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Short Communication

A step closer in defining glycosylphosphatidylinositol anchored proteins role in health and glycosylation disorders

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ABSTRACT

Glycosylphosphatidylinositol anchored proteins (GPI-APs) represent a class of soluble proteins attached to the external leaflet of the plasma membrane by a post-translation modification, the GPI anchor. The 28 genes currently involved in the synthesis and remodelling of the GPI anchor add to the ever-growing class of congenital glycosylation disorders. Recent advances in next generation sequencing technology have led to the discovery of Mabry disease and CHIME syndrome genetic aetiology. Moreover, with each described mutation known phenotypes expand and new ones emerge without clear genotype-phenotype correlation. A protein database search was made for human GPI-APs with defined pathology to help building-up a physio-pathological mechanism from a clinical perspective. GPI-APs function in vitamin-B6 and folate transport, nucleotide metabolism and lipid homeostasis. Defining GPI-APs role in disease bears significant clinical implications.

1. Introduction

In 1970, Mabry et al. made the first observation of the Hyperphosphatasia with mental retardation syndrome (HPMRS) with the following findings: severe mental retardation, seizures, various neurologic abnormalities, and elevated serum levels of alkaline phosphatase. With recent advances in the next generation sequencing technology both hypomorphic and loss of function mutations of the genes involved in synthesis or remodelling of the GPI-APs have been described.

This helped expanding HPMRS clinical phenotype to multi-system involvement. PIGA gene defect, previously associated with paroxysmal nocturnal haemoglobinuria (PNH), was also attributed multiple congenital anomalies, hypotonia and seizures X-linked syndrome. Moreover, PNH was also described in a PIGT gene mutation. Other clinical phenotypes associated with molecular defects in the biosynthesis of the GPI anchor include: CHIME syndrome (coloboma, heart defects, ichthyosiform dermatosis, intellectual disability, and either ear defects or epilepsy), MCAHS syndrome (multiple congenital anomalies, hypotonia and seizures, type 1–3) and early-onset epileptic encephalopathies (Table 1).

Pending on the cell polarisation type, the GPI-anchor is required for trafficking proteins to certain domains of the plasma membrane. There, the GPI-APs oligomerize in the rich cholesterol/sphingolipid areas by saturated fatty acids interactions within the GPI anchor and with other molecules building up “signalling platforms”. Several studies showed that GPI-APs oligomerize/cluster at the cell surface of different cell types such as fibroblasts, immune T and epithelial cells [1–5]. Importantly, GPI-AP clustering at the cell surface is cholesterol-sensitive and dynamically regulated by the cortical cytoskeleton. Crucial for their biological role, GPI-AP clustering at the membrane rafts permits interaction with side partners such as enzymes, adaptors, co-factors and scaffolding proteins, initiating spatio-temporal compartmentalization and context-specific activation of downstream signalling cascades [6, 7].

The role of the GPI-APs at the plasma membrane is even more complex, considering their recruitment to exosomes, release in the extracellular environment by proteolysis or further trafficking via endocytic pathway [8–11]. Broadly, a defect in the later stages of biosynthesis / remodelling of the GPI anchor results in shedding of the soluble protein in the extracellular environment, with or without the abnormal GPI signal; in defective early GPI anchor biosynthesis, the soluble protein will be subjected to intracellular degradation [12]. This mechanism explains high plasma alkaline phosphatase levels in patients with HPMRS [13].

Abnormal surface expression of the GPI-APs was demonstrated by transfection of patients' DNA to GPI-AP defective cell lines. In vitro functional analysis has shown variable degrees of GPI-APs restoration compared to wild gene transfection [14–23].

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Table 1
Syndromic clinical presentation of GPI-AP defects (https://www.omim.org).

