HCP / Caregiver(s): Dr. Robert

Detailed Summary - Rare Diagnosis

Name	Bob Doe
DOB	11 May 2010
Medical record number	123456754
Based on evaluation through the Undiagnosed Diseases Program (UDP), the likely cause of the patient's condition has been identified as	ABC123-related disorder

Main signs/symptoms

Brain
Epilepsy – seizures started in the first year of life and have been difficult to control
Clinically, Bob's symptoms began with seizure onset on 4/3/2011 in the setting of a febrile illness. This was considered a 'complex' febrile seizure, due to focal onset (head and eye deviation to the right) and repetitive events. He was initially treated with levetiracetam.

Development, learning & behaviour
At 10 months (seizure onset), Bob was not rolling or sitting. He sat without support at 12 months and at 4 years was nonverbal and nonambulatory

Growth
Global developmental delays – Bob is currently non