Gene Technology
ISSN: 2329-6682
Kor et al., Gene Technol 2016, 5:1
DOI: 10.4172/2329-6682.1000140
Case Report Open Access

# Two Novel Mutations in the AGK Gene: Two Case Reports with Sengers Syndrome

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**Abstract**

Mutations in the AGK gene are known to cause Sengers Syndrome, a rare recessive disorder characterized by congenital cataracts, hypertrophic cardiomyopathy, skeletal myopathy, exercise intolerance and lactic acidosis with normal mental development. Since the first report in 1975 by Sengers et al. about 50 individuals have been described as having this syndrome.

Here we report two novel mutations in the AGK gene in two patients with neonatal Sengers syndrome.

**Keywords:** AGK gene; Sengers syndrome; Cardiomyopathy; Myopathy; Cataract

## Introduction

Sengers Syndrome (OMIM 212350), also known as cardiomyopathic mitochondrial DNA depletion syndrome-10 (MTDPS10) is a rare autosomal-recessive disorder characterized by congenital cataracts, hypertrophic cardiomyopathy, skeletal myopathy, exercise intolerance and lactic acidosis with normal mental development. Sengers Syndrome is caused by the lack of mitochondrial protein acylglycerol kinase due to the mutations in the acylglycerol kinase (AGK) gene on chromosome 7q34 [1]. There are two phenotypic forms of Sengers Syndrome, a fatal neonatal form, and a late onset chronic, slowly progressive form [2]. Cause of death is invariably due to heart failure as a result of hypertrophic cardiomyopathy [3].

Biochemical studies showed a defect in multiple mitochondrial oxidative enzymes and decreased levels of mitochondrial adenine nucleotide translocator-1 (ANT-1) protein (SLC25A4; 103220) in muscle [4]. Histopathological investigations have shown abnormal structure of mitochondria and storage of lipid and glycogen in both skeletal and heart muscle and severe mtDNA depletion in skeletal muscle, mitochondrial complex I, II, III, IV, and V with combined deficiency and defective ATP synthesis [1,3,5,6].

In this paper, we report two novel mutations in the AGK gene in two patients with neonatal Sengers Syndrome.

## Case Report

### Case 1

The patient was born full term with cesarean section after an uneventful pregnancy. The parents are second-degree consanguineous and of Turkish origin. Their first child was healthy. There was no family history of an inherited disease or a child death. A cataract was noticed in his left eye when he was five days old and a cataract in his right eye when he was two weeks old. Bilateral cataract extractions were performed in another hospital. When he was 4 months old, failure to thrive and motor retardation was noticed. During the detailed examination for the etiology of cataract, cardiomegaly and hypertrophic cardiomyopathy was detected and the patient was referred to our outpatient clinic at the age of 7 months. On physical examination, his height was 70 cm (10-25 p), weight was 6950 g (<3 p) and, head circumference was 43 cm (3-10 p). He had no dysmorphic features. Systemic evaluation was normal except cardiac insufficiency, severe hypotonia, and bilateral contact lenses. His routine hematologic, biochemical and metabolic tests (carnitine-acylcarnitine levels, plasma amino acids and urine organic acids) were within normal limits except elevated levels of creatine kinases and lactate. Echocardiographic evaluation documented hypertrophic cardiomyopathy with an ejection fraction of 30%. Electromyography and cerebral MRI showed no abnormality. A quadriceps muscle biopsy revealed fatty infiltrations in the muscle fibers and myopathic changes. Based on these observations a clinical diagnosis of Sengers Syndrome was made. Sequence analysis of AGK gene showed a novel homozygous missense mutation, p.K99N (c.297G>T) (Figure 1), and the diagnosis of Sengers Syndrome was confirmed (NM_018238.3) The patient died at 22 months of age after an upper respiratory tract infection with cardiac failure. This mutation was not found in the literature. In silico analysis of this variation was done. Mutation taster software was predicted this variant a s a disease causing variation (prob: 0.999999328415186 ) and Polyphen2 software predicted as possibly damaging with the prediction scores (HDivPred 0.886 and HVarProb 0.878) while SIFT score was 0.27 (Tolerated). This variation was in a mostly conserved area in different species like, Macaca Mulata, Felis catus, Mus musculus while it was unconserved in Gallus gallus. Human Splicing finder software predicts some splicing changes like broken wild type splice site at position 165 (Wild type 77.02, mutant 48.07). This variation was not found in 500 clinical exome sequencing data of our patients. This variant was evaluated as a variant of unknown significance but as the clinical picture is clear enough and as parents are heterozygotes, we thought that this variation is most likely a disease-causing variant. Functional studies are needed for exact decision.

