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Permalink

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Journal

Gene, 726(Pediatr Cardiol 18 1997)

ISSN

0378-1119

Authors

Garlid, Anders O
Schaffer, Calvin T
Kim, Jaewoo
[et al.](#)

Publication Date

2020-02-01

DOI

10.1016/j.gene.2019.144148

Peer reviewed



Published in final edited form as:

Gene. 2020 February 05; 726: 144148. doi:10.1016/j.gene.2019.144148.

TAZ encodes tafazzin, a transacylase essential for cardiolipin formation and central to the etiology of Barth syndrome

Anders O. Garlid^{1,2}, Calvin T. Schaffer^{1,2}, Jaewoo Kim^{1,2}, Hirsh Bhatt^{1,2}, Vladimir Guevara-Gonzalez^{1,5}, Peipei Ping^{1,2,3,4,6,†}

¹Cardiovascular Data Science Training Program at UCLA, University of California at Los Angeles, CA 90095, USA

²Department of Physiology, University of California at Los Angeles, CA 90095, USA

³Department of Medicine/Cardiology, University of California at Los Angeles, CA 90095, USA

⁴Department of Bioinformatics, University of California at Los Angeles, CA 90095, USA

⁵Department of Mathematics, University of California at Los Angeles, CA 90095, USA

⁶Scalable Analytics Institute (SCAi), University of California at Los Angeles, CA 90095, USA

Abstract

Tafazzin, which is encoded by the *TAZ* gene, catalyzes transacylation to form mature cardiolipin and shows preference for the transfer of a linoleic acid (LA) group from phosphatidylcholine (PC) to monolysocardiolipin (MLCL) with influence from mitochondrial membrane curvature. The protein contains domains and motifs involved in targeting, anchoring, and an active site for transacylase activity. Tafazzin activity affects many aspects of mitochondrial structure and function, including that of the electron transport chain, fission-fusion, as well as apoptotic signaling. *TAZ* mutations are implicated in Barth syndrome, an underdiagnosed and devastating disease that primarily affects male pediatric patients with a broad spectrum of disease pathologies that impact the cardiovascular, neuromuscular, metabolic, and hematologic systems.

[†]To Whom Correspondence Should be Addressed: Peipei Ping, Ph.D., FAHA, FISHR, UCLA David Geffen School of Medicine, Departments of Physiology, Medicine (Cardiology) and Bioinformatics, Suite 1-609 MRL Building, 675 Charles E. Young Dr. South, Los Angeles, CA 90095-1760, Phone: 310-267-5624, ppingucla@gmail.com.

CRediT (Contributor Roles Taxonomy) Document

Anders O. Garlid: Conceptualization; Data curation; Formal analysis; Methodology; Project administration; Software; Supervision; Validation; Roles/Writing - original draft; Writing - review & editing. Investigation; Visualization; Roles/Writing - original draft; Writing - review & editing.

Calvin T. Schaffer: Data curation; Roles/Writing - original draft.

Jaewoo Kim: Data curation; Roles/Writing - original draft.

Hirsh Bhatt: Data curation; Roles/Writing - original draft.

Vladimir Guevara-Gonzalez: Software; Visualization.

Peipei Ping: Conceptualization; Funding acquisition; Project administration; Resources; Supervision.

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Competing Interests

The authors have no competing interests to declare.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Keywords

mitochondrial biology; rare mitochondrial diseases; apoptosis; clinical case reports

1. Introduction

TAZ, also known as *G4.5*, is a 10kb gene located at position 28 on the q arm of chromosome X within a gene-rich, 450kb cluster of 13-16 small genes with CpG islands initially identified by Bione *et al.* as potential candidates for involvement in neuromuscular and cardiovascular disorders (Bione *et al.*, 1993; Bione *et al.*, 1996). *TAZ* encodes the transacylase protein tafazzin (Table 1), so named by Bione *et al.* based on a masochistic comic character named Tafazzi from an Italian sports show, apparently due to the difficulty they encountered in the original identification and characterization of this protein (Bione *et al.*, 1996). Tafazzin, located in the inner and outer mitochondrial membranes (IMM and OMM), acts as an acyl-specific transacylase that is essential to lipid metabolism through cardiolipin (CL) remodeling. CL remodeling, in turn, is essential for mitochondrial respiratory chain homeostasis, and disruptions to this process as a result of *TAZ* mutations have been shown to be a major cause of the complex, multi-system Barth syndrome. Mutations in the *TAZ* gene are associated with severe cardiovascular defects observed in Barth syndrome (BTHS), including endocardial fibroelastosis (EFE), X-linked dilated cardiomyopathy 3A (CMD3A), and left ventricular noncompaction (LVNC). As such, the gene is known by several aliases, including BTHS, EFE and EFE2, CMD3A, and LVNCX (Table 1). Due to unfortunate naming conventions, the *TAZ* gene and its tafazzin protein product have been confused in the literature with the *TAZ protein*, and WWTR1 gene, which are associated with various cancers (NCBI, 2019). *TAZ* and tafazzin are not known to have any role in cancer. To date, there is no cure for Barth syndrome, and treatments for tafazzin deficiencies have focused on symptom-based management. Deeper investigation of *TAZ*, tafazzin, and cardiolipin is necessary to increase our collective understanding of mitochondrial biology and may help find treatments for Barth syndrome and mitochondrial myopathies.

2. Structure

Tafazzin is part of a superfamily of acyltransferases based on conserved regions and motifs identified through sequence alignment with other acyltransferase proteins involved in phospholipid biosynthesis (Neuwald, 1997; Acehan *et al.*, 2007). The crystal structure of tafazzin has not been determined by x-ray crystallography; the closest homologous protein is plant glycerol-3-phosphate acyltransferase (G3PAT) from *Cucurbita moscata* and *Spinacea oleracea* (PDB ID: 1IUQ) (Tamada *et al.*, 2004), which has just 18.1% sequence identity with human tafazzin (Waterhouse *et al.*, 2018). The half-life of tafazzin in mammalian cells is much shorter than that of many other mitochondrial proteins at only 3-6 hours (Xu *et al.*, 2015); the median half-life for mouse mitochondrial proteins is 17.2 days in the heart and 4.26 days in the liver (Kim *et al.*, 2012). This rapid turnover rate has likely contributed to the difficulty in elucidating the structure of tafazzin or acquiring a detailed understanding of its post-translational modifications (PTMs) from mass spectrometry data.

2.1. Tafazzin active site.

The putative phospholipid-binding site of human tafazzin is a 57 amino acid cleft with two open ends and a stretch of conserved, positively charged residues, based on homology modeling using ALAdeGAP for improved amino acid sequence alignment (Hijikata et al., 2011; Hijikata et al., 2015). Tafazzin and related hydrolases contain a conserved histidine residue required for their enzymatic action (Neuwald, 1997). In human tafazzin, His-69 (His-77 in yeast) and Asp-74 form part of a conserved HX₄D motif seen in acyltransferases composed of a histidine (His) and aspartic acid (Asp) separated by any 4 amino acids (X₄) (Heath and Rock, 1998; Xu et al., 2006; Abe et al., 2016). The HX₄D motif facilitates the Asp-His dyad mechanism seen commonly in serine proteases, whereby Asp raises the pK_a of His and aids the deprotonation of a hydroxyl group (Tang et al., 2018).

2.2. Mitochondrial localization and membrane anchoring.

Mitochondrial localization and membrane anchoring domains in tafazzin are of critical importance to its role in cardiolipin remodeling. In the H9c2 rat cardiomyocyte cell line, *TAZ* encodes two peptides external to the active site of the tafazzin protein that act independently to direct it to mitochondria (Dinca et al., 2018). The first of these sequences, encoded in exon 3 and spanning residues 84-95 on the tafazzin protein, targets exclusively to mitochondria, while the second, encoded in exon 7/8 and forming residues 185-220, also targets other cytosolic compartments (Dinca et al., 2018). The yeast *TAZI* orthologue is homologous to human *TAZ* and has been used extensively to study the structure of tafazzin, its function, and in modeling Barth syndrome (Vaz et al., 2003; Gu et al., 2004; Ma et al., 2004; Claypool et al., 2006). In yeast, tafazzin has been shown to localize to membrane leaflets facing the intermembrane space (IMS) between the IMM and OMM, where it associates peripherally due to its lack of a transmembrane domain (Gawrisch, 2012; Abe et al., 2016). A hydrophobic sequence from residues 215-232 in yeast tafazzin confers its characteristic interfacial anchoring behavior in both the IMM and OMM (Herndon et al., 2013). Together, the translocase of the outer membrane (TOM) and the translocase of the inner membrane (TIM) facilitate tafazzin's movement across and insertion into the outer membrane, as well as its anchoring to inner membrane regions of intermediate density (Herndon et al., 2013).

