Lack of the Mitochondrial Protein Acylglycerol Kinase Causes Sengers Syndrome

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Exome sequencing of an individual with congenital cataracts, hypertrophic cardiomyopathy, skeletal myopathy, and lactic acidosis, all typical symptoms of Sengers syndrome, discovered two nonsense mutations in the gene encoding mitochondrial acylglycerol kinase (AGK). Mutation screening of *AGK* in further individuals with congenital cataracts and cardiomyopathy identified numerous loss-of-function mutations in an additional eight families, confirming the causal nature of AGK deficiency in Sengers syndrome. The loss of AGK led to a decrease of the adenine nucleotide translocator in the inner mitochondrial membrane in muscle, consistent with a role of AGK in driving the assembly of the translocator as a result of its effects on phospholipid metabolism in mitochondria.

Sengers syndrome (MIM 212350) is an autosomal-recessive disorder characterized by congenital cataracts, hypertrophic cardiomyopathy, skeletal myopathy, exercise intolerance, and lactic acidosis but normal mental development. Since the first report in 1975 by Sengers et al.,[1] about 40 individuals have been described as having this unique mitochondrial disease.[2–8] The clinical course varies from severe forms that cause death in infancy to more benign forms that allow survival into the fourth decade. Cause of death is invariably heart failure due to a hypertrophic form of cardiomyopathy. Histopathological investigations have shown abnormal structure of mitochondria and storage of lipid and glycogen in both skeletal and heart muscle. In 2002, Jordens et al. described a decrease in both the amount of skeletal muscle and the activity of adenine nucleotide translocator 1 (ANT1 [SLC25A4]) in two families with Sengers syndrome.[9] Because mutations in *SLC25A4* (MIM 103220) were excluded by linkage analysis, Jordens et al. proposed that transcriptional, translational, or posttranslational events might cause the carrier deficiency. The phenotype of hypertrophic cardiomyopathy, exercise intolerance, and lactic acidemia of *Slc25a4*-knockout mice shows a broad overlap with the clinical findings seen in Sengers syndrome.[10] However, the molecular basis underpinning the defect has remained elusive.

To identify the disease-causing sequence variation, we performed exome sequencing in a single German index case (54027 in Table 1) with Sengers syndrome. Written informed consent was obtained from all participants or their guardians at the recruiting center, and the study was approved by the ethical committee of the Technical University of Munich. The boy was born a dizygotic twin from unrelated parents of Italian origin. The primary adaptation was uneventful. Bilateral central cataracts were noticed in a routine physical examination performed at day 5. On the boy's 13th day of life, the family noticed that the child was very fatigued and had muscular hypotonia. The next day, he arrived at the hospital with decompensated cardiomyopathy and tachydyspnea. Echocardiography revealed massive hypertrophy of both ventricles. Lactate was 7.3 mmol/liter in plasma (normal is 0.5–2.2 mmol/L). The boy died on the 18th day of life as a result of cardiac failure. A muscle biopsy was taken on the 15th day of life and revealed mild myopathic abnormalities and deposition of fine lipid droplets in a histological investigation. Activity staining of cytochrome *c* oxidase and succinate dehydrogenase was normal.

We performed in-solution targeted enrichment of exonic sequences from index case 54027 by using the 50 Mb SureSelect Human All Exon kit from Agilent. The library was subsequently sequenced as 76 paired-end runs on the GAIIx from Illumina. Read alignment to the human genome assembly hg19 was done with Burrows-Wheeler Aligner (BWA, version 0.5.8) and yielded a total of 9.6 Gb of sequence data corresponding to an average coverage of 113× (Table S1, available online). Single-nucleotide variants and small insertions and deletions were detected with SAMtools (version 0.1.7). Because Sengers syndrome is known to be a rare condition, we first excluded all variants present in 666 control exomes. We then filtered for

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Table 1. Genetic and Clinical Findings in Sengers Individuals with *AGK* Mutations