Clinical presentation	HPMRS (6 types)	CHIME OMIM # 280000	MCAHS 1 OMIM # 614080	MCAHS 2 OMIM # 300868
Inheritance	AR	AR	AR	X-linked
Dysmorphism	Secondary microcephaly Plagiocephaly Coronal synostosis Midface hypoplasia Prognathism Hypertelorism Long palpebral fissures Broad nasal bridge Broad nasal tip Short philtrum Large fleshy earlobes Downturned mouth corners Tented mouth Cleft palate	Brachycephaly Hypertelorism Broad, flat nasal root Short philtrum Full lips Anomalous dentition Cleft palate Epicathic folds Macrosomia at birth	Macrocephaly Macrosomia at birth Poor growth Coarse facial features Light hair Bitemporal narrowing Depressed nasal bridge High arched palate with wide alveolar ridge Frontal bossing Long philtrum Micrognathia Large, fleshy ears Overfolded helices Low-set ears Posteriorly rotated ears Cupped ears Epicanthal folds Hypertelorism Depressed nasal bridge Small nose Upturned nares Thin lips Open mouth High-arched palate Cleft palate	Macrosomia at birth Accelerated linear growth Obesity *Macrocephaly* Microcephaly Micrognathia Coarse facies Overfolded helix Upslanting palpebral fissures Widely spaced eyes Depressed nasal bridge Short, anteverted nose Small mouth Downturned corners of the mouth Triangular mouth High-arched palate Gingival hyperplasia Microdontia Pointed teeth Widely-spaced teeth Short neck
Cardiovascular	ASD VSD Peripheral pulmonary stenosis Tetralogy of Fallot	VSD Tetralogy of Fallot Transposition of great arteries Peripheral pulmonary stenosis	VSD ASD Over-riding aorta Hypoplastic pulmonary trunk Non-compacting cardiomyopathy	ASD Right ventricular hypertrophy and arrhythmia
Respiratory			Lung hypoplasia (in some patients) Diaphragmatic hernia Poor respiratory drive requiring tracheostomy and assisted ventilation.	Obstructive apnoea
Gastrointestinal	Feeding difficulties requiring tube feeding Esophageal atresia Intestinal malrotation Hirschsprung disease Anorectal abnormalities (anal stenosis, atresia anovestibular fistula, anteriorly displaced anus)	Upper GI dysmotility	Feeding difficulties requiring tube feeding Congenital diaphragmatic hernia Gastroesophageal reflux Hepatomegaly Intestinal malrotation Anal stenosis or atresia	Upper GI dysmotility Hepatomegaly Cirrhosis Iron deposition (1 family)
Genitourinary	Dilated / mega ureter Ectopia of ureter/urethra Hydronephrosis Kidney duplication Vesicoureteral reflux	Duplicated renal collecting system Hydronephrosis Ureteropelvic junction obstruction Bicornuate uterus	Dysplastic kidney Hydrocele Hydronephrosis Hypoplasia of the ureter Vesicoureteral reflux Duplicated collecting system Microphallus, cryptorchidism	Multicystic kidneys Unilateral hydronephrosis Duplicated collecting system Vesicoureteral reflux Microphallus
Skeletal	Pectus excavatum Joints contractures Brachytelephalangy Tapered fingers Broad halluces Hypoplastic toes Clinodactyly/syndactily Osteopenia Hip dysplasia Proximal limb shortening	Hip dysplasia Pectus excavatum Nipples small, low set Brachydactyly Fifth finger camptodactily and clinodactily	Hip dysplasia Narrow inferior iliacs Fifth finger clinodactyly Hypoplastic distal phalanx Hypoplastic nails, anonychia	Joint contractures
Skin, nail, hair	Hypertrichosis Supernumerary nipples Hypoplastic or absent nails Bilateral hypoplastic fifth fingernail Severe ichtyosis Inguinal hernia	Migratory ichthyosiform dermatosis Thickened palms and soles Light coloured, fine and spars scalp hair	Deep plantar crease Supranumery nipples	Ichthyosis Seborrheic dermatitis Linear plaque-like scales Pigmentation abnormalities Hypoplastic nails

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