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**Review**

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# Barth Syndrome: A Genetic Ailment with a Lipid Component and Bioenergetic Ramifications

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## Abstract

**In eukaryotes membranes are structural components that are necessary for compartmentalization of function. Membranes consist of a lipid bilayer with a multitude of proteins on or in this sandwich. Nevertheless, membranes are not solely structural in function but also, they serve as basis for cellular signaling and metabolism. Membranes vary with respect to their lipid composition, protein:lipid ratio, thickness, carbohydrate content, etc., and hence their functions are not necessarily identical in the different compartments. In the mitochondrial inner membrane (mtIM), as in its bacterial ancestor, a special phospholipid is present. Cardiolipin (CL) is a phospholipid consisting of four hydrophobic tails. It is essential for the assembly of the electron transfer system (ETS) and its components, and hence CL is required for efficient mitochondrial bioenergetics. Mutations in CL remodeling enzyme encoded by the tafazzin gene (*TAZ*) are associated with a syndrome first identified by Dutch scientist Peter Barth, hence the name Barth Syndrome. Here, we review recent research on this devastating syndrome focusing on CL biosynthesis and remodeling and relationship between the phospholipid component and mitochondrial bioenergetics. We further by exploring management and possible future techniques in the treatment of this syndrome.**

## 1. Definition

Barth syndrome (BTHS) is a rare X-linked inherited disease that mainly affects males. It is caused by different mutations in the taffazin (*TAZ*) gene (Figure 1) [1]. BTHS was first described in 1983 by Dr. Peter Barth, a pediatric neurologist, who noticed a high infant mortality rate among males in a large pedigree of a family in his native the Netherlands. The deaths were linked to heart failure or sepsis [2]. The condition showed an X-linked recessive inheritance pattern, and was primarily characterized by dilated cardiomyopathy, skeletal myopathy, and neutropenia [2-4]. Barth was interested in pursuing the underlying cause of this disease and he observed abnormalities in the electron transfer system (ETS) in a patient's sample [2]. This was consistent with a previous discovery of an X-linked case of cardiomyopathy by Neustein in 1979, who also noticed mitochondrial abnormalities [5]. In 1991, Richard Kelley illustrated that organic aciduria, especially 3-methylglutaconic aciduria, is another feature found in individuals with this syndrome [3]. The prevalence of BTHS has been estimated to be 1 in 300 000–400 000 births. However, recent studies approximate the incidence to be around 1 case per million males. BTHS manifests mainly in infancy, as 90 % of patients with BTHS show symptoms of cardiomyopathy and neutropenia at less than 1 year old. The diagnosis of BTHS can be challenging, as 50 % of individuals are diagnosed after 1 year of age [6].

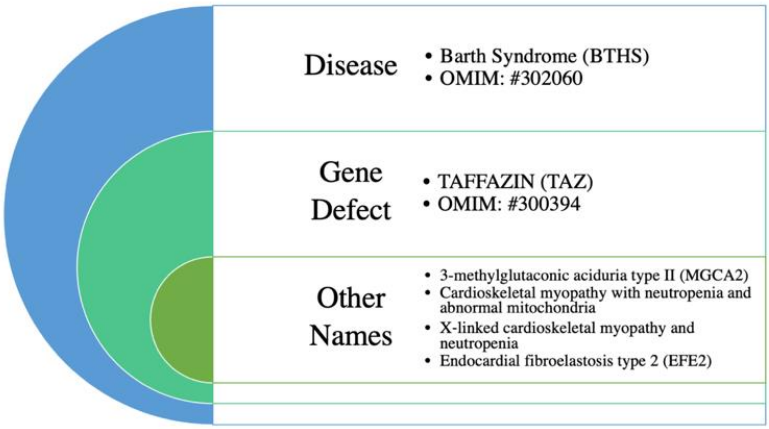


**Figure 1. The disease card.** Barth syndrome (BTHS) and its other used names, defective gene and Online Mendelian Inheritance in Man (OMIM) identification numbers.

## 2. Etiology

The primary cause of Barth Syndrome is a genetic mutation in the *TAZ* gene, which is located in the long *q* arm of chromosome X, most specifically in the Xq28 region [7, 8]. The *TAZ* gene spans 11 kbp and consists of 11 exons with a highly conserved sequence; the first two exons are non-coding [1, 7]. Over 160 mutations have been detected and identified in all different exons of the *TAZ* gene [9]. The majority of these are missense mutations and small insertion-deletion mutations. However, a small fraction of patients exhibited large exon deletions, and even in one case, a whole gene deletion was reported [4, 8].