2.3. *TAZ* mutations and effects on tafazzin structure.

In characterizing the mutations of a family of patients with Barth syndrome, many unique forms of tafazzin were identified based on differential splicing events, ranging in length from 129 to 292 amino acids and affecting regions throughout the protein (Bione et al., 1996). Many of the shorter forms of the protein lack a 30-residue hydrophobic N-terminus thought to contain a localization signal sequence, as well as modifications to the hydrophilic center of the protein in a 71 amino acid domain profuse with glycine and glutamic acid (Bione et al., 1996). Mutations within the localization region result in mistargeting that directs the protein into inner membrane leaflets facing the matrix, rather than facing the IMS (Herndon et al., 2013). Whited *et al.* categorized *TAZ* mutations into 7 functional classes based on the pathogenic loss-of-function mechanisms of each mutation (Whited et al., 2013). The largest class of mutations, Class 1, contains frameshift and splice-site mutations

along the length of the gene. Class 2 and 3 mutations are both found in the membrane anchor domain: Class 2 mutations, including V224R, V223D, and I226P variants, represent pleiotropic biochemical defects and often result in mitochondrial mistargeting, while Class 3 mutations (G230R) affect tafazzin macromolecular assembly. Class 4 mutations are composed primarily of missense mutations resulting in catalytically inactive tafazzin and Class 5 mutations, including L90P and N109V, encode hypomorphic alleles which retain transacylase activity. Class 6 mutations, including A88R and L148H, have folding and assembly defects, and Class 7 mutations result in temperature sensitive proteins that undergo activity loss before degradation. There is limited knowledge regarding a link between the different classes of *TAZ* mutations and disease severity. Whether tafazzin is rendered catalytically inactive, mistargeted, or incapable of membrane anchoring, there does not appear to be a clear distinction between phenotypic presentations of patients with different mutations. The diverse nature of *TAZ* mutations is clearly demonstrated in the expansive database maintained and regularly updated by the Barth Syndrome Foundation, which actively collects new data from healthcare professionals on both pathogenic and benign variants (<https://barthsyndrome.org/research/tazdatabase.html>). Mutations along the length of the *TAZ* gene, their frequency, and their pathogenicity (benign, pathogenic, or unknown effect) are depicted in Figure 1. Exonic, pathogenic variants along the length of the tafazzin protein, their frequency, and the type of genetic mutation from which they arise (deletion, frame shift, point mutation, or stop codon) are represented in Figure 2, along with the primary protein domains extracted from the literature.

3. Function

Tafazzin plays a critical role in cardiolipin remodeling, limits the structural diversity of CL molecular species, and restricts CL composition to two fatty acids, typically linoleic and oleic acids (Schlame, 2008). Tafazzin displays a preference for the transfer of linoleic acid (LA) from phosphatidylcholine (PC) to monolysocardiolipin (MLCL) and may be affected by and contribute to the negative curvature of the IMM and OMM (Schlame et al., 2017). Through its effects on CL, tafazzin impacts many aspects of mitochondrial structure-function, including inner membrane curvature, oxidative phosphorylation (OXPHOS), supercomplex formation, oxidative stress repair, apoptosis, and fission and fusion (Haines and Dencher, 2002; Schug and Gottlieb, 2009; Baile et al., 2014; Vernon et al., 2014; Frohman, 2015).

3.1. Transacylase activity.

Tafazzin is an acyl-specific transferase that catalyzes reversible acyl transfer reactions between phospholipids and lysophospholipids in a CoA-independent manner, playing a critical role in the deacylation-reacylation cycle of cardiolipin (Xu et al., 2006; Epanand et al., 2015; Schlame et al., 2017). Generally, transacylases exhibit phospholipase activity and catalyze acylation and deacylation through a free enzyme acyl intermediate. Tafazzin, on the other hand, does not exhibit phospholipase activity, nor does it utilize the free enzyme acyl intermediate mechanism; it acylates and re-acylates, but deacylation occurs independently of tafazzin (Xu et al., 2006). After *de novo* synthesis of CL from phosphatidylglycerol by CL synthase (Crd1 in yeast, hCLS1 in humans) (Chen et al., 2006; Ye et al., 2016), the

remodeling process is initiated with cardiolipin deacylation to form MLCL by the cardiolipin specific phospholipase Cld1 in yeast (Beranek et al., 2009) or the calcium-independent phospholipase A2 (iPLA2) in humans (Mancuso et al., 2007a; Mancuso et al., 2007b; Malhotra et al., 2009; Yoda et al., 2010; Hsu et al., 2013). In order for MLCL produced by Cld1 to be exposed to tafazzin in the IMS, it must be transported through a different and unknown remodeling step (Baile et al., 2013). In mammals, tafazzin functions along with other enzymes to achieve CL remodeling, including MLCL acyltransferase (MLCLAT), acyl-CoA:lysocardiolipin acyltransferase (ALCAT), and phospholipase (Ye et al., 2016). Remodeling by tafazzin adds an acyl residue to immature CL, most frequently in the form of a linoleoyl residue in humans (Houtkooper et al., 2009b; Minkler and Hoppel, 2010). Tafazzin reacylates MLCL in a single-step acyl group transfer reaction (Figure 3) from a variety of phospholipids (PL), including CL, PC, phosphatidylethanolamine (PE), and phosphatidic acid (PA). Thus, tafazzin effectively acts as a shuttle for specific acyl groups between different phospholipids (Xu et al., 2006; Schlame, 2013).

3.2. Acyl specificity and sensing curvature.

Tafazzin shows a clear preference for the transfer of an LA group from PC to MLCL to form mature CL (Schlame et al., 2017). This remodeling process converts cardiolipin into a mature composition that contains a predominance of tetralinoleoyl moieties. This results in an enrichment of tetralinoleoyl-cardiolipin (CL₄) in the IMM (Houtkooper et al., 2009b). Indeed, Xu *et al.* report that, in *Drosophila melanogaster*, tafazzin can catalyze acyl transfer using multiple substrates, yet has a preference for the transfer of linoleoyl groups from PC to MLCL at a rate 10 times greater than that of oleoyl groups and twenty times greater than that of arachidonoyl groups, indicating a clear predilection for CL and PC substrates (Xu et al., 2006). Conflicting explanations for this preference have been proposed, namely that tafazzin has an inherent enzymatic preference for specific acyl residues, or that it acts on the basis of energy minimization and is influenced by the surrounding mitochondrial microenvironment. Abe *et al.* propose that tafazzin exhibits acyl specificity for the PC to MLCL reaction, and that its function is predominately centered on the transacylation of unsaturated acyl PC to MLCL under any conditions (Abe et al., 2016). Schlame *et al.*, on the other hand, propose the ‘thermodynamic remodeling’ hypothesis, whereby a perturbation of the lipid bilayer state and the physical properties of the lipid membrane determines tafazzin’s preference for specific acyl groups (Schlame et al., 2012; Epand et al., 2015). Schlame *et al.* propose that alternative phospholipases and acyltransferases (MLCAT and ALCAT), as well as the thermodynamic properties of lipids, provide the acyl specificity in CL remodeling and that tafazzin itself has no kinetic properties that suggest any sort of acyl-specificity. This mechanism proposes that since CL formation by tafazzin is reversible and has a minimal overall free energy, tafazzin’s role is to non-specifically transfer acyl groups among phospholipids to achieve optimal lipid composition and reduce the impact of membrane constraints (Schlame et al., 2012; Schlame et al., 2017).