### Case 2

The patient was born full term with cesarean section after an uneventful pregnancy. Her parents are first-degree cousins of Syrian origin. Their first child was healthy, and second child died at the age of 6 months with similar clinical picture. Bilateral cataract extractions were

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**Received** December 29, 2015; **Accepted** May 16, 2016; **Published** May 21, 2016

**Citation:** Kor D, Yılmaz BS, Horoz OO, Ceylaner G, Sızmaz S, et al. (2016) Two Novel Mutations in the AGK Gene: Two Case Reports with Sengers Syndrome. Gene Technol 5: 140. doi: 10.4172/2329-6682.1000140

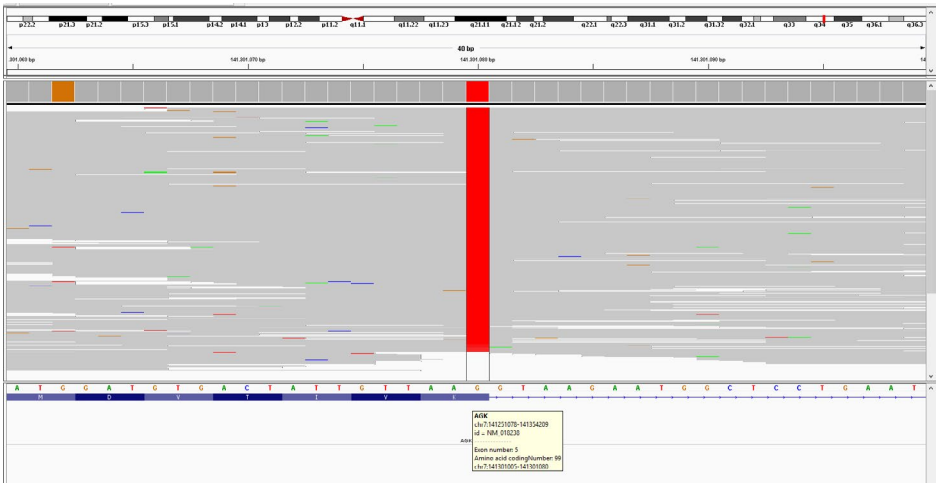

**Figure 1:** A novel mutation homozygous p.K99N (c.297G>T) in AGK gene.

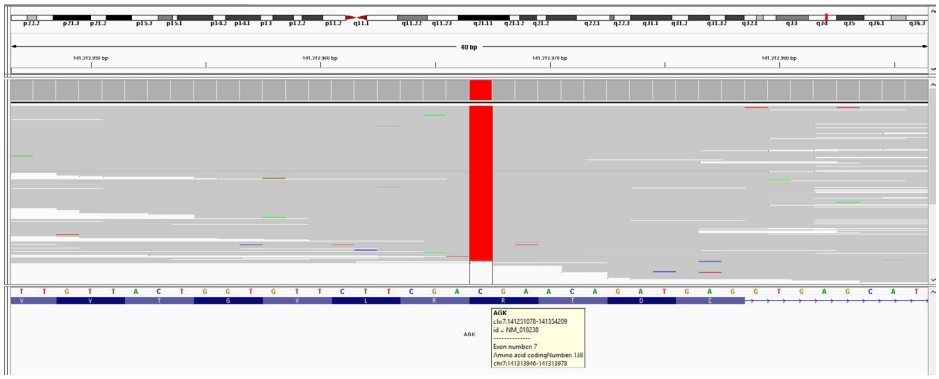

**Figure 2:** A novel mutation homozygous p.R138* (c.412C>T) in AGK gene.

performed in another hospital. During the detailed examination for the etiology of cataract, cardiomegaly and hypertrophic cardiomyopathy was detected and the patient was referred to our clinics at the age of 23 days. On physical examination her height was 53 cm (50-75 p), weight was 4050 g (50-75 p) and, head circumference was 36 cm (10-25 p). She had no dysmorphic features. Systemic evaluation was normal except cardiac insufficiency, severe hypotonia, and bilateral contact lenses. Her routine hematologic, biochemical and metabolic tests (carnitine- acylcarnitine levels, plasma amino acids and urine organic acids) were within normal limits except elevated levels of creatine kinase and lactate. Echocardiographic evaluation documented hypertrophic cardiomyopathy with an ejection fraction of 65%. Based on these observations a clinical diagnosis of Sengers Syndrome was made. With genetic analysis of AGK gene a novel homozygous p.R138* (c.412C>T) mutation was detected (Figure 2), and the diagnosis of Sengers Syndrome was confirmed. The patient died at 3 months of age with cardiac failure. This mutation was not found in the literature. This variation causes a premature stop codon and causes a severe truncation. While the normal sequence of protein includes 422 amino acids, this mutation causes a short protein includes just 138 amino acids. Although this is a novel variant, we speculate that, this is a disease-causing variant due to its severe damaging nature. Functional studies are needed for exact decision.