		AGK Mutations Identified		Biochemical Investigations			Clinical Features					
ID	Sex	cDNA (NM_018238.3)	Protein (NP_060708)	OXPHOS Defect	ATP Synthesis	Substrate Oxidation	AO	Course	CM	Cataract	Other Clinical Features	Literature
54027[a]	male	c.306C>T c.841C>T	p.Tyr102* p.Arg281*	I, II+III, and V	impaired	impaired	1 weeks	death at 18 days	yes	congenital	floppy infant, tachydyspnoea, lactic acidosis plasma, and CSF	this study
60453	male	c.3G>C c.517C>T	p.Met1Ile p.Gln173*	normal	ND	ND	3 months	alive for 36 years	yes	3 months	motor developmental delay, muscular hypotonia, exercise intolerance, normal mental development, and lactic acidosis	Lalive d'Epinay et al. ("fall 1")[3]
60455 [b]	male	c.412C>T c.1137_1143del	p.Arg138* p.Gly380Leufs*16	normal	ND	ND	1 week	death at 11 months	yes	congenital	muscular hypotonia, moderate motor retardation, and lactic acidosis depending on exercise	this study
62014 [b]	female	NA	NA	ND	ND	ND	1 week	death at 7 months	ND	congenital	muscular hypotonia and motor retardation	this study
60456 [c]	male	c.3G>C c.672C>A	p.Met1Ile p.Tyr224*	normal	ND	ND	3 months	alive for 35 years	yes	3 months	motor developmental delay, exercise intolerance, normal mental development, and lactic acidosis depending on exercise	Lalive d'Epinay et al. ("fall 3")[3]
62013 [c]	female	NA	NA	normal	ND	ND	10 weeks	death at 19 years	yes	10 weeks	motor developmental delay, exercise intolerance, normal mental development, esotropia, and nystagmus	Lalive d'Epinay et al. ("fall 2")[3]
60182 [d]	male	c.1131+5G>A c.1131+5G>A	splicing defect	I, II+III, IV, and PDHc	impaired	impaired	1 year	death at 12 years	yes	18 months	muscular hypotonia, muscle weakness, and exercise intolerance	Morava et al. (case 1)[6]
60183 [d]	female	c.1131+5G>A c.1131+5G>A	splicing defect	I, II+III, IV, and PDHc	impaired	impaired	birth	alive for 10 years	yes	5 months	lactic acidosis and exercise intolerance	Morava et al. (case 2)[6]
60186	female	c.1131+5G>A c.1131+5G>A	splicing defect	normal	impaired	impaired	3.5 years	alive for 41 years	yes	congenital	lactic acidosis and cerebrovascular accident	van Ekeren et al. (case 12)[4]
62216	female	c.672C>A c.870del	p.Tyr224* p.Gln291Argfs*8	I, II, III, IV, and very high CS	impaired	ND	birth	death at 10 months	yes	4 months	lactic acidosis	this study
62217	male	c.101+?_222-?del c.101+?_222-?del	ND ND	I, II, III, IV, and very high CS	impaired	ND	4 months	death at 8 months	yes	congenital	lactic acidosis, seizures, paresis of upper-left limb, dilation of brain ventricles, and axial hypotonia	this study
62218	female	c.221+1G>A c.1213C>T	splicing defect p.Gln405*	I, II, III, IV, and very high CS	ND	ND	10 months	alive for 12 years	yes	congenital	lactic acidosis and severe muscle weakness	Di Rosa et al., (case 3);[7] this study

Abbreviations are as follows: OXPHOS, oxidative phosphorylation; AO, age of onset; CM, cardiomyopathy; CSF, cerebrospinal fluid; NA, no material available; ND, not determined; I, complex I; II+III, succinate cytochrome *c* oxidoreductase; IV, cytochrome *c* oxidase; V, oligomycin-sensitive ATPase; PDHc, pyruvate dehydrogenase complex; and CS, citrate synthase.

[a] Investigated by exome sequencing.

[b] Individuals 60455 and 62014 are siblings.

[c] Individuals 60456 and 62013 are siblings.

[d] Individuals 60182 and 60183 are siblings.