Barth Syndrome follows an X-linked recessive inheritance pattern. According to the Barth Syndrome Foundation and data collected by the human *TAZ* gene mutation and variation database [10], roughly 13 % of males carry *de novo* mutations, which were not identified in the maternal DNA of somatic cells [4]. However, gonadal mosaicism has been recorded, which raises the likelihood that unaffected mothers who do not carry any mutations in the TAZ gene in their somatic DNA would pass the mutation through gametes that contain a defective gene. It is still possible for females to show symptoms of BTHS [4, 8]. This was recorded in a female who had two different defective genes, the first had a large deletion of exons 1-5, and the second was a ring form with a large deletion of the long arm that included the Xq28 region of the chromosome. Skewed X-inactivation can cause females to show symptoms of BTHS with a variation in severity [4]. It has been suggested that a post-inactivation selection mechanism might happen causing ETS abnormalities or other damaging effects in different cell types [4, 8].

*TAZ* gene encodes for Tafazzin protein which is a phospholipid acyltransferase [11] required for the remodeling of cardiolipin (CL) [12]. CL, or diphosphatidylglycerol is a dimeric phospholipid (Figure 2) that is highly abundant in the mitochondrial inner membrane (mtIM) [13]. In fact, CL is the only phospholipid specific to mitochondria, making up about 15–20 % of the total phospholipids in the mtIM [13]. It assumes essential roles in the structure, function and physiology of mitochondria. It is implicated in mitochondrial dynamics [14-16], autophagy [17], mitophagy [18], apoptosis [19], mitochondrial DNA replication [20] and mitochondrial bioenergetics and metabolism [21-23]. Moreover, CL is required for cristae organization and biogenesis [24], as well as for lipid-protein interaction particularly with proteins involved in oxidative phosphorylation such as respiratory Complexes I, III, IV, and ATP synthase [25].

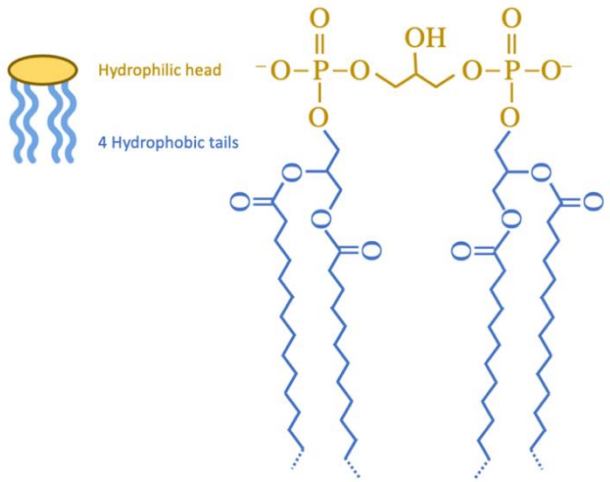


**Figure 2. Structure of CL.** A cartoon (left) and molecular (right) structures of CL show a wide hydrophilic head composed of two phosphates and four hydrophobic tails with varying chain lengths (dotted bonds). The structure is effectively a diphosphatidylglycerol.

## 2.1. Properties and biosynthesis of CL

CL is a double phosphatide linked to a glycerol moiety (Figure 2). Depending on the cell and tissue types, CL may contain several acyl chain configurations [6]. For instance, CL with four linoleoyl species ($L_4$-CL or tetra linoleoyl CL) is normally abundant in highly oxidative tissues such as cardiac and skeletal muscles accounting for up to 70-80 % of total CL [4].

The biosynthesis of CL (Figure 3) is exclusively located to the mitochondria without the involvement of the endoplasmic reticulum. This multistep synthesis starts in the mtIM after the import of phosphatidic acid (PA) from the endoplasmic reticulum. The enzymatic activation of PA produces cytidine diphosphate-diacylglycerol (CDP-DAG), in a reaction catalyzed by CDP-DAG synthase (CDS). CDP-DAG is then converted to phosphatidylglycerol phosphate (PGP) by condensing with glycerol 3-phosphate (Gp). This step, which is catalyzed by PGP synthase (PGPS), is the committed step in synthesizing CL. Phosphatidylglycerol phosphate phosphatase (PGPP) then dephosphorylates PGP producing phosphatidylglycerol (PG), which ultimately condenses with another CDP-DAG molecule via CL synthase (CLS), a protein found in the inner leaflet of the mtIM facing the matrix, generating nascent (premature) CL [26, 27].

