CASE 1: AISHA

Case

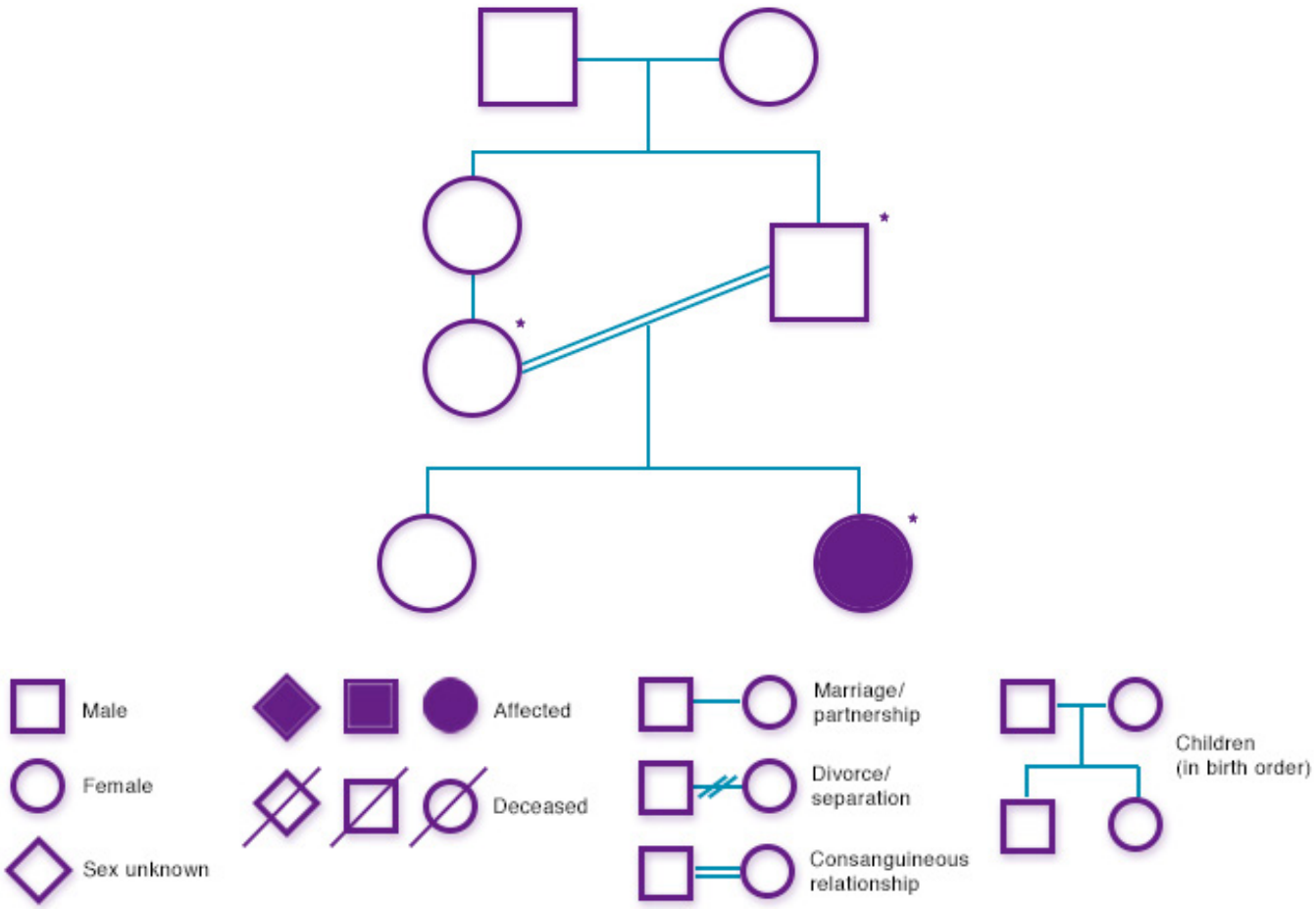
A young girl, Aisha, presents to you with spastic paraplegia (which she began experiencing when she was 3 years old) as well as developmental delay and spastic gait.

Her parents are consanguineous (related) and do not have any of their daughter's symptoms.

You've ruled out other possible causes that you identified in your differential diagnosis, and suspect that this could be genetic. You discuss genome sequencing with the family, and they agree to go ahead.

Genome sequencing is performed in all three (marked by an asterix in the pedigree).

To review the sequencing data:
1. Log in to Seave (https://seave.bio/login)
2. Enter email: drtraining@seave.bio and password: rPucZ0ce
3. Click 'Take me to the data'
4. Select the CaseStudy1 database (CaseStudy1.sorted.vep.db)
5. Follow the written or video instructions for Seave to filter the data then review the remaining variants to find the cause of Aisha's condition.



Answer

Analysis confirms that Aisha has a form of hereditary spastic paraplegia. This condition is highly heterogeneous, with a range of clinical features and over 40 genetic loci 20 genes identified so far. Genome sequencing can therefore be a useful diagnostic tool for this condition.

The cause of her phenotype is identified as a homozygous frameshift deletion in the **CYP2U1** gene (NM_183075.2:c.(782_785delTCTG), NP_898898:p.(Cys262*).

The deletion of these four bases (TGTC) caused the reading frame to be shifted by one base (i.e. a frameshift mutation).

The CYP2U1 gene is known to cause hereditary spastic paraplegia and your patient's variant is at the site of a previously reported pathogenic missense mutation. For more information see Tesson et al., 2012.

This variant is heterozygous in both parents, meaning that they still had one functional copy of the gene.

This diagnosis allowed for appropriate genetic counselling and family planning.

Note: This case adapted from Kumar et al., 2016 (open access) with some details changed.