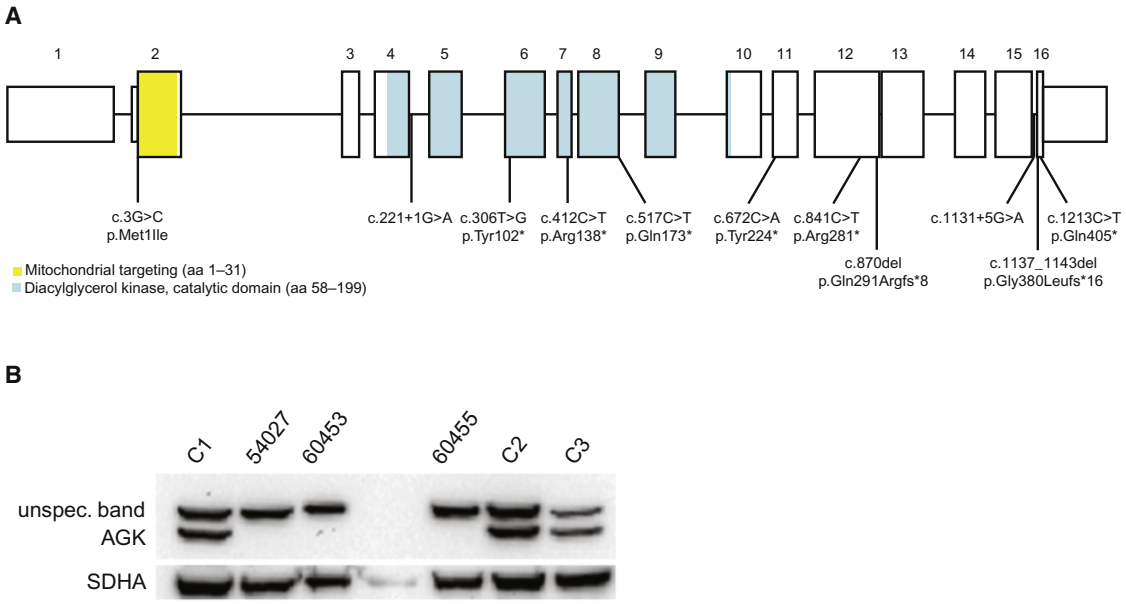


Figure 1. Distribution of the *AGK* Mutations and Their Consequences on AGK
Structure of *AGK* (A) and localization of identified mutations. AGK (B) was not detectable with immunoblot analysis (primary AGK antibody [1:1,000; rabbit polyclonal; GTX107413, Genetex]) in myoblasts form affected individual 54027 and in fibroblasts of individuals 60453 and 60455.
(C1) Myoblast control.
(C2 and C3) Fibroblast controls.

compound heterozygous or homozygous nonsynonymous variants affecting genes that encode mitochondrial proteins[11] (Table S2). This approach identified a single gene harboring the compound heterozygous nonsense mutations c.306T>G (p.Tyr102*) and c.841C>T (p.Arg281*) in *AGK* (RefSeq NM_018238.3), the gene coding for mitochondrial acylglycerol kinase (AGK). The parents and the healthy brother carried a single heterozygous mutation each, as confirmed by Sanger sequencing.

Mutation screening of *AGK* (MIM 610345) in 13 individuals with congenital cataracts and cardiomyopathy discovered that there were 12 alleles with predicted loss of function in ten affected individuals, confirming the causal nature of *AGK* variants in Sengers syndrome (Figure 1). All affected individuals displayed the clinical signs of Sengers syndrome, but they experienced a varying course of the disease and had different biochemical alterations; five individuals had a combined respiratory-chain-complex deficiency in muscle tissue. Clinical phenotypes of most individuals have been reported previously (Table 1). For the remaining individuals, the clinical manifestation and course of the disease are described in the following five paragraphs.

Individual 62014 was a girl from healthy nonconsanguineous Swiss parents. Bilateral cataracts were noticed when she was born but were interpreted as rubella embryopathy. The girl always had muscular hypotonia and failed to thrive. She died at the age of 7 months as a result of sudden infant death syndrome.