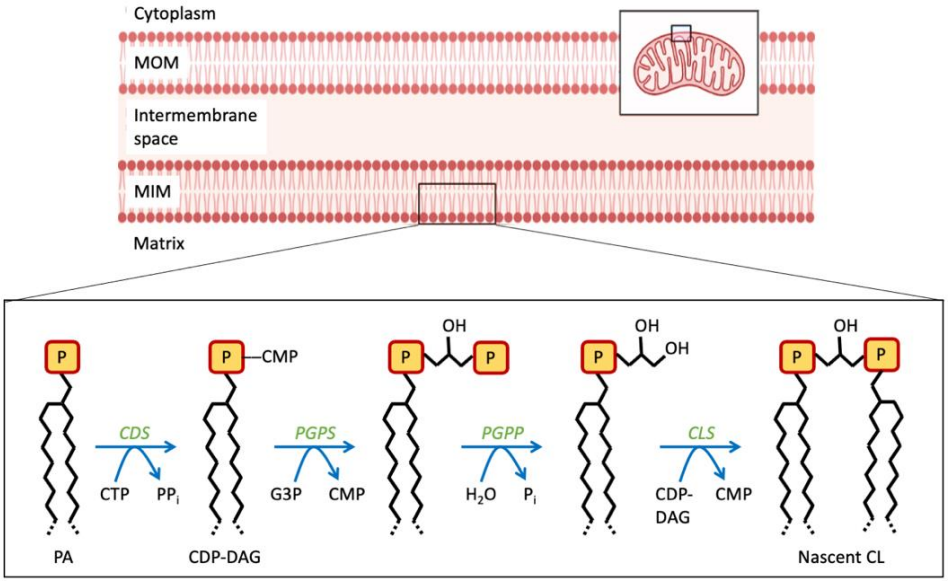


**Figure 3. *De novo* biosynthesis of CL**. The pathway of CL generation occurs in the mitochondrial inner membrane facing the mitochondrial matrix where a sequence of four enzymes converts phosphatidic acid to nascent CL molecule. Note that the tails of CL are arbitrary and do not reflect the actual length of the acyl chains which vary. CDS, CDP-DAG synthase; CLS, CL synthase; CMP, cytidine monophosphate; Gp (G3P in figure), glycerol 3-phosphate; PGPP, phosphatidylglycerol phosphate phosphatase; PGPS, phosphatidylglycerol phosphate synthase; $P_i$, inorganic phosphate; mtIM (MIM in figure), mitochondrial inner membrane; mtOM (MOM in figure), mitochondrial outer membrane.

Nascent cardiolipin is then remodeled by exchanging its fatty acyl moieties (Figure 4). Remodeling (Figure 4) starts by the deacylation of one acyl group by several phospholipases of the $PLA_2$ family [28, 29] producing monolysocardiolipin (MLCL). Tafazzin is a coenzyme A-independent acyltransferase that reacylates MLCL to form the mature CL molecule [30, 31]. It is noteworthy that Tafazzin is not the only CL remodeling enzyme as other coenzyme A-dependent acyltransferases can also acylate MLCL [32]. Disruption in remodeling cardiolipin would result in transforming MLCL into dilysocardiolipin (DLCL) by $PLA_2$ followed by the degradation of CL [26]. Mutations in the *TAZ* gene results in a reduction in the formation of mature forms of CL such as $L_4$-CL and an increase in the intermediate species with different acyl compositions (MLCL) [33]. This disrupts and increases the ratio of MLCL to $L_4$-CL [4, 8]. In fact, analysis of $L_4$-CL content in fibroblasts is a specific biochemical approach to detect this disorder [6]. In BTHS, MLCL accumulates due to impaired Tafazzin activity, which leads to abnormal mitochondrial structure with inefficient oxidative phosphorylation [22, 34-36].