According to the model proposed by Schlame *et al.* tafazzin specificity ultimately depends on the physical characteristics and packing properties of the lipid domain, including structural order and state. In *D. melanogaster*, tafazzin requires phospholipids that have a propensity to form non-bilayer phases such as HII phase, which is characterized by its

negative curvature, disorganized acyl chains, and low packing order (Schlame et al., 2012; Schlame et al., 2017). Stable lipid bilayers were found to have the lowest rate of reaction by tafazzin, while lipids in the hexagonal or micellar phases, which were characterized by packing order changes due to positive or negative curvature, had significantly higher reaction rates. In addition to the rate of reaction, curvature was also shown to determine the specificity of acyl transfer (Erand et al., 2015). The cristae of the IMM have negatively curved lipid monolayers and a predominance of phospholipids with small polar head groups, such as CL, and asymmetric, unsaturated hydrocarbon chains, such as linoleic acid. CL and linoleic acid specificity may thus be driven by curvature segregation of phospholipids based on physical properties of the lipid domains, which causes tafazzin to transacylate phospholipids that are located in negatively curved monolayers (Gawrisch, 2012; Schlame et al., 2012). In *Saccharomyces cerevisiae*, however, Abe *et al.* determined that tafazzin can efficiently catalyze a transacylation reaction even in a highly ordered lipid bilayer domain. Further, they posit that tafazzin has a unique acyl chain specificity for the PC to MLCL reaction in which tafazzin acts selectively to transfer PC's *sn*-2 acyl chain to MLCL's *sn*-1 and *sn*-2 positions. They determined that these reactions can occur in any environment, regardless of packing order and thermodynamic considerations (Abe et al., 2016). These studies illustrate the propensity of tafazzin to transfer a linoleoyl group from PC to MLCL; however, more research into the specific mechanisms is required to fully understand the process and specificity of tafazzin's actions. Further experiments with NMR analysis by groups such as Erand *et al.* may aid in elucidating these mechanisms due to its ability to probe curvature properties of lipid assemblies and observe structures with minor isotropic resonance (Erand et al., 2015).

3.3. Tafazzin and cardiolipin in mitochondrial structure and function.

Cardiolipin, modified by tafazzin, constitutes 13 - 20% of the total phospholipid mass and exhibits a cone-shaped structure that facilitates its distribution into mitochondrial cristae (Daum and Vance, 1997; Vernon et al., 2014). In the tafazzin-impaired fibroblasts of Barth syndrome patients, a greater proportion of saturated acyl chain substitution compromises this cone-shaped structure, and CL is heavily depleted with a concurrent accumulation of MLCL species (Oemer et al., 2018). CL assists in various aspects of OXPHOS, supporting the stability and function of the mitochondrial respiratory chain complexes through linkages between acyl chains (Houtkooper et al., 2009b). CL binds selectively to the c-rings of ATP synthase, which is required for the function and assembly of the ATP synthase. It also smooths the rotation (Mehdipour and Hummer, 2016) and facilitates dimerization for efficient ATP synthesis (Acehan et al., 2011). The structural properties of CL and its pK above 8 facilitate trapping proteins in the IMS. This is thought to achieve proton localization for ATP synthase function and minimization of pH fluctuations (Haines and Dencher, 2002). CL also interacts with other proteins such as the ATP/ADP translocase, pyruvate carrier, and carnitine carrier, assisted by glycerol bridges which enable flexibility for interaction with diverse surface shapes.

The lipid-to-protein mass ratio of OXPHOS complexes located in the mitochondrial cristae is 22:78 (Lotan and Nicolson, 1981), meaning that each complex is surrounded by just 40-400 lipid molecules (Xu et al., 2019). The molecular packing of lipids in a bilayer with

such a high protein density causes elastic stress on the curvature of the membrane (Brown, 2017). Tafazzin remodeling is triggered by OXPHOS complex assembly so as to mitigate this stress and stabilize the membrane by generating CL species with reduced free energy (Xu et al., 2019). The OXPHOS complexes I, III, and IV also form supercomplexes within the mitochondrial cristae such as the I₁III₂IV_{n=1-4} “respirasome” (Schagger and Pfeiffer, 2000; Schagger, 2001; Stuart, 2008; Gu et al., 2016). CL is directly involved in the formation and maintenance of supercomplexes, providing structural support for trimer- and tetramerization (Zhang et al., 2002; Mileykovskaya and Dowhan, 2014). Furthermore, supercomplexes are disrupted and destabilized in Barth syndrome patients due to the loss of mature CL from the IMM (McKenzie et al., 2006).

Cardiolipin’s intimate association with the electron transport chain brings it into close proximity with reactive oxygen species (ROS) generated by OXPHOS complexes and which have been shown to target CL. The proximity and its enrichment in long-chain polyunsaturated fatty acid (PUFA) chains make CL susceptible to the attack. In the process of lipid peroxidation, highly reactive oxygen free radicals oxidize the fatty acid chains of CL to form lipid peroxides (Paradies et al., 2002). Oxidative damage leads to a loss of functional CL, a basis for mitochondrial dysfunction (Lesnefsky and Hoppel, 2008; Shi, 2010). CL remodeling removes and replaces acyl chains damaged by oxidative stress and is thought to play a key role in oxidative stress repair mechanisms (Baile et al., 2014) and the recovery of the normal oxidative functions of mitochondria (Baile et al., 2013). Aside from its damaging effects, ROS is also critical in mitochondrial and intracellular signaling, particularly in the context of cardioprotection from ischemia-reperfusion injury (Garlid, 2000). Phospholipids in the bilayer, such as cardiolipin, can be oxidized to form hydroperoxy fatty acids, which are hypothesized to carry the cardioprotective signal from mitochondria (Garlid et al., 2013).

CL forms membrane domains localized to negatively curved regions and induced by mitochondrial creatine kinase (mtCK) and cytochrome *c* that play critical roles in energy transfer, apoptosis, and functional recovery from ischemic insult (Laclau et al., 2001; Epanand et al., 2007; Renner and Weibel, 2011). The microdomains occur at contact sites where the IMS narrows such that the IMM and OMM are positioned in close proximity to one another (Epanand et al., 2007; Renner and Weibel, 2011; Pennington et al., 2018). The IMS at these contact sites is replete with mtCK, which induces their formation, recruits CL, and provides stabilization (Speer et al., 2005; Epanand et al., 2007). Mature tetralinoleoyl-CL species generated by tafazzin remodeling are required for the formation of these domains and CL₄ depletion disrupts their formation, which may explain the mitochondrial impairment observed in Barth syndrome and cardiac ischemia-reperfusion injury (Sparagna et al., 2007; Paradies et al., 2015; Pennington et al., 2018). Further, mtCK is functionally coupled to adenine nucleotide translocase (ANT) in the IMM to facilitate efficient energy transfer by shuttling high-energy phosphates from the mitochondria to the cytosol through the voltage-dependent anion channel (VDAC) of the outer membrane (Laclau et al., 2001; Saks et al., 2006). During ischemia, for example, this IMS structure-function is disrupted, reducing the functional coupling of mtCK and ANT and increasing the permeability of the OMM to ADP, thereby limiting energy transfer processes and exacerbating damage from an ischemic event such as a heart attack (Laclau et al., 2001). The cardioprotective ischemic preconditioning (IPC) protocol opens the mitochondrial ATP-sensitive K⁺-channel (mitoK_{ATP}), which causes

matrix swelling and results in preservation of IMS volume, contact sites, and tight coupling between mtCK and ANT (Garlid, 2000; Laclau et al., 2001; Costa and Garlid, 2009). CL clustering at these contact sites is dependent on the octameric structure of mtCK, which readily binds to anionic phospholipids and may mediate intermembrane contact by binding to VDAC on the OMM (Epand et al., 2007).

Cardiolipin mediates apoptosis through its interactions with members of the Bcl-2 family, caspases, Bid, Bax, and Bak, with a direct impact on the apoptotic signaling cascade (Schug and Gottlieb, 2009). The total level of CL as well as the oxidative state of its acyl side chains directly impacts apoptosis by regulating cytochrome *c* mobilization; decreased CL content or oxidation of the normally unsaturated acyl side chains releases cytochrome *c* from the membrane (Schug and Gottlieb, 2009). This can be prevented with antioxidants (Petrosillo et al., 2003; Tyurina et al., 2006) and by the presence of mitochondrial redox proteins (Ran et al., 2004; Enoksson et al., 2005). Therefore, CL remodeling by tafazzin restores cytochrome *c* affinity for CL and its localization in the membrane by replacing oxidized fatty acids with non-oxidized acyl groups (Ye et al., 2016). Mobilized cytochrome *c* released from the mitochondrial membrane activates caspases 8 and 9, which cleave Bid to produce its truncated and active form, tBid (Kantari and Walczak, 2011). Once recruited by mitochondrial carrier homologue 2 (MTCH2), tBid activates apoptosis via Bax and Bak activation (Katz et al., 2012). Caspases 8 and 9, activate caspase 3, which drives apoptosis and inhibits ROS production (Brentnall et al., 2013). The apoptotic pathway is further amplified by this ROS inhibition, as it is a ROS signal that is responsible for protective mitoK_{ATP} opening that blocks the mitochondrial permeability transition (MPT) and prevents apoptosis (Costa and Garlid, 2008; Garlid et al., 2013).

