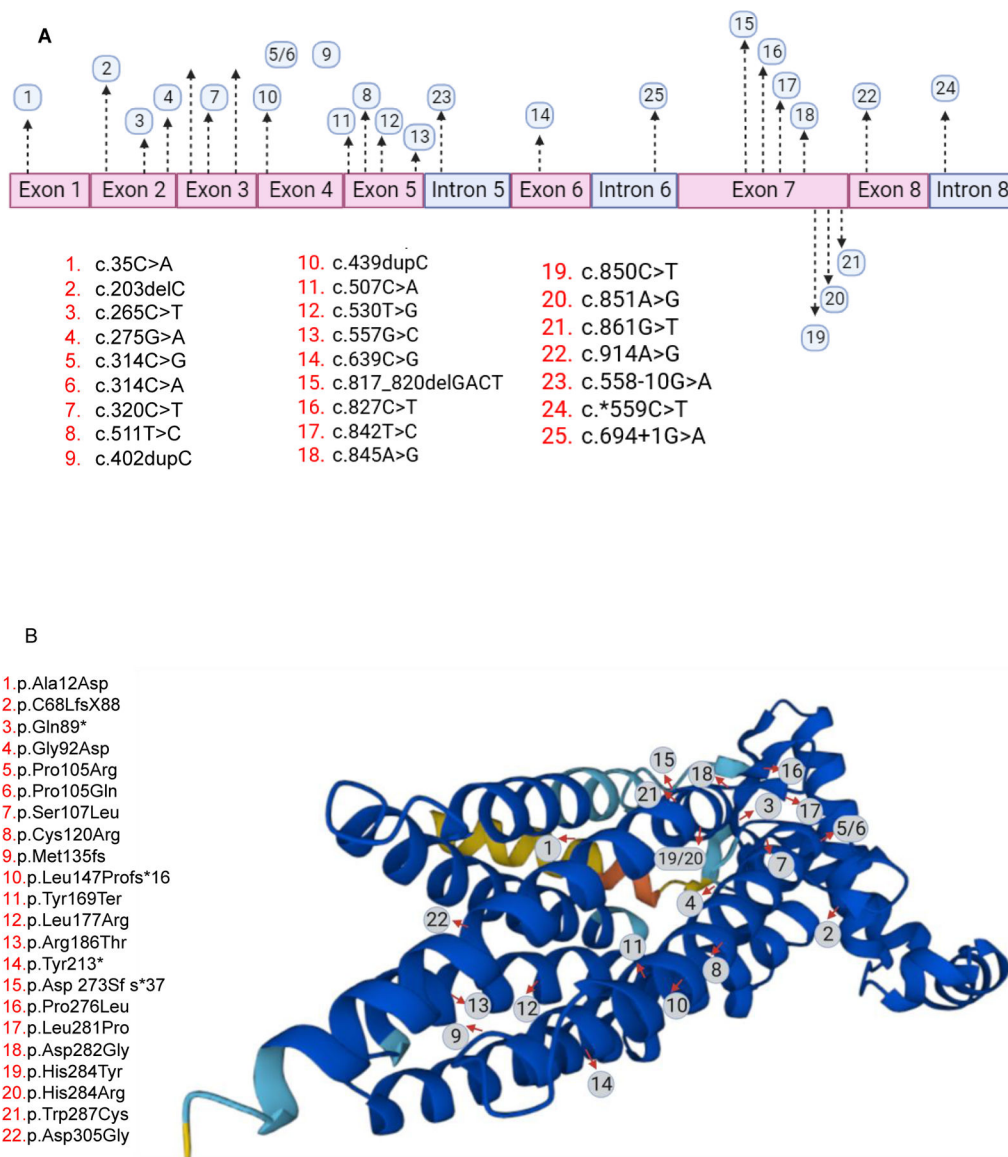


Fig.2.
Reported pathogenic *PGAP3* variants
References: [28,29]