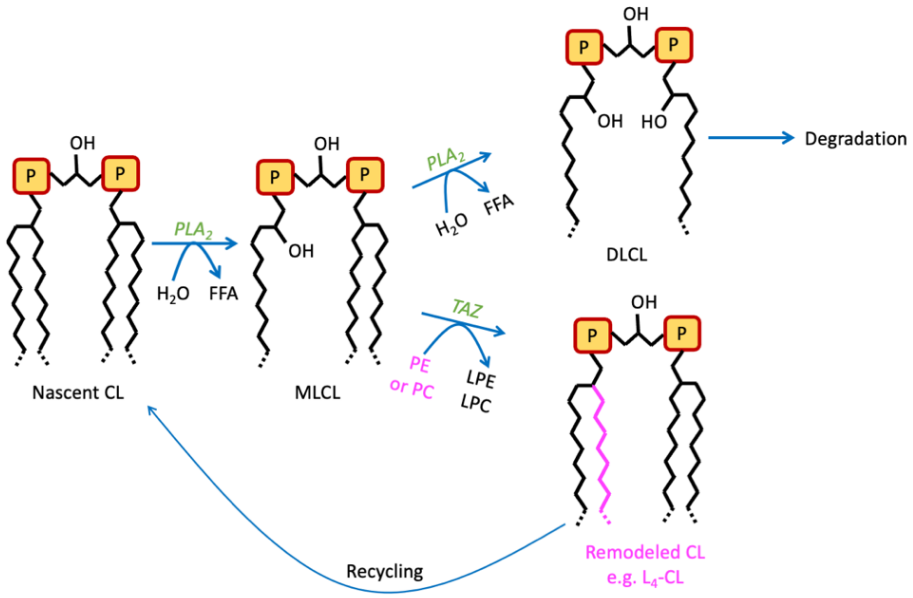


**Figure 4. Remodeling of CL.** CL is remodeled by the removal of its fatty acyl chains by phospholipase 2A and reinsertion of new fatty acyl moieties by different enzymes including tafazzin, to produce $L_4$-CL. Lyso-CL that is generated after the action of $PLA_2$ and left unremodeled is later degraded. Note that the tails of CL are arbitrary and do not reflect the actual length of the acyl chains which vary. FFA, free fatty acid; $L_4$-CL or tetra linoleoyl CL; LPC, lysophosphatidylcholine; LPE, lysophosphatidylethanolamine; MLCL, monolyso-CL; $PLA_2$, phospholipase A2.

## 2.2. CL and bioenergetics

Respiratory complexes reside in the mtIM and carry electrons from NADH or succinate ultimately to molecular oxygen, while pumping protons in the process. Reentry of protons down their concentration gradient results in a concomitant generation of ATP via ATP synthase. CL is both highly acidic and hydrophobic enabling it to interact favorably with the respiratory complexes embedded in the mtIM. Such an interaction is required for the optimal function of these proteins [37-39]. CL has been shown to interact with all components of the ETS. Indeed, specific binding sites for CL were observed in Complexes I, III and IV, which are required for the electron transfer from NADH [40-42]. Other *in vitro* studies have demonstrated strict dependence of respiratory Complex IV and ATP synthase on CL [43, 44]. Multiple molecules of CL were present in Complexes III and IV and the removal of these molecules led to the dissociation of the subunits and the loss of activity, indicating an essential role of CL in maintenance of structure and function of respiratory complexes [40]. Using molecular dynamics simulation and resolving of the crystal structure, CL was shown to spontaneously locate near the catalytic site of Complex III [45]. CL is found buried in the crevices of integral membrane proteins of the ETS, between the transmembrane helices [42]. Depending on the complex one or more CL molecules associate with it (Table 1). Those CL molecules are thought to glue complexes together and are required for their full functioning, including proton translocation [40, 41].