## AGK gene analysis

AGK gene sequencing analysis was performed using the MiSeq next generation sequencing (NGS) platform, a FDA approved diagnostic system (Illumina, San Diego, CA, USA). Genomic DNA was extracted according to the manufacturer's standard procedure using the QIAamp DNA Blood Midi Kit (Qiagen, Hilden, Germany). Exons 1 to 16 of the AGK gene and their flanking splice site junctions were amplified using PCR primers, designed with PRIMER©–Primer Designer v.2.0 (Scientific and Educational Software programme) software. PCRs were validated by using agarose gel electrophoresis. After PCR amplification, the libraries were prepared with the NexteraXT kit (Illumina Inc.), according to the manufacturer's instructions. Next-gene sequencing was carried on MiSeq (Illumina Inc.). Sequences were aligned to the hg19 genome within MiSeq Reporter software (Illumina Inc.). Visualization of the data was performed with IGV 2.3 (Broad Institute) software.

## Discussion

Sengers Syndrome also named MTDPS10 is a rare OR disorder caused by the mutations in the AGK gene located on chromosome 7q34. There are two clinically different forms. The clinical course varies from the severe one that causes death in early infancy to the more benign one which allows surviving into the fourth decade [3]. Except the time of death there is no discriminative feature between the two forms [7]. The molecular mechanisms leading to the variable expression of clinical features are still mostly unknown. Current diagnosis of Sengers Syndrome is very important for genetic counseling.

Recently AGK gene has been confirmed as the causative gene in

four studies, identifying two patients, four patients and ten patients with Sengers Syndrome, and three siblings with isolated cataracts [3,5,8,9]. In all studies the gene was identified by exome sequencing.

In this paper we present two novel homozygous mutations of the AGK gene with in two patients with infantile form of Sengers Syndrome. To the best of our knowledge the homozygous c.297G>T missense mutation and c.412C>T stop codon mutation found with AGK gene sequencing analysis in our cases are being reported for the first time.

In differential diagnosis of hypertrophic cardiomyopathy, the key point of diagnosis of Sengers Syndrome is bilateral cataracts. The confirmation of the diagnosis should be done with mutation analysis of the AGK gene. We are reporting these patients due to novel mutations in such a rare disorder. In our patients, these novel mutations caused severe clinical symptoms, including congenital cataracts, hypertrophic cardiomyopathy, lactic acidosis and early death. It also causes skeletal myopathy in one of our cases. Additive clinical data and genetic investigations are still necessary to learn more about this rare disease.

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