Individual 60455, the younger brother of individual 62014, was born at the 40th week of gestation after an uneventful pregnancy. He had a length of 47 cm, a body weight of 2,620 g, a head circumference of 33 cm, and Apgar scores of 9, 10, and 10. His mother first noticed a cataract in his right eye when he was three days old and another cataract in his left eye when he was two weeks old. Therefore, a cataract extraction was performed. Electro- and echocardiography were normal when the boy was 2 months of age; there was no lactate elevation in plasma and urine. When he was 4 months old, a failure to thrive was noticed. When he was 7 months old, a moderate concentric hypertrophic cardiomyopathy was first documented and was thereafter rapidly progressive. Depending on motor activity, lactate was intermittently elevated. At the age of 8.5 months, the boy presented with muscular hypotonia and moderate motor retardation. Electromyography and nerve-conduction velocity were normal. Magnetic resonance imaging (MRI) investigation of his muscle tissue showed hypotrophy without fat infiltration, and magnetic resonance spectroscopy revealed a normal ^{31}P-spectrum of phosphate, phosphocreatine, and ATP. A muscle biopsy revealed fatty infiltrations in the muscle fibers, and electron microscopy revealed abnormal mitochondria. Lactate in the blood and urine was elevated depending on muscular activity. At 11 months old, the boy died as a result of heart failure. Autopsy was performed 15 min after his death; both muscle and heart tissue showed a normal concentration of L-carnitine. Enzymatic investigations of muscle tissue showed normal activity of creatine kinase and complexes I, II, II+III, IV, and V (ATPase). No abnormalities were found in the liver or kidneys.

Table 2. Investigations of the Mitochondrial Energy Metabolism in Individual 54027

Enzymatic Investigations in Muscle Tissue	Individual 54027	Controls
Substrate Oxidation Rates [μmol/h/g protein]		
[1-^{14}C]pyruvate + malate + ADP	34	263–900
[1-^{14}C]pyruvate + carnitine + ADP	52	302–856
[1-^{14}C]pyruvate + malate (−ADP)	15	32–102
[1-^{14}C]pyruvate + malate + CCCP	119	304–889
[U-^{14}C]malate + pyruvate + malonate + ADP	50	282–874
[U-^{14}C]malate + acetylcarnitie + malonate + ADP	30	273–678
[U-^{14}C]malate + acetylcarnitine + arsenite + ADP	32	156–378
[1,4-^{14}C]succinate + acetylcarnitine + ADP	22	167–488
Enzyme Activities [unit/g protein]		
Citrate synthase	161	150–338
Complex I	23	28–76
Complex I+III	92	49–218
Complex II	57	39–102
Complex II+III	32	65–180
Complex III	491	304–896
Complex IV (cytochrome *c* oxidase)	310	181–593
Complex V (oligomycin-sensitive ATPase)	60	86–257

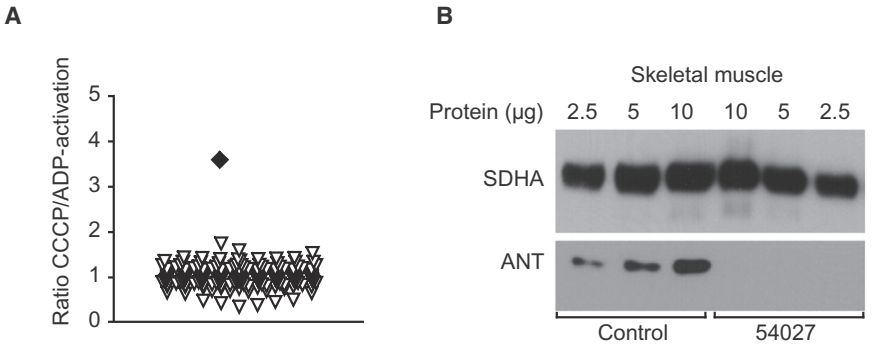
Individual 62216, the only daughter of healthy nonconsanguineous Italian parents, died at 9 months of age. She was born at term by normal vaginal delivery, and her birth weight was 2,750 g. Growth delay was noted during the third trimester of pregnancy (50–25th percentile) and again postnatally (<tenth percentile). When she was 4 months of age, bilateral cataracts were noted. When she was 4.5 months of age, an ultrasound examination of the heart showed severe concentric left-cardiac hypertrophy. She then suffered from recurrent bronchitis. After vitrectomy removed the cataracts, the baby worsened and died from cardiac arrest. High lactate was only present during infections or motor activity. Biochemical analysis of bioptic and autoptic muscle fragments showed marked reduction of all respiratory-chain complexes and elevated activity of citrate synthase.