*In vivo*, respiratory complexes are rarely present as represented in biochemistry books, as individual entities; they are organized into supercomplexes termed respirasomes [46-51]. There are multiple conformations and compositions of respirasomes depending on the origin of mitochondria among other things [51, 52]. Respirasomes are thought to increase substrate channeling and increase efficiency of electron transfer. CL has been found to be instrumental in the formation and proper functioning of these supercomplexes [38, 53-55]. The tight binding of CL to Complex IV is important for the formation of Complex III and Complex IV tetramers [54]. Moreover, CL was demonstrated to be involved in the supramolecular organization of ATP synthase, carnitine palmitoyl-transferase, creatine phosphokinase, and other mtIM proteins [26, 56]. CL is therefore essential for the assembly of higher order mitochondrial complexes and supercomplexes. Mitochondria bioenergetics thus depend strongly on CL [40, 45, 57]. Mutations in the *TAZ* gene can result in decreased mitochondrial enzymatic activity, especially the respiration rate, lowering the optimum ATP production. This decrease in ATP synthesis is counteracted and compensated by increased mitochondrial content [19] and hypertrophic cardiomyopathy [58].

**Table 1. CL molecules in the solved crystal or cryo-EM structures of the respiratory complexes.**

| *Complex* | *Species* | *CL molecules* | *Refs.* |
|---|---|---|---|
| *I (NADH dehydrogenase)* | *Ovine heart* | *4* | *[59]* |
| *II (succinate dehydrogenase)* | *E. coli* | *1* | *[60]* |
| *III (cytochrome c oxidoreductase)* | *S. cerevisiae* | *1* | *[41, 61]* |
| *IV (cytochrome c oxidase)* | *Bovine heart* | *2* | *[62]* |

## 3. Clinical Manifestations

**Table 2. Clinical manifestations of Barth syndrome [4].**

| *Systems* | *Major (Signs/Symptoms)* | *Minor (Signs/Symptoms)* |
|---|---|---|
| Cardiovascular | • Dilated Cardiomyopathy<br>• Left Ventricular Non-Compaction<br>• Prolonged corrected QT interval | • Endocardial Fibroelastosis<br>• Ventricular arrhythmia/Sudden cardiac death<br>• Undulating Cardiomyopathy<br>• Hypertrophic Cardiomyopathy (rarely) |
| Hematological & Infectious | • Neutropenia<br>• Recurrent aphthous ulcers & sore gums<br>• Perianal dermatitis | • Recurrent bacterial infections<br>• Septicemia |
| Neuromuscular | • Delayed motor milestones<br>• Exercise intolerance<br>• Abnormal fatigability<br>• Proximal myopathy | |
| Neurological | • Mild learning disabilities<br>• Attention deficits | • Strokes (cardiac embolism) |
| Endocrine and Metabolic | • 3-methylglutaconic aciduria<br>• Constitutional bone delay with delayed bone age<br>• delayed puberty | • Hypercholesterolemia<br>• Hypoglycemia<br>• Lactic acidosis (often accompanies cardiac failure)<br>• Osteopenia |
| Dysmorphic features | • Deep-set eyes<br>• Large ears (older boys)<br>• Full cheeks | |

## 4. Diagnosis

The clinical diagnosis of BTHS had been based on the triad of neutropenia, cardiomyopathy, and high levels of 3-methylglutaconic acid (3-MGA) in urine and plasma. Cardiomyopathy is present in approximately 70 % of patients with BTHS, and many BTHS patients have a 5– to 20–fold increase in 3-MGA levels. However, some BTHS patients with cardiomyopathy were not diagnosed with BTHS even though they exhibited other clinical manifestations such as muscle weakness and growth delay, because these patients had normal 3-MGA levels in urine. Therefore, measuring 3-MGA as a tool for diagnosing BTHS is insufficient.

Measurement of the ration of MLCL to CL ratio in dried blood spot specimens is a better tool for the diagnosis of BTHS. It is critical to measure the ratio because many BTHS patients have normal levels of CL but an elevated MLCL:CL ratio. Thus, measuring the MLCL:CL ratio is considered a sensitive and 100 % specific test for the diagnosis of BTHS. Once elevated MLCL:CL ratio has been detected, sequencing the *TAZ* gene and detecting any mutations is considered as a final confirmatory test for the diagnosis of BTHS [36].

## 5. Disease Management

Many BTHS patients show responsiveness to drugs that are usually used to manage standard heart failure, including beta blockers, angiotensin converting enzyme inhibitors, digoxin and diuretics [63]. It is recommended to observe BTHS patients for any signs of ventricular arrhythmia or other symptoms such as syncope. Such findings would require additional testing and the placement of an implantable cardioverter-defibrillator should be considered [36].

