

# CASE 2: ALI, SARA AND NADIA

## Case

Another family presents to you with spastic paraplegia, the parents hoping to find a diagnosis for their children Ali, Nadia and Sara.

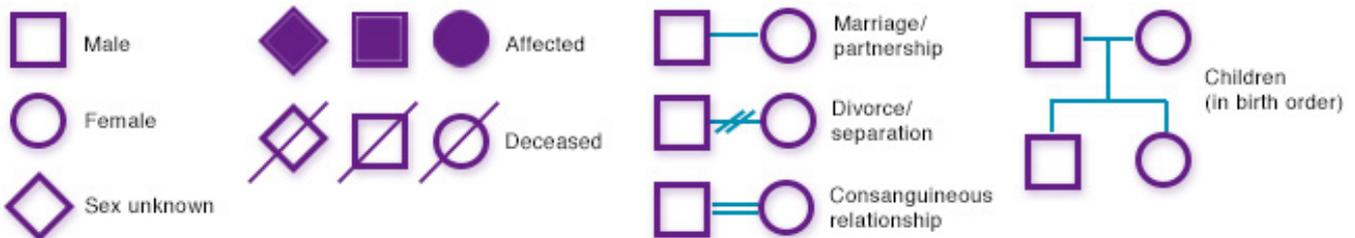
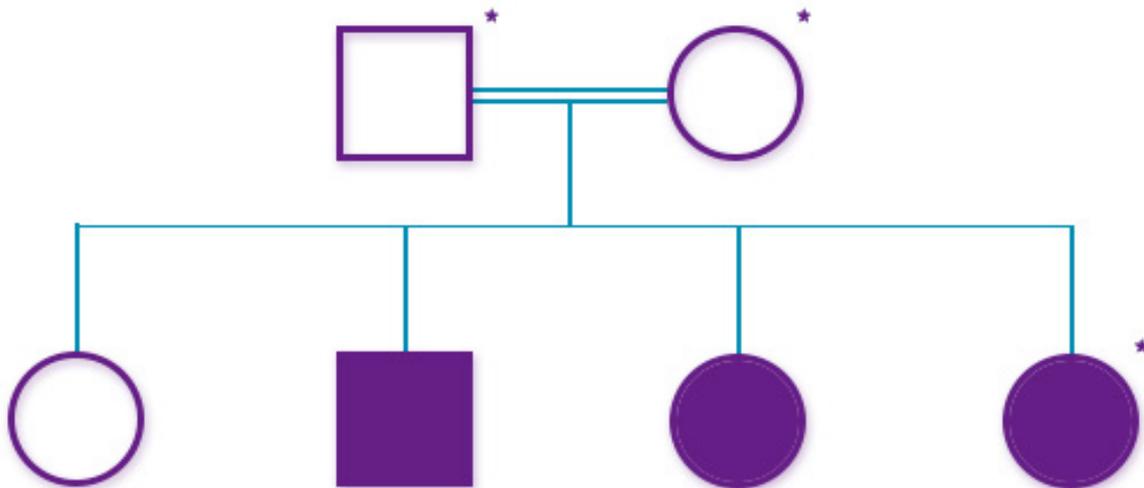
Their son and two of their daughters all have a severe, early onset phenotype, which includes spastic paraplegia, limb dystonia and developmental delay.

Similarly to Case 1, the parents are consanguineous and unaffected.

Genome sequencing is performed in the parents and one of the affected daughters, Sara (marked by an asterisk in the below pedigree).

To review the sequencing data:

1. Log in to Seave (<https://seave.bio/login>)
2. Enter username: drtraining@seave.bio and password: rPucZ0ce
3. Click 'Take me to the data'
4. Select the CaseStudy2 database (CaseStudy2.sorted.vep.db)
5. Follow the written or video instructions for Seave to filter the data and review the remaining variants to find the cause of the children's condition.



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## Answer

No variants were found in known hereditary spastic paraplegia genes that explained the three children's clinical phenotype. Furthermore, no disease-relevant homozygous variants were found despite the history of consanguinity.

Further analysis revealed Sara has compound heterozygous variants in the **GLB1 gene**. This gene encodes beta-galactosidase-1 and is known to cause GM1 gangliosidosis. For more information see [OMIM 230500](#).

Sara has a maternally inherited pathogenic variant (NM\_000404.2:c.(1325G>A); NP\_000395:p.(Arg442Gln)) which has been reported before ([Caciotti et al., 2009](#)). She also has a paternally inherited splice site variant (NM\_000404.2:c.(553-2A>G)) which had not been previously reported.

Further genetic testing found that her two affected siblings shared the same variants.

Wanting to be sure of the diagnosis, you order enzymology for GM1 gangliosidosis on peripheral blood leukocytes. This shows reduced  $\beta$ -galactosidase enzyme activity of 1.6 (normal range 32.5–206.5 nmol/h/mg protein), confirming the diagnosis.

This diagnosis allowed for appropriate genetic counselling and family planning. In addition, screening for complications of GM1 gangliosidosis was introduced, including regular electrocardiogram, echocardiogram, and eye examination.

Note: Case adapted from [Kumar et al., 2016](#) (open access) with some details changed

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