Individual 62217, a boy, was the third child of reportedly nonconsanguineous Italian parents. His older sister, who had hypertrophic cardiomyopathy and congenital cataracts, died at 4 days old, and his older brother is alive and well. At birth, bilateral cataracts and moderate hypertrophy of the interventricular septum were noted. Two surgical interventions for cataracts were performed at 2 weeks and 2 months of age, when a paresis of the upper-left limb was noted. A brain MRI showed thinning of the corpus callosum and moderate dilation of cerebral ventricles. Axial hypotonia and hypertonia of the upper limbs were present. When the boy was 4 months of age, a cardiac ultrasound examination showed severe left-ventricular hypertrophy (the posterior wall was 12 mm; the normal value is <4), modest mitral regurgitation, and preserved ejection fraction. No pulmonary arterial hypertension was detected. At the same age, he had an episode of generalized hypertonic seizures with no clonic phase. Anisocoria of the pupils and severe axial hypotonia were present. High levels of lactate were detected in his blood. Analysis of respiratory-chain complexes in the homogenate of a muscle biopsy showed reduction of all activities except for that of citrate synthase, which was elevated, whereas activities in fibroblasts and in a liver biopsy were normal. He died at 8 months old as a result of cardiac failure.

The case of individual 62218 was published by De Rosa et al. in 2006.[7] At that time, the girl was 7 years old and had clinical features typical of Sengers syndrome; bilateral cataracts were noticed at 10 months of age, and hypertrophic cardiomyopathy was documented by ultrasound examination at 18 months of age and stabilized from 7 years of age on. She is now 12 years old. Although her cardiac conditions are relatively stable under therapy with propranolol and idebenone, her muscle weakness has progressively worsened, and she has required the aid of a wheelchair for distances of more than 100 m. Additional features include reduced body growth (<tenth percentile) and a mild neurogenic electromyography pattern, but she has no sign of CNS involvement (there is no cognitive regression, cerebellar signs, or pyramidal or extrapyramidal abnormalities). A recent brain MRI was normal. One younger brother died at 14 months old as a result of hypertrophic cardiomyopathy with bilateral cataracts. A muscle biopsy showed diffuse complex-IV deficiency with numerous ragged-red fibers. Two younger siblings, a girl and a boy, are alive and well.

All affected individuals carried mutations that are predicted to result in truncated proteins that are missing conserved parts of AGK and that therefore represent loss-of-function alleles (Figure 1 and Figure S1). In two affected individuals from Switzerland, we identified a heterozygous mutation (c.3G>C, p.Met1Ile) altering the *AGK* initiation codon in combination with two different nonsense mutations. Three individuals from two more families from The Netherlands harbored homozygous mutations that the splice-port algorithm predicted to affect the splice donor site of intron 16 (c.1131+5G>A).[12] A second heterozygous splice-site mutation (c.221+1G>A) affecting the donor site of intron 4 was found in an Italian individual (62218) in combination with a heterozygous nonsense mutation (p.Gln405*). An additional Italian individual, 62217, showed a homozygous deletion of exons 3 and 4. All variants identified were absent from 1,200 European control chromosomes.

Immunoblot experiments confirmed the absence of full-length AGK in muscle tissue from individual 54027



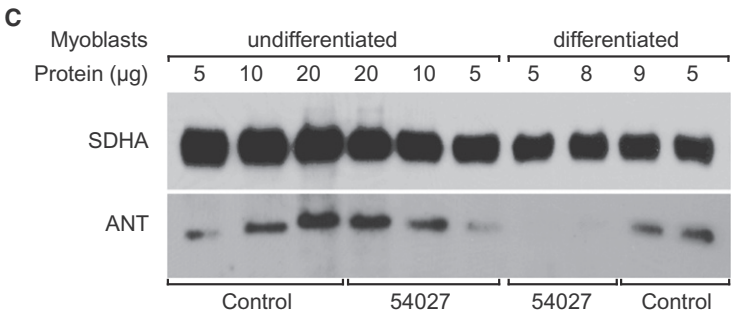


Figure 2. Deficiency in ATP Synthesis and ANT in Sengers Syndrome
The increased ratio of [1-^{14}C]pyruvate + malate + CCCP over [1-^{14}C]pyruvate + malate + ADP oxidation (A) in affected individual 54027 (filled square) versus controls (triangles) indicates a deficiency in ATP synthesis. A decreased amount of ANT (B) was detected with immunoblot analysis in skeletal muscle and in differentiated myoblasts (C) of affected individual 54027. Primary antibodies and their conditions are as follows: ANT antibody (1:1,000; mouse monoclonal; MSA02, Mitosciences) and SDHA (1:30,000; mouse monoclonal; MS204, Mitosciences).