Cardiac transplantation is another treatment protocol that has shown good results in general, even though it carries high pre-operative risks. In some boys with severe cardiac dysfunction, left ventricular assist devices have been used to aid them until a heart donor can be found. Using an assist device has major risks including infection caused by neutropenia, and strokes caused by clots forming in the chambers of the heart [4].

Neutropenia is usually treated with subcutaneous granulocyte colony-stimulating factor (G-CSF). The dose and frequency of the G-CSF injection varies depending on the severity of neutropenia, drug responses, and infections. The goal of using G-CSF is to increase the average count of neutrophils rather than cure neutropenia or normalize the neutrophil count. This treatment approach has resulted in noticeable improvements, as it reduces bacterial infections, lethargy, and mouth ulcers [4]. Neutropenia can also be managed with prophylactic antibiotics along with the G-CSF injections, which lower the risk of serious infections [64].

Many promising experimental therapeutic strategies to treat or even cure Barth syndrome are in progress, including lipid replacement therapy, which is the use of oral

supplements containing cellular phospholipids and antioxidants to treat various lipid deficiencies and syndromes [65]. These oral supplements are protected against oxidative damage during storage, ingestion, digestion, and absorption by the introduction of antioxidants, and they are protected from chemical enzymatic activity and bile by using protective molecules to bind to phospholipid micelles non-covalently [36, 66, 67]. Elamipretide, also known as Bendavia [68], is a synthetic lipophilic tetrapeptide experimental drug with the potential to treat Barth Syndrome. Elamipretide has the ability to penetrate cellular and mitochondrial membranes by diffusion where it gets associated with ionic phospholipids, especially cardiolipin in the mtIM. This peptide-lipid interaction stabilizes ETS complexes and results in increased ATP synthesis [69]. There are only a few clinical trials to test the efficacy and tolerability of elamipretide. The initial results are promising, as they showed actual improvement in ATP synthesis and positive effects on the left ventricular volumes [70]. However, further studies and tests are required to ensure the safety of this product on the long term. Moreover, *TAZ* gene replacement therapy, mitochondria-targeted antioxidants, induced pluripotent stem cells [7] have been used as possible treatment strategies.

In addition to the pharmacological and surgical treatment of the disease, a team of different specialists consisting of psychologists, speech and language therapists, educational support workers, as well as others, are needed for achieving a top-level management of the disease [1].

## 6. Conclusions and Future Directions

Barth syndrome is a rare X-linked disease where the *TAZ* gene is mutated rendering the protein product, Tafazzin, nonfunctional. Tafazzin is responsible for the CL remodeling, specific to the mtIM. CL was found to be associated with different mitochondrial proteins, especially those involved in oxidative phosphorylation and electron transfer pathway complexes. CL stabilizes these complexes and proteins which enhances ATP production and maintains the whole mitochondrial membrane. Barth syndrome patients struggle from cardiomyopathy, myopathy, neutropenia, and other symptoms as a result of this mutation. Currently a known cure or a complete treatment for Barth syndrome is lacking. However, multiple strides have been made in disease management using varying techniques and treatment plans. Clinical studies and basic mitochondrial research are ongoing to find a way to cure Barth syndrome using novel drugs, gene therapy, lipid replacement therapy, and others.

## Abbreviations

| | |
|---|---|
| 3-MGA | 3-methylglutaconic acid |
| BTHS | Barth syndrome |
| CDP-DAG | cytidine diphosphate-diacylglycerol |
| CLS | CL synthase |
| CDS | CDP-DAG synthase |
| CL | Cardiolipin |
| DLCL | dilyso-CL |
| ETS | electron transfer system |
| FFA | free fatty acid |
| Gp | glycerol 3-phosphate |
| G-CSF | granulocyte colony-stimulating factor |
| mtIM | mitochondrial inner membrane |
| $L_4$-CL | tetra linoleoyl CL |
| LPC | lysophosphatidylcholine |
| LPE | lysophosphatidylethanolamine |
| MLCL | monolyso-CL |
| PA | phosphatidic acid |
| PC | phosphatidylcholine |
| PE | phosphatidylethanolamine |
| PGP | phosphatidylglycerol phosphate |
| PFPP | phosphatidylglycerol phosphate phosphatase |
| PFPS | phosphatidylglycerol phosphate synthase |
| $PLA_2$ | phospholipase A2 |
| *TAZ* | Tafazzin gene |

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