CASE STUDY

Diagnosis of *LAMA2*-Dystrophy Provided by the Strand Clinical Exome Test

Introduction

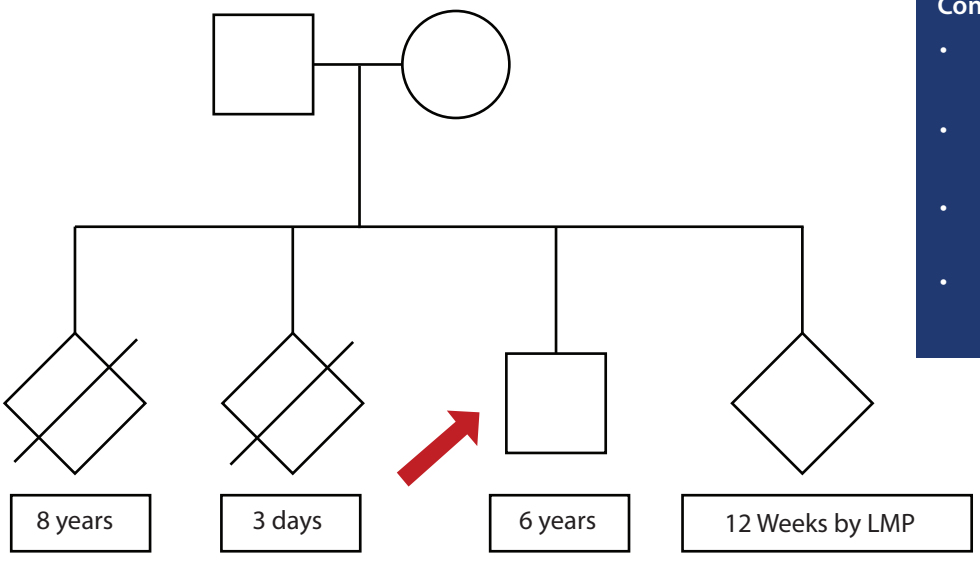
Inherited muscular dystrophies are characterized by progressive muscle degeneration that results in several health problems. Early onset inherited muscular dystrophies can have high mortality and guarded prognosis.

Family History

Radhika* and Sundar, a couple from a southern state in India, had lost two children, one at age 8 years and the other within a few days after birth. Their third child, 6-year-old Aditya*, had been diagnosed with congenital muscular dystrophy. In their subsequent pregnancy, Radhika and Sundar were anxious to understand whether the newborn was likely to survive or not. Even if the child survived, they were not sure if the child would have the same kind of health problems that Aditya has.

Sundar and Radhika were referred to a prominent clinical geneticist in the country. Going by Aditya's symptoms, their doctor suspected the incidence of early-onset, heritable muscular dystrophy and advised them to get genetic tests done to confirm the diagnosis.

Family Tree - Pre-test Genetic Counselling



Proband : Child
Gender : Male
Age : 6 years
Unborn Fetus : 12 weeks

Diagnosis : *LAMA2* Muscular Dystrophy

Strand Test : Clinical Exome

MST : Parents and unborn sibling

Conclusion :

- Proband compound heterozygous for 2 mutations in the *LAMA2* gene.
- Parents are carriers of one mutation each.
- Fetus negative for one mutation and heterozygous for one.
- Expected to be unaffected by the same condition

Aditya had an older brother who had also suffered from muscular dystrophy and was lost to the disease. Another sibling had expired within a few days of birth.

The Strand Clinical Exome Test was prescribed, in order to understand the genetic mutations that caused his muscular dystrophy.

** Name changed to protect patient privacy*

Results of Genetic Testing (Aditya's DNA)

RESULT **Positive** for two heterozygous 'pathogenic' variants, which were detected in exon 50 and exon 62 of the *LAMA2* gene.

Key Findings

Gene	Variation	Zygosity	Clinical significance
LAMA2	chr6:129785589C>T c.7147C>T p.Arg2383Ter	Heterozygous	Pathogenic
LAMA2	Chr6:129828697>T c.8767G>T p.Glu2923Ter	Heterozygous	Pathogenic

Two distinct mutationss were identified in the *LAMA2* gene during Aditya's genetic testing. Both variants are known to cause an inherited muscular dystrophy known as *LAMA2* dystrophy.