(Figure 1). Measurement of respiratory-chain enzymes in fresh muscle tissue only indicated a slight reduction in the activity of complexes I, II+III, and V (Table 2). However, the analysis of ^{14}C-labeled mitochondrial substrate in 600 g supernatants from fresh muscle tissue[13] had already demonstrated a clearly abnormal ratio of CCCP- to ADP-stimulated oxidation rates in the affected individual, indicating a defective ATP synthesis (Table 2 and Figure 2). Defects in ATP synthesis either affect the F_1F_O ATP synthase, the mitochondrial phosphate carrier, or the adenine nucleotide translocator (ANT).[13] Immunodecoration[14] with an ANT-specific antibody confirmed the absence of the inner-mitochondrial-membrane ANT in muscle tissue (Figure 2). However, normal ANT levels in undifferentiated myoblast cells generated from the same muscle-biopsy material suggested that a specific posttranslational defect of proper inner-membrane ANT assembly only occurs in differentiated muscle fibers. In agreement with this hypothesis, myoblast cells of affected individual 54027 lost ANT during differentiation (Figure 2 and Figure S2).

AGK is commonly described as a multisubstrate lipid kinase that catalyzes the phosphorylation of diacylglycerol (DAG) and monoacylglycerol (with lower affinity).[15] The resulting products, phosphatidic acid (PA) or lysophosphatidic acid (LPA), respectively, can either act as signaling molecules[15,16] or take part in the synthesis of phospholipids. Furthermore, AGK scavenges mitochondrial DAG, which has been reported to induce reactive oxygen species (ROS) signaling via a pathway mediated by protein kinase D1.[17] It has been shown that DAG kinase 1 in *S. cerevisiae* has an essential function in membrane-lipid biosynthesis in the case of growth resumption after a stationary phase, especially when the de novo fatty-acid biosynthesis was inhibited by cerulenin.[18] AGK might play a similar function in the mitochondria (Figure 3) of proliferating or differentiating tissues (e.g., muscle and heart tissue) that predominately procure their energy from fat and are devoid of fatty-acid synthesis; in Sengers syndrome, such tissues are affected the most. Indeed, the most striking effect of AGK depletion in PC-3 cells by siRNA has been a reduction of LPA and PA in mitochondria.[15] PA and its downstream product, cardiolipin, are both found in crystals of ANT,[19] the most abundant mitochondrial protein, which is severely decreased in the muscle tissue of individuals with Sengers syndrome. A disturbed membrane-lipid composition might also be responsible for the zonular nuclear cataract, a region of differentiating cells where the cellular architecture and exact arrangement of the cells are critical for light transmission and lens transparency.

The clinical manifestation of Sengers syndrome resembles defects of mitochondrial ATP synthesis, either of F_1F_O ATP synthase (e.g., *TMEM70* [MIM 612418][20] and *ATP5E* [MIM 606153][21]) or of the mitochondrial phosphate carrier, *SLC25A3* (MIM 600370)[13]. Symptoms of Sengers syndrome also resemble the known cardiolipin-metabolism defect (such as in X-linked Barth syndrome [MIM 302060],[22] which is caused by *TAZ* [MIM 300394][23] mutations) in terms of neonatal onset of the disease, cardiomyopathy, and myopathy. Lactic acidosis is found in Sengers syndrome and in the other defects of ATP synthesis but usually not in Barth syndrome. Elevated excretion of 3-methylglutaconic acid (3-MGA) in urine is found in F_1F_O-ATP-synthase deficiency[20,21] and in Barth syndrome.[24] However, it is usually not found in Sengers syndrome with ANT deficiency or in the SLC25A3 defect,[13] although a mild elevation of 3-MGA in urine was reported in individual 62218.[7] Therefore, Sengers syndrome includes aspects of both ATP-synthesis and cardiolipin-metabolism defects.