Additionally, through interactions with both inner and outer mitochondrial membranes and proteins such as the GTPase Opa1, CL plays an important role in mitochondrial fission, fusion, and mitophagy (Frohman, 2015; Hsu et al., 2015). *TAZ* deficiency reduces the generation of mitophagosomes and prevents initiation of mitophagy, further exacerbating the already reduced function of mitochondrial populations in *TAZ*-deficient organisms (Hsu et al., 2015). Under mitochondria-stress conditions, CL has been shown to promote mitochondrial fusion and membrane tethering with L-Opa1 and *trans*-Opa1, respectively, further illustrating its multifunctional importance in mitochondrial form and function (Ban et al., 2017).

4. Clinical Significance: Barth syndrome

Considering its critical role in the construction and maintenance of the IMM, it is of little surprise that *TAZ* has been implicated in a broad spectrum of disease pathologies that impact the cardiovascular, neuromuscular, metabolic, and hematologic systems. *TAZ* mutations are specifically associated with the multi-faceted Barth syndrome. An X-linked autosomal recessive disorder also known as 3-Methylglutaconic Aciduria Type II (3MGA2) (Barth et al., 1983; Aprikyan and Khuchua, 2013; Clarke et al., 2013). Characterized initially by Barth *et al.* in 1983 (Barth et al., 1983) as a uniformly lethal disease that affects only males, it has now been found that the age distribution ranges between 0 to 49 years, and symptoms peak around puberty (Barth et al., 2004). At least one female patient with BTHS has been

identified (Cosson et al., 2012). The Barth Syndrome Foundation reports that 151 living Barth patients have been identified up to 2012 and 10 new patients are diagnosed each year in the United States with no apparent racial or ethnic predilections. BTHS is estimated to appear in 1 out of every 300,000 to 400,000 live births, although predictions have suggested that the prevalence is actually closer to 1 out of every 140,000 live births as a result of the generally accepted notion that the disease is underdiagnosed (Cantlay et al., 1999; Barth Syndrome Foundation, 2019). In an effort to impose structure on otherwise unstructured clinical language contained in clinical case reports on BTHS (among other diseases), Caufield *et al.* extracted metadata from the reports and characterized patient symptomology using codes from the International Statistical Classification of Diseases and Related Health Problems (ICD-10) (Caufield et al., 2018b; Caufield et al., 2018a). The MitoCases platform (<http://mitocases.org/>) houses data on mitochondrial diseases, including Barth syndrome. Figure 4 displays the distribution of 997 instances of 206 unique ICD-10 codes represented across 54 clinical case reports covering 133 patients with BTHS, including top symptoms overall as well as top cardiovascular symptoms. Classifying Barth syndrome symptomology using ICD-10 codes has the potential to facilitate a greater understanding of the disease, its phenotypes, as well as to aid in diagnosis and treatment.

BTHS diagnosis and treatment is complicated and frequently delayed due to the complexity and variation of disease presentation. Early cardiomyopathy and hypertrophy combined with neutropenia (a low neutrophil count in the blood) is a hallmark of the disease, but confirmation of the diagnosis typically relies on genetic analysis of *TAZ*. Over 160 mutations or errors in the *TAZ* gene have been identified in BTHS patients, with a wide variety of onset, progression, and severity (Aprikyan and Khuchua, 2013). 3-methylglutaconic acid (3-MGA) and CL content levels are often used to identify BTHS, but they are not always a reliable indicator, which led some to propose using an HPLC-tandem mass spectrometry blood spot assay to measure the ratio of MLCL to CL₄. Although indirect, this highly specific biochemical measure of tafazzin function has the potential to provide a clinically valid method for BTHS diagnosis (Kulik et al., 2008; Houtkooper et al., 2009a; Bowron et al., 2015; Thompson et al., 2016). Combining biochemical analyses with physical tests, such as the 6-minute walk test (6MWT), may allow clinicians to determine the extent of the musculoskeletal impact and cardiac function in patients who survive infancy and those with unknown mitochondrial deficiencies. A combination of these procedures may help to improve diagnostic abilities and shape patient-specific treatment plans (Thompson et al., 2016).

4.1 Cardiovascular pathology.

Cardiomyopathy is a major characteristic of BTHS resulting from *TAZ* mutations. *TAZ* mutations lead to altered acyl chain composition and lipid peroxidation, and this can result in a failure of the sarcomeric action required to generate a sufficient power stroke. Disruption of the uniform contraction of sarcomeres can severely weaken the tissue, enlarge the left ventricular chamber, result in partial or incomplete contraction, and lead to decreased ejection volume. This results in the gradual thinning of the ventricular wall, stretching and dilation of cardiac chambers, and a cardiomyopathic phenotype of Barth syndrome, characterized by a weakened heart and diminished contractility (Barth et al., 2004; Ikon and

Ryan, 2017). Among all patients, about 95% exhibited a history of cardiomyopathy, with 41.5% of all diagnosed cardiomyopathies occurring from birth to one month of age. Furthermore, statistical analysis revealed that cardiac function of patients declines over time (Roberts et al., 2012). Contrary to ATP depletion, Wang *et al.* suggest ROS as the main cause of cardiomyocyte dysfunction and cardiovascular impairments such as defective sarcomere assembly and contractile stress (Wang et al., 2014). The typical approach to treating the cardiovascular symptoms of Barth syndrome is to follow the treatment paradigm for heart failure. This includes: 1) diuretics for fluid retention (e.g., spironolactone or furosemide), 2) angiotensin-converting enzyme (ACE) inhibitors for vasodilation to reduce afterload (e.g., captopril), 3) positive inotropes to increase contractility and as an antiarrhythmic (e.g., digoxin), and 4) beta blockers to reduce heart rate (e.g., propranolol, carvedilol). Regular echocardiography is used to monitor cardiovascular function and ejection fraction (McCanta et al., 2008; Masarone et al., 2017). Severe forms of cardiac symptoms in BTHS patients necessitate heart transplantation. Spencer *et al.* reported nine out of 73 (12%) patients referred to the BTHS Registry (<https://barthsyndromeregistry.patientcrossroads.org>) who have undergone cardiac transplantation are alive at the last update (Roberts et al., 2012; Clarke et al., 2013). Transplantation is generally successful (Clarke et al., 2013); among four BTHS patients described in Mangat *et al.*, one developed a severe infection but they did not show an increased rate of rejection and rated their quality of life as good (Ronghe et al., 2001; Mangat et al., 2007).

Cardiomyopathy in BTHS includes dilated cardiomyopathy (DCM) and left ventricular noncompaction (LVNC) (Barth et al., 2004). DCM is a specific type of cardiomyopathy characterized by an enlarged heart that is limited in function due to its inability to contract and pump blood efficiently (Araco et al., 2017; Soares et al., 2017). A patient with BTHS resulting from a c.83T>A mutation in tafazzin exhibited DCM with an ejection fraction of 30%, providing a direct association between the gene and DCM (Zapala et al., 2015). LVNC is a condition that exhibits prominent trabeculations and deep intertrabecular recesses in the left ventricle that resemble a spongy structure on the ventricular wall (Shemisa et al., 2013). One such case involves a family of 6 affected members that presented with LVNC with BTHS due to *TAZ* mutations (Bleyl et al., 1997). Isolated noncompaction of the ventricular myocardium (INVM) has also been found to affect the right ventricle and the interventricular septum (Bleyl et al., 1997; Barth et al., 2004). Despite the general occurrence of cardiomyopathy, there have been instances of BTHS caused by *TAZ* mutations with mild or late-onset cardiac involvement, as seen in Woiewodski *et al.* and again in Rigaud *et al.* Each discuss a cohort of BTHS patients exhibiting varying levels of cardiomyopathy, including two infantile patients who did not present with cardiomyopathy at the time of diagnosis (Woiewodski et al., 2017), another infantile patient whose autopsy revealed no cardiomyopathy, and one 12-year-old patient with no manifestation of cardiomyopathy (Rigaud et al., 2013). There is no clear structural or functional reason for the relatively mild presentations of certain patients, nor a direct mechanistic link between different mutations and disease presentations, representing an intriguing area of research necessary to glean a greater understanding of tafazzin and its role in disease.

