

Is the BCS1L variant c.232A>G truly responsible for a GRACILE-like condition?

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Dear Editor,

We read with interest the article by Serdaroglu et al. about a neonate with GRACILE-like syndrome due to the BCS1L mutation c.232A>G who died 5 weeks after birth¹. We have the following comments and concerns.

It is reported that the amount of BCS1L protein, the amount of respiratory chain complex-III, and the assembly of respiratory chain complex-III were not different between the patient and controls.¹ These findings suggest that the variant c.232A>G had no effect on the amount and function of BCS1L or the respiratory chain activity and makes it rather unlikely that the variant was responsible for the phenotype. Were biochemical investigations of the muscle homogenate or of fibroblasts carried out to investigate if the function of complex-III was impaired or not? To confirm pathogenicity of a mutation, the variant and the phenotype not only need to segregate within a family but functional studies need to confirm that the mutation had indeed a pathogenic effect. Obviously, this is not the case with the presented patient.

When looking at the family tree in Figure 1, both parents seem to have the same de novo mutation in the same gene.¹ This is a highly unlikely condition. The constellation more likely suggests that the parents were consanguineous either without being aware of this fact or because of hiding this fact for personal, religious, or ethical reasons.

Both parents were heterozygous for the same BCS1L variant.¹ Did they manifest clinically and were they prospectively investigated for subclinical phenotypic manifestations of the variant? Were first degree relatives of the parents prospectively investigated for phenotypic features of a mitochondrial disorder (MID)?

Though it is mentioned that cerebral involvement was excluded we should be informed if the exclusion was based on the clinical exam or on imaging studies and the EEG. Since GRACILE syndrome may go along with encephalopathy² it would be interesting to know if the cerebral MRI and the EEG were truly normal. In a previously described female neonate carrying a novel BCS1L mutation, intracerebral hemorrhage was reported.³ Additionally, psychomotor development was severely delayed and autopsy showed a specific pattern of astrogliosis and widespread loss of microglia in the cortex.³ Two other children with BCS1L mutations presented with early-onset developmental delay, spasticity, seizures, lactic acidosis, brain atrophy and MRI signal changes in the basal ganglia.⁴ A 20 year-old Kenyan female carrying a BCS1L mutation had focal seizures and optic atrophy.⁵ Did the reported patient ever develop seizures?

Overall, this interesting case could be more meaningful by more convincing confirmation that the reported variant was truly pathogenic, by in-depth investigations of the parents and their relatives for a clinically or subclinical MID, and by investigation of the index case for subclinical involvement of organs other than the ones reported. Cerebral involvement in BCS1L mutations needs to be excluded by functional and imaging studies.

Key words: mitochondrial, respiratory chain, complex-iii, Gracile syndrome, lactic acidosis.

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Response to "Is the BCS1L variant c.232A>G truly responsible for a GRACILE-like condition?"

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Dear Editor,

We thank to the author(s) for interest in our research. The Fellman group has performed many studies showing that the BCS1Lc.232A>G (p.S78G) homozygous mutation is causative for the GRACILE-disorder in humans.¹⁻⁵ By producing a knock-in mouse model with the same mutation, the Fellman group has showed that the mutation results in homozygous mice in a similar disease entity.⁶⁻¹¹ In the mouse model, however, the genetic background has a considerable impact on the phenotype of the homozygotes. The short-lived homozygotes have a similar mitochondrial liver and kidney manifestation as in humans⁶⁻⁹, whereas in another mouse strain the homozygotes survive several months and display several organ manifestations¹⁰, including a typical change in the barrel cortex.¹¹

There is no reason to question that the homozygous mutation of c.232A>G is the etiology of GRACILE syndrome. Heterozygous humans and mice are healthy.¹⁻¹⁰ Interestingly, in a patient with two novel mutations (compound heterozygosity) in the gene, the patient had a severe neurological disease.¹¹ This is in line with the literature on human BCS1L-mutations, that there is wide variation in the phenotypes. Likewise, we show in the criticized article that a homozygous mutation in an adjacent region of gene (c.296C>T, p.P99L) in an infant of Turkish genetic background had a disease similar to GRACILE syndrome, but not fully identical.¹² This mutation with the GRACILE-like phenotype has been found in several Turkish newborn infants. Thus, also in humans, the genetic background has an impact on the phenotype.

In regard of the phenotype of the presented infant, clinical seizures were not noted. Cranial ultrasonography was normal; thus, we did not have cranial magnetic resonance imaging in the early phase of the disease. Unfortunately, we also could not obtain postmortem brain tissue.

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