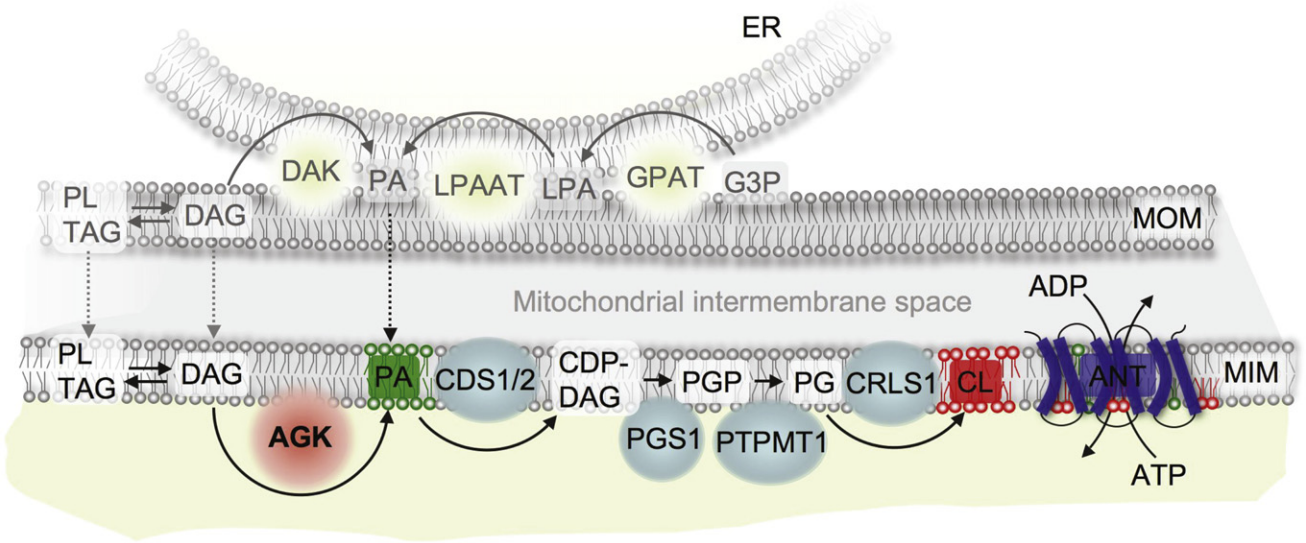


Figure 3. Potential Role of AGK in the Mitochondrial Lipid Metabolism
Abbreviations are as follows: AGK, acylglycerol kinase; CDS, CDP-diacylglycerol synthase; PGS, phosphatidylglycerophosphate synthase; PTPMT, phosphatidylglycerol-phosphate phosphatase; CRLS, cardiolipin synthase; ANT, adenine nucleotide translocator; DAK, diacylglycerol kinase; GPAT, glycerol-3-phosphate acyltransferase; LPAAT, 1-acylglycerol-3-phosphate O-acyltransferase; G3P, glycerol 3-phosphate; LPA, lyso-phosphatidic acid; PA, phosphatidic acid; DAG, diacylglycerol; TAG, triacylglycerol; PL, phospholipid; CDP-DAG, cytidine diphosphate diacylglycerol; PGP, phosphatidylglycerol-phosphate; PG, phosphatidylglycerolll; CL, cardiolipin; ER, endoplasmic reticulum; OMM, outer mitochondrial membrane; and IMM, inner mitochondrial membrane.

At the moment, it is purely speculative whether the tissue expression of the four different ANT isoforms correlates with the pathomechanism in Sengers syndrome. ANT1 encoded by *SLC25A4* is the major isoform in muscle and heart tissue, whereas ANT3 (*SLC25A6* [MIM 300151]) is ubiquitously expressed.[25] ANT2 (*SLC25A5* [MIM 300150]) is mainly associated with smooth muscle cells,[25] and ANT4 (*SLC25A31* [MIM 610796]) is mainly expressed in the liver, testes, and brain.[26]

In summary, the biochemical data are consistent with a defined role of AGK in driving the assembly of ANT and, in some circumstances, respiratory-chain complexes as a result of its effects on phospholipid metabolism in mitochondria. Given the strong pre-existing evidence of mitochondrial dysfunction in Sengers syndrome, exome sequencing of a single affected individual coupled with the appropriate filtering of candidates for mitochondrial functions allowed us to identify *AGK* variants as the cause of Sengers syndrome in a significant proportion of individuals and to reveal an unexpected link between lipid metabolism and ATP synthesis.

Supplemental Data

Supplemental Data include two figures and two tables and can be found with this article online at http://www.cell.com/AJHG.

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Web Resources

The URLs for data presented herein are as follows:

Online Mendelian Inheritance in Man (OMIM), http://www.omim.org
MitoP2, http://www.mitop.de

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