Interestingly, Aditya was found to be compound heterozygous for these two mutations. This suggested that he had inherited one gene variant each, from either parent. Given this status, Radhika and Sundar decided to undergo genetic testing in order to ascertain their status as carrier individuals. Radhika was also pregnant with another baby and they were anxious to understand the risk of transmitting these variants to the unborn child.

Genetic Analyses of DNA from Sundar and Radhika

Mutation-specific tests* were offered to Sundar and Radhika to understand whether they were carriers for these *LAMA2* variants.

Test details

Strand® Mutation Specific Test:

- To detect the variant, c.7147C>T (p.Arg2383Ter), in exon 50 of the *LAMA2* gene (RefSeq id : NM_000426)
- To detect the variant, c.8767C>T (p.Glu2923Ter), in exon 62 of the *LAMA2* gene (RefSeq id : NM_000426)

Results of Genetic Testing (Radhika)

Results

- **Heterozygous** for the tested variant, c.7147C>T (p.Arg2383Ter), in the *LAMA2* gene.
- **Negative** for the tested variant, c.8767G>(p.Glu2923Ter), in the *LAMA2* gene.

The parameter marked with an * are not accredited by NABL and CAP.

Results of Genetic Testing (Sundar)

Results

- **Negative** for the tested variant, c.7147C>T (p.Arg2383Ter), in the *LAMA2* gene.
- **Heterozygous** for the tested variant, c.8767G>(p.Glu2923Ter), in the *LAMA2* gene.

Genetic analyses show that Radhika is a carrier (heterozygous) for the c.7147C>T mutation and does not have the c.8767G>T variant. Conversely, Sundar is heterozygous for the c.8767G>T mutation but does not have the c.7147C>T variant in his genome. Aditya inherited one variant each from either of his parents.

It is possible that the deceased children of this couple had been compound heterozygous for these variations in the LAMA2 gene. Since the couple was pregnant with another child, chorionic villus sampling was advised, in order to obtain tissue which essentially has the same genetic makeup as the fetus, for genetic testing.

Genetic Analysis of DNA from Radhika's Fetus

Results

- **Negative** for the tested variant, c.7147C>T (p.Arg2383Ter), in the *LAMA2* gene.
- **Heterozygous** for the tested variant, c.8767G>(p.Glu2923Ter), in the *LAMA2* gene.

The fetus had not inherited the c.7147C>T variant of the *LAMA2* gene. However, the fetus was heterozygous for the c.8767G>T variant in the same gene.

Inheritance of *LAMA2* Mutations

Disease-causing variations in the *LAMA2* gene can cause dystrophy in skeletal muscles. These are muscles that are required for voluntary movements such as eating, swallowing, walking and holding objects. *LAMA2* dystrophy is manifested in two forms: early-onset and late-onset dystrophies. Early-onset *LAMA2* dystrophy can result in severe retardation of growth because of inability to swallow and in some cases may be fatal (Quijano-Roy et al. 1993). Mutations in the *LAMA2* gene are inherited in an autosomal recessive manner. Therefore, heterozygous or carrier individuals are usually not affected by the disease. However, homozygous or compound heterozygous individuals, like Aditya, manifest symptoms like dystonia, scoliosis and lordosis of the spine, problems with speech, cardiovascular issues and seizures.

Summary

- Aditya (6 years) was found to be compound heterozygous for two distinct mutations in the *LAMA2* gene, thus confirming the diagnosis of *LAMA2*-related muscular dystrophy.
- Mutation-specific testing (MST) was performed on the parents' DNA samples, thereby establishing their status as carriers of one variation each.
- The probability of the unborn fetus inheriting both mutations is 25%. Hence, chorionic villus sampling was done in the current pregnancy to enable genetic testing of the fetus.
- The fetus had not inherited the c.7147C>T variation and was heterozygous for the c.8767G>T mutation.
- Since congenital muscular dystrophy resulting from mutations in the *LAMA2* gene is inherited in an autosomal recessive manner, the fetus found to be heterozygous for one of the two variations is likely to be unaffected with the same condition.
- Radhika's pregnancy was allowed to reach full-term and a healthy baby girl was born to the couple.

Strand Clinical Exome Test

The Strand® Clinical Exome test is a Laboratory Developed Test (LDT) that was developed and its performance characteristics determined by Strand Center for Genomics and Personalized Medicine at Strand Life Sciences.

References

Quijano-Roy, S., Sparks, S.E. & Rutkowski, A., 1993. LAMA2-Related Muscular Dystrophy, University of Washington, Seattle. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22675738 [Accessed October 31, 2017].

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