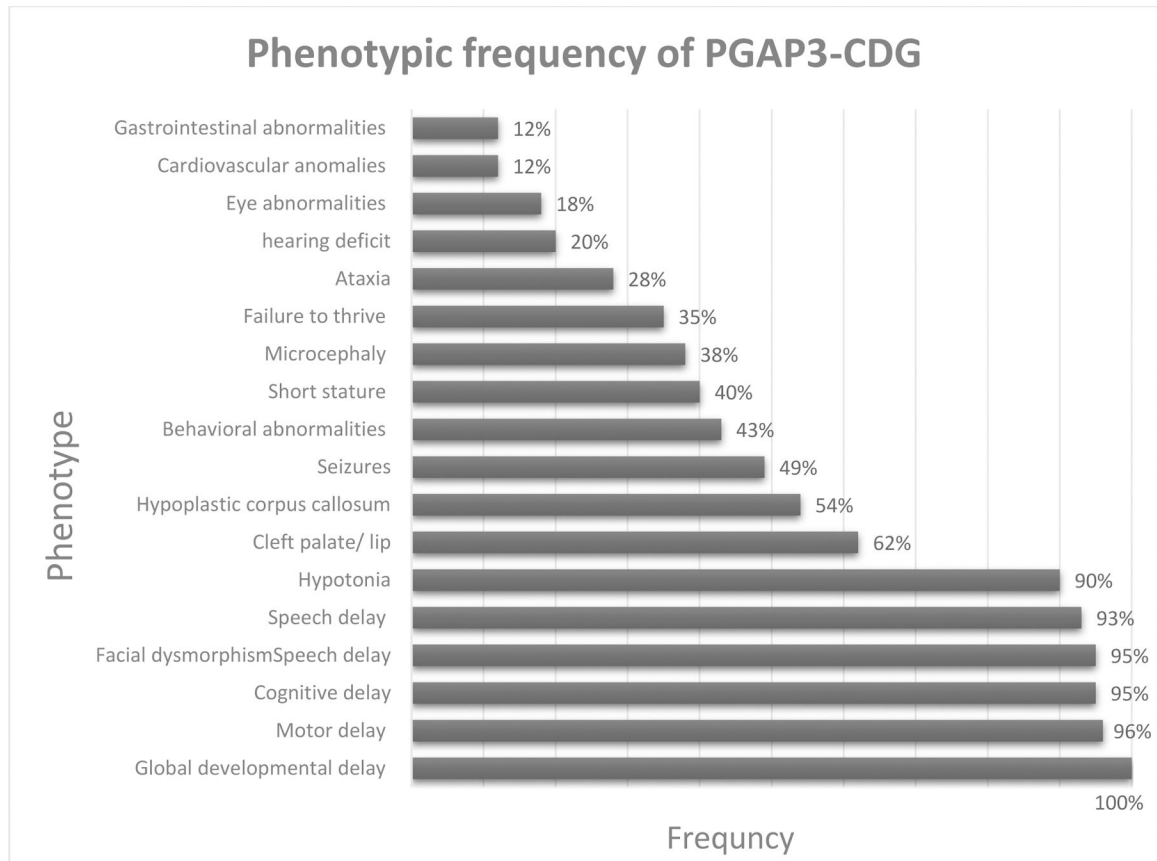


Fig.3.
Phenotypic frequency of PGAP3-CDG

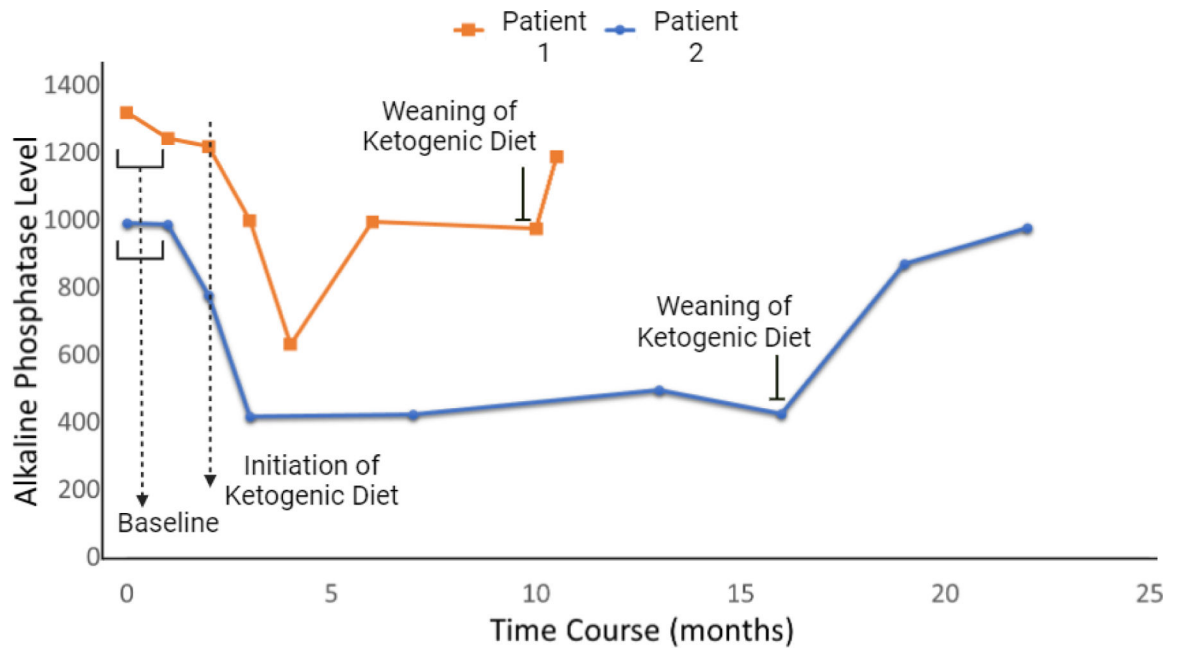


Fig.4. ALP levels during ketogenic diet therapy in two PGAP3-CDG patients

Table 1.

Assessment and management guidance for PGAP3-CDG

Detailed developmental assessment
Hypotonia severity
Motor function
Abnormal movement
Speech assessment
Hearing assessment
Eye exam
Seizure evaluation (EEG, neuroimaging)
Behavioral assessment
Echocardiogram
Swallowing assessment and upper GI study
Growth evaluation
Alkaline phosphatase level
Other glycoproteins (liver function test, coagulation profiles, and hormonal assays)
Vitamin B6 supplements
Ketogenic diet for seizures management
ALP monitoring during ketogenic diet

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