4.2. Musculoskeletal pathology.

Although skeletal myopathy is often a typical characteristic of patients with disease-causing *TAZ* mutations, it manifests itself in a wide range of symptoms from nonexistent to severe. One of the most common musculoskeletal symptoms in BTHS patients is general and localized weakness. This includes overt muscle weakness and increased exertional fatigue due to skeletal myopathy and exaggerated by the cardiovascular complications associated with Barth syndrome (Spencer et al., 2011). Hypotonia, fatigue, and weakness can present early in life, persist, and may result in delayed motor development; most patients can walk unassisted by 2 years of age. Common phenotypes include short stature and facial dysmorphism and can extend to rarer phenotypes such as clubfoot (bilateral talipes) (Ades et al., 1993). Christodoulou *et al.* describes 6 cases of BTHS from four families with dysmorphic features, all of which exhibited persistent short stature. Four of the patients had also been found to exhibit similar myopathic facial appearances in conjunction with neuromuscular, cardiovascular and infectious symptoms (Christodoulou et al., 1994). A growth curve generated by examining 73 BTHS patients in Roberts *et al.* revealed a common down-shift in weight, length, and height relative to the normal population. Developmental delays are prevalent in BTHS patients with motor skills being the most affected, as indicated by a 65% prevalence of a delay in sitting up and a 71.6% delay in walking (Roberts et al., 2012).

Developmental delay has been treated with some success using cornstarch supplementation. This alternate source of glucose production ameliorates muscle wasting due to overnight fasting (Clarke et al., 2013). Other treatments, including oral arginine and carnitine supplementation, have centered on treating metabolic deficiencies, which improves cardiac function and muscle weakness in some patients (Ferreira et al., 1993; Rigaud et al., 2013; Vernon et al., 2014). However, while carnitine supplementation was initially offered as a treatment paradigm for all cases of BTHS (Ino et al., 1988), its effect has subsequently been called into question, and no formal assessment of the utility of arginine supplementation has been published. Thus far, both carnitine and arginine have demonstrated efficacy only in patients with those specific deficiencies (Ferreira et al., 1993; Rigaud et al., 2013; Vernon et al., 2014).

4.3. Neurological pathology.

Neurological complications tend to manifest as mild cognitive impairments in BTHS patients with *TAZ* mutations. While these patients were found to have a higher incidence of cognitive impairment (Mazzocco et al., 2007) and mild learning and speech difficulties (Roberts et al., 2012), many patients were found to have normal cognitive development, including a three-generation family with no cognitive impairment despite BTHS diagnosis (Ades et al., 1993). The limited neurologic involvement of BTHS is interesting given that tafazzin has been shown to play an important role in brain mitochondrial respiration and normal cognitive function (Cole et al., 2018). One postulate contends that the brain's reliance on glucose, over tissues in the heart and liver that require high mitochondrial activity, allows the brain to have a more diverse and less tetralinoleoyl-dependent CL composition. Reducing the need for highly symmetric remodeled tetralinoleoyl-CL to achieve sufficient mitochondrial function may allow the brain to mitigate or avoid the

detrimental effects of a tafazzin deficiency (Houtkooper et al., 2009b). Indeed, CL in the brain has higher amounts of arachidonic (AA) and docosahexaenoic (DHA) acids, distinct from the preference for tetralinoleoyl-CL seen in other tissues (Houtkooper et al., 2009b). Over 80% of CL in the liver and heart take the 18:2n-6 form, whereas the brain demonstrates less of a preference and has a higher concentration of saturated acyl chains, with only 48% polyunsaturated fatty acids and just 20% of its CL in the 18:2n-6 form (Corazzi and Roberti, 2009). It has also been proposed that the higher ROS scavenging capability of the brain, which is about 100 times higher than the rate of ROS generation (Starkov et al., 2014), may allow the brain to avoid the harmful effects more effectively than in other tissues even though it generates higher total levels of ROS (Cole et al., 2018).

4.4. Metabolic disorder.

3-methylglutaconic aciduria (3-MGA) is a major indicator of a variety of syndromes including BTHS, and is the result of mutations, including those in *TAZ*, that are linked to mitochondrial dysfunction (Su and Ryan, 2014). 3-MGA refers to increased levels of the organic acids 3-methylglutaconic acid, 3-methylglutaric acid, and 2-ethyl-hydracrylic acid in urine (Wortmann et al., 2012). BTHS patients typically demonstrate a large and consistent increase in the excretion of 3-MGA (Wortmann et al., 2013). A diagnosis of 3-MGA type II is synonymous with BTHS. While most BTHS patients exhibit varying severities of 3-MGA, a case report by Schmidt *et al.* describes a 15 year-old-boy with typical BTHS symptoms, such as dilated cardiomyopathy, but normal levels of organic acids, amino acids, and mucopolysaccharides in urine. Thus, there was no diagnosis of 3-MGA, despite a *TAZ* missense mutation in nucleotide 877 at exon 8 (Schmidt et al., 2004). Therapeutics such as riboflavin or coenzyme Q10 have been reported to show substantial improvement in some patients with 3-MGA (Wortmann et al., 2012). Overall, however, metabolic treatments vary between patients and are largely designed to target symptomatic deficiencies rather than the underlying cause of the disease (Clarke et al., 2013; Reynolds, 2015).

4.5. Hematologic pathology.

Neutropenia is one of the most frequent characteristics of BTHS caused by *TAZ* mutations, characterized by a decline in total number of circulating neutrophils accompanied by an increase in monocytes and eosinophils with no fluctuations in lymphocyte numbers (Clarke et al., 2013). Makaryan *et al.* found that neutropenia in BTHS is caused by a disruption of mitochondrial membrane potential as well as caspase-3 activation resulting in an increased rate of apoptosis of myeloid progenitor cells (Makaryan et al., 2009; Makaryan et al., 2012). Neutropenia is a particularly variant symptom, and can present itself in many different forms, from severe to mild, cyclical to non-cyclical, and intermittent to chronic (Steward et al., 2019). Severe chronic neutropenia (SCN), defined by an absolute neutrophil count of < 500/ μ L, is the most detrimental phenotype (Dale et al., 2006).

In a cohort study, Roberts *et al.* describe 73 patients with BTHS and indicate that 69.1% self-reported neutropenia with varying severity (Roberts et al., 2012). Ranging from a complete lack of neutrophils to a mild decline, neutropenia may be absent at presentation and change over the course of the disease in the same patient (Clarke et al., 2013). For instance, all seven members of a family with *TAZ* mutations exhibited no signs of

neutropenia (Ferri et al., 2015), while another case of siblings with severe BTHS both exhibited intermittent neutropenia (Bowron et al., 2015). Including persistent or intermittent forms of neutropenia, nearly 90% of BTHS patients exhibit the symptom to some degree (Clarke et al., 2013), though it is mentioned in just over 65% of available clinical case reports on Barth syndrome (Figure 4). Neutropenia is an immune system deficiency that results in diminished response to invading organisms. Therefore, decreased defense mechanisms leads to serious bacterial infections including prolonged upper respiratory tract infections, mouth ulcers (chronic aphthous stomatitis) due to *Candida* infections, inflamed gums and perianal dermatitis, as well as sepsis and multi-organ failure, which are frequently treated by prophylactic antibiotics (Barth et al., 2004; Dale et al., 2006; Clarke et al., 2013). Among 73 BTHS patients in Roberts *et al.*, 65% of those with neutropenia exhibited mouth ulcers, relative to only 35% of patients without neutropenia, while 28% had a history of pneumonia and 10% had a history of blood infections (Roberts et al., 2012). Granulocyte colony-stimulating factor (G-CSF) has been identified as an effective and safe treatment for SCN (Dale et al., 2006), leading to improvement in many BTHS patients with symptoms including aphthous ulcers, bacterial infections, and lethargy (Clarke et al., 2013).

4.6. Therapies in Barth syndrome.

Although several therapeutic strategies have proved successful in select clinical presentations, treatments are focused on treating the cardiovascular, musculoskeletal, and metabolic disorders, rather than the root cause of the disease. There is currently no cure for Barth syndrome (Barth Syndrome Foundation, 2019). Based on the observation that the fatty acid environment of cells impacts CL composition, ATP synthesis, membrane potential, and ROS production, dietary fatty acids have been suggested as a therapeutic strategy to target mitochondrial lipid metabolism and ameliorate effects on bioenergetics and cardiac function in mitochondrial diseases such as BTHS (Monteiro et al., 2013). It is unclear whether these treatments have significant effects in clinical practice. Direct modulation of CL content by lipid replacement therapy using CL nanodisks has also been tested in cell and animal models of Barth syndrome. Apoptosis induced by shRNA-mediated knockdown of *TAZ* in cultured HL60 myeloid progenitor cells (Makaryan et al., 2012) is attenuated by incubation with CL nanodisks and confers a significant increase in cellular CL content (Ikon et al., 2015). However, translation to an *in vivo* setting was unsuccessful, with no alteration in the CL profile of either wildtype mice or a *TAZ* knockdown mouse model of Barth syndrome (Ikon et al., 2018). Another study aimed to investigate whether overexpression of an alternate CL remodeling enzyme could restore CL in *TAZ*-deficient cells. Lymphoblasts from Barth syndrome patients transfected with *MLCLAT1* saw increased CL levels, improved mitochondrial basal respiration and proton leak, and reduced superoxide production, but only partial compensation for respiratory function and no restoration of OXPHOS supercomplex formation (Taylor et al., 2012; Mejia et al., 2018). These results show some promise, but it remains to be seen whether they can be recapitulated in a live animal model.

Elevated ROS and oxidative stress have been proposed as significant culprits in Barth syndrome and the development of cardioskeletal myopathy in these patients (Xu et al., 2005; Dudek et al., 2013; Saric et al., 2015). *In vitro* studies of *TAZ*-deficient cardiomyocytes treated with the mitochondrially-targeted Mito-Tempo antioxidant demonstrated improved

contractile function, cardiac hypertrophy, and cell death (He et al., 2014; Wang et al., 2014). Mice with *TAZ* deficiency (TAZKD) and mitochondria-specific overexpression of catalase, however, developed cardiomyopathy and muscle weakness similar to the Barth syndrome mouse, indicating that amelioration of oxidative stress is insufficient in the *in vivo* setting (Johnson et al., 2018).

Peroxisome proliferator-activated receptors (PPARs) and the PPAR-gamma coactivator-1 alpha (PGC-1 α) are central to energy metabolism and bioenergetics in mitochondria, presenting opportunities for treatment in a variety of mitochondrial and metabolic disorders. Bezafibrate is a fibric acid derivative pan-agonist of PPAR signaling pathways that activates oxidative metabolism genes (Huang et al., 2017). In patients with dyslipidemia or metabolic syndrome, bezafibrate reduces triglyceride levels and the incidence of myocardial infarction (Arbel et al., 2016). It also significantly decreases HbA1c in diabetic patients with dyslipidemia (Teramoto et al., 2012). Because of its role in mitochondrial bioenergetics, it has been proposed as a potential treatment for Barth syndrome as well. In a TAZKD mouse model with isoproterenol (iso) treatment to induce more significant cardiac dysfunction, bezafibrate rescued iso-induced heart failure with marked increases in left ventricular fractional shortening and ejection fraction and prevention of the development of cardiomyopathy (Huang et al., 2017). However, the treatment also caused a significant reduction in CL content and increase in MLCL/CL ratio in both wild type and *TAZ* knockdown mice, a common biomarker for Barth syndrome. Concurrently, mitochondrial biogenesis was amplified drastically, as indicated by a two-fold increase in mtDNA content and mitochondrial citrate synthase activity in bezafibrate-treated hearts. Additionally, the dose used in the mouse model was 60-80 times greater than is typically prescribed in dyslipidemic humans. The modification of CL content and dosage discrepancy presents significant hurdles to determine the mechanism of action, further evaluate the importance of MLCL and CL concentrations, and conduct toxicity studies before any enrollment in clinical trials (Huang et al., 2017).

Gene replacement therapy presents another avenue of exploration that has the potential to address underlying tafazzin deficiencies resulting from the *TAZ* mutations that cause Barth syndrome. Recombinant adeno-associated virus (rAAV) vectors provide stable and long-lasting gene transfer to the nucleus of an organism's cells using a non-pathogenic virus with minimal immune response (Schnepf et al., 2003). The successful application of an AAV-delivered gene therapy in spinal muscular atrophy also establishes an important precedent for the safety and efficacy of this approach in a clinic setting (Mendell et al., 2017). AAV serotype 9 (AAV9) demonstrates high affinity for the heart and skeletal muscle, making it ideal for application to Barth syndrome (Bish et al., 2008). In the TAZKD mouse model of Barth syndrome, an AAV9-*TAZ* vector with a desmin promoter resulted in significant *TAZ* gene and tafazzin protein expression levels in the heart and muscle and minimal levels in the liver (Suzuki-Hatano et al., 2019a). Measures of muscular strength and fatigue as well as whole body activity (e.g., exercise and distance travelled) of the treated mice improved significantly. Increased fractional shortening and ejection fraction as well as decreased heart weight/body weight ratio indicate significant improvements in cardiac function. Mitochondrial structure and function defects were ameliorated, with improved cristae and sarcomeric organization, greater numbers and size, as well as improved mitochondrial

respiration and OXPHOS complex activity (Suzuki-Hatano et al., 2019a). In further studies, multiplex tandem mass tagging-based proteomics has provided a deeper mechanistic insight into the progression of Barth syndrome and its impact on critical proteins involved in cardiac development, heart failure, transcription, translation, and carnitine biosynthesis. (Suzuki-Hatano et al., 2019b). The striking result of AAV9-*TAZ* gene therapy across a range of treatment ages in the mouse model of Barth syndrome paints an optimistic picture for its potential as a future clinical option for these patients.

Elamipretide (MTP-131, SS-31, Bendavia) is a novel mitochondria-targeted tetrapeptide designed to temporarily bind to CL and protect it from oxidative damage by blocking CL-mediated conversion of cytochrome *c* into a peroxidase, thereby preserving cristae structure, promoting OXPHOS, and maintaining mitochondrial integrity (Birk et al., 2014; Szeto, 2014). In the canine model of intracoronary microembolization-induced chronic heart failure (Sabbah et al., 1991), long-term therapy with elamipretide was demonstrated to improve left ventricular ejection fraction, normalize key plasma biomarkers including tumor necrosis factor- α (TNF- α) and C-reactive protein (CRP), and reverse mitochondrial deficiencies in the heart (Sabbah et al., 2016) and skeletal muscle (Sabbah et al., 2019). In explanted human cardiac ventricular tissue from patients with a wide demographic range, elamipretide improved impaired mitochondrial function in heart failure and had no effect on normal mitochondrial function in nonfailing hearts. Additionally, supercomplex function was improved, but no change was observed in the activities of OXPHOS complexes II or V (Chatfield et al., 2019). In a clinical trial for patients with heart failure with reduced ejection fraction (HFrEF), elamipretide was safe, well-tolerated, and achieved significant decreases in left ventricular end-diastolic volume (LVEDV) and end-systolic volume (LVESV) in the highest dose cohort. Ejection fraction also improved in the treatment group as compared to those administered a placebo, though the measures did not reach statistical significance (Daubert et al., 2017). Elamipretide is currently in Phase 2 clinical trials (TAZPOWER) to treat Barth syndrome specifically, and recruitment is in progress for a Phase 3 clinical trial (MMPOWER-3) in patients with primary mitochondrial myopathies ([ClinicalTrials.gov](https://clinicaltrials.gov) [Internet]). The previous animal studies and clinical trials in heart failure bode well for successful applications of Elamipretide in the Barth syndrome and mitochondrial myopathy patient populations.

5. Conclusions

Tafazzin is a transacylase responsible for remodeling cardiolipin in the mitochondrial membrane and plays an integral role in maintaining mitochondrial structure and function. The tight bends of the cristae in the inner membrane require a specific acyl profile, afforded by the activity of tafazzin. The protein has targeting and anchoring domains that direct it to the IMM and OMM and position it to face the IMS, build mature, tetra-linoleoyl cardiolipin species, and repair damaged membranes. Mutations in *TAZ* produce a dysfunctional or improperly localized protein that causes Barth syndrome, a multi-factorial and devastating disease that presents in infancy and results in heart failure, neutropenia, and musculoskeletal abnormalities. Current therapeutic paradigms are wide-ranging and attempt to treat the symptoms of individual systems. No cure exists for Barth syndrome, though there are a number of different treatments in development aimed at modulating metabolic processes,

reducing oxidative stress, protecting CL from degradation, as well as conducting targeted gene-replacement of *TAZ*. Additional studies are necessary to fully characterize and understand the unique and integral role of tafazzin in mitochondrial biology and in the manifestation of Barth syndrome.

Acknowledgements

The authors would like to acknowledge the support of National Institutes of Health (T32 EB16640 to Anders O. Garlid, R35 HL135772 to Peipei Ping), and the Theodore C. Laubisch endowment at UCLA to Peipei Ping. The authors are grateful to Keith Garlid and Hirsh Bhatt for their significant contributions and revisions to this manuscript, as well as Erik Lontok from the Barth Syndrome Foundation for his invaluable input.

This review and the corresponding Gene Wiki article are written as part of the Gene Wiki Review series – a series resulting from a collaboration between the journal GENE, the Gene Wiki Initiative, and the BD2K initiative. The Gene Wiki Initiative is supported by National Institutes of Health (R01 GM089820, U54 GM114833). Additional support for Gene Wiki Reviews is provided by Elsevier, the publisher of GENE. The corresponding Gene Wiki entry for this review can be found here: <https://en.wikipedia.org/wiki/tafazzin/>.

Abbreviations

3-MGA	3-methylglutaconic aciduria
AA	arachidonic acid
aa	amino acid
rAAV	recombinant adeno-associated virus
AAV9	adeno-associated virus serotype 9
ACE	angiotensin-converting enzyme
ALCAT	acyl-CoA:lysocardiolipin acyltransferase
ANT	adenine nucleotide translocase
BTHS	Barth syndrome
CL	cardiolipin
CL₄	tetralinoleoyl-cardiolipin
CMD3A	cardiomyopathy, dilated 3A (X-linked)
DCM	dilated cardiomyopathy
DHA	docosahexaenoic acid
EFE2	endocardial fibroelastosis 2
G3PAT	glycerol-3-phosphate acyltransferase
G-CSF	granulocyte colony-stimulating factor
HFrEF	heart failure with reduced ejection fraction
IMM	inner mitochondrial membrane

IMS	intermembrane space
INVM	isolated noncompaction of the ventricular myocardium
iPLA2	calcium-independent phospholipase A2
LA	linoleic acid
LVEDV	left ventricular end-diastolic volume
LVESV	left ventricular end-systolic volume
LVNC	left ventricular noncompaction
mitoK_{ATP}	mitochondrial ATP-sensitive K ⁺ -channel
MLCL	monolysocardiolipin
MLCLAT	monolysocardiolipin acyltransferase
mtCK	mitochondrial creatine kinase
nt	nucleotide
OMM	outer mitochondrial membrane
OXPHOS	oxidative phosphorylation
PA	phosphatidic acid
PC	phosphatidylcholine
PE	phosphatidylethanolamine
PL	phospholipids
PPAR	peroxisome proliferator-activated receptor
PGC-1α	PPAR-gamma coactivator-1alpha
PUFA	polyunsaturated fatty acid
ROS	reactive oxygen species
SCN	severe chronic neutropenia
TIM	translocase of the inner membrane
TOM	translocase of the outer membrane
VDAC	voltage-dependent anion channel

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Highlights

- *TAZ* encodes the tafazzin transacylase responsible for cardiolipin (CL) remodeling.
- Tafazzin localizes to the mitochondrial membranes for direct access to CL.
- Tafazzin generates mature CL to maintain mitochondrial structure-function.
- Mutations throughout *TAZ* cause the rare mitochondrial disease Barth syndrome.
- There is no cure for Barth syndrome, but PPAR agonists, AAV9 gene therapy, CL protection, and protection from oxidative stress are in development.



Figure 1. *TAZ* genetic mutations, frequency and pathogenicity.

The frequency of intronic and exonic mutations across the length of the *TAZ* gene are shown here, categorized by pathogenicity and mapped to the nucleotide (nt) position on the gene, with exons represented by thick grey bars below the x-axis. Patient mutation data was acquired from the Barth Syndrome Foundation *TAZ* database (<https://barthsyndrome.org/research/tazdatabase.html>).

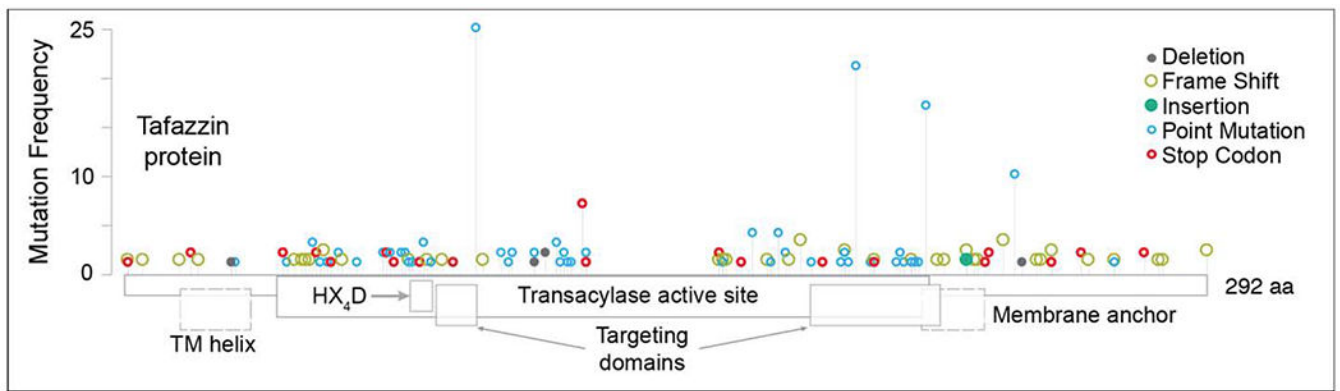


Figure 2. Tafazzin domains, mutation frequency, and mutation type.

The frequency of pathogenic, exonic mutations across the length of the tafazzin protein are shown here, categorized by mutation type, with key functional domains of the tafazzin protein displayed below the x-axis. Tafazzin contains a transmembrane helix (TM helix) and a membrane anchor at positions 15-34 and 215-232, respectively. The acyltransferase active site spans 176 amino acids (aa) from residue 41-217, with His77 forming part of the His-Asp motif (HX₄D). Mitochondrial targeting domains are encoded in exon 3 as well as exon 7/8, spanning protein residues 84-95 and 185-220, respectively. Patient mutation data was acquired from the Barth Syndrome Foundation *TAZ* database (<https://www.barthsyndrome.org/research/tazdatabase.html>).

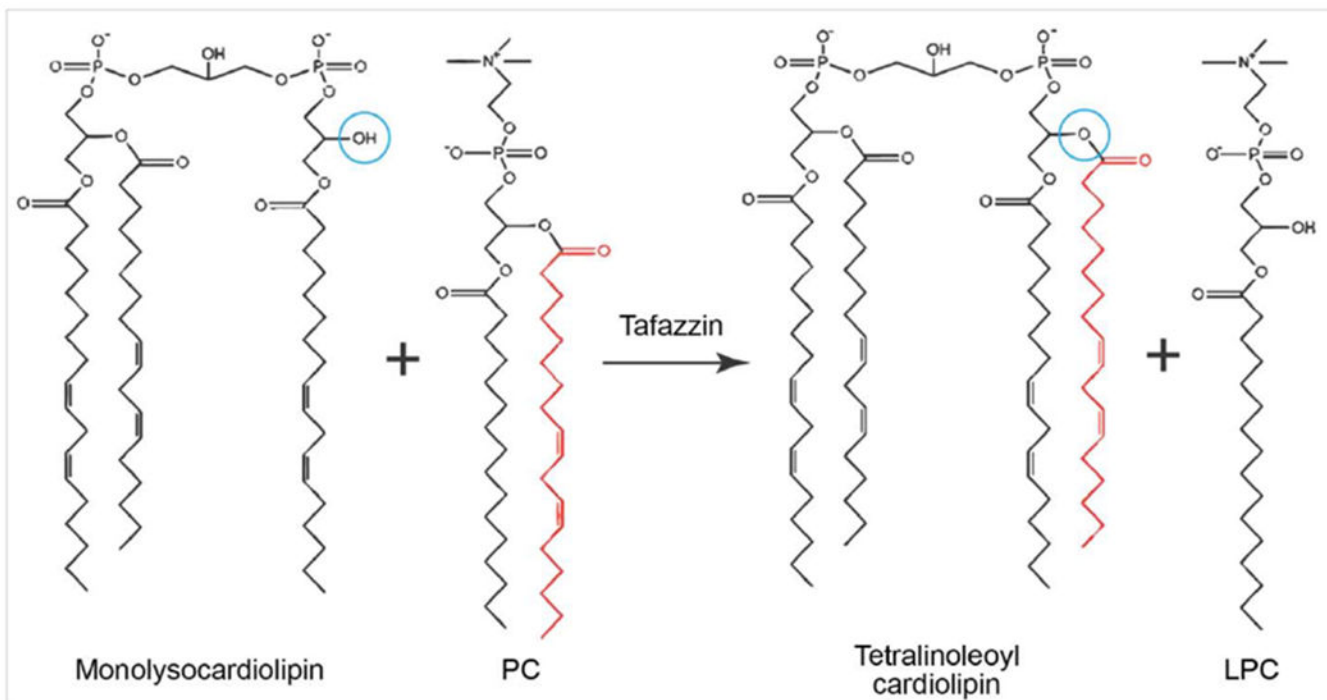


Figure 3. Mechanism of acyltransferase activity by tafazzin.

Tafazzin acts as a shuttle for specific acyl groups between different phospholipids to generate mature cardiolipin. Tafazzin transfers an acyl side chain from a phospholipid such as phosphatidylcholine (PC) to reacylate monolysocardiolipin (MLCL) in a single-step acyl group transfer reaction, resulting in the formation of lysophosphatidylcholine (LPC) and the mature tetralinoleoyl form of cardiolipin. The red acyl side chains indicate the acyl group that is transferred by tafazzin, and the blue circles indicate the location on MLCL where the new acyl chain is added to form the mature tetralinoleoyl cardiolipin.

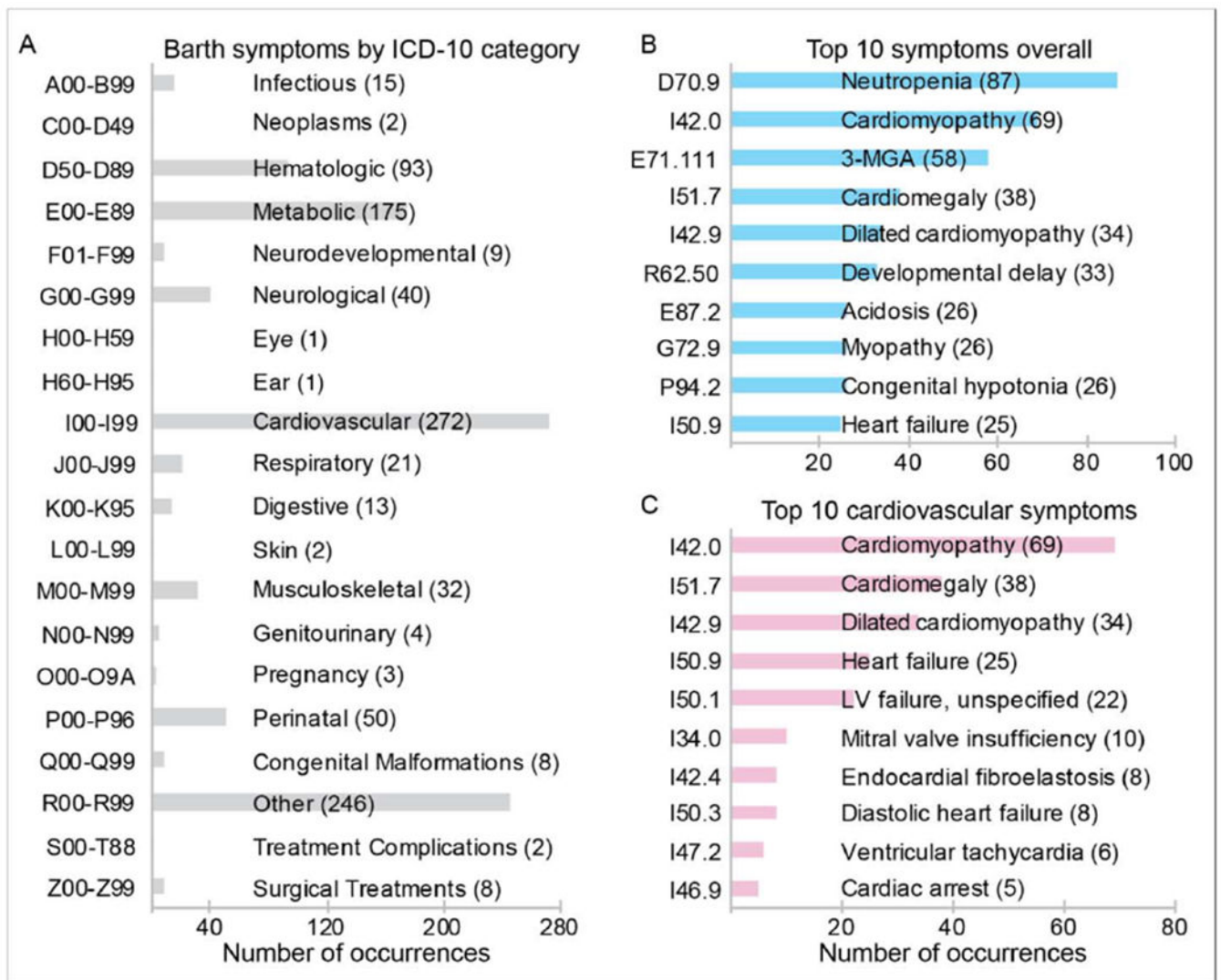


Figure 4. Complex symptomology of Barth syndrome codified by ICD-10.

Symptom occurrence codified using the 10th edition of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) from 133 Barth syndrome patients described in 54 clinical case reports (please see **References Cited: Clinical Case Reports**). Panel (A) presents the full collection of 997 instances of 206 unique ICD-10 codes across all patients in these reports, grouped by disease category (Caufield et al., 2018b; Caufield et al., 2018a). Cardiovascular diseases and symptoms are the most highly represented among all ICD-10 categories ($n = 272$). Panel (B) highlights the top 10 symptoms from all ICD-10 categories. Panel (C) depicts the top 10 cardiovascular symptoms. All data is housed on the MitoCases platform (<http://mitocases.org/>) along with detailed metadata on the medical information contained in the text of each CCR.

Table 1.
Essential properties and identifiers of *TAZ* and tafazzin.

The table contains a summary of the essential properties, identifiers, and names of the *TAZ* gene and the encoded tafazzin protein in *Homo sapiens* (human) and *Mus musculus* (mouse) (NCBI, 2019).

Species	<i>Homo sapiens</i> (human)	<i>Mus musculus</i> (mouse)
Gene	<i>TAZ</i>	<i>TAZ</i>
Synonyms	BTHS, EFE, EFE2, CMDA3, LVNCX, G4.5	5031411C02Rik, 9130012G04Rik, AW107266, AW552613, G4.5
NCBI Gene ID	6901	66826
Chromosomal location	chrXq28:154,411,524-154,421,726	chrX:74,282,697-74,290,151
Length (nt)	10,171	7,454
Exons/Introns	11/10	10/9
NCBI Gene ID	6901	66826
UniProt ID	Q16635	I7HJS2
Ensembl ID	ENSG00000102125	ENSMUST00000069722.12
Length (aa)	292	263
Molecular weight (Da)	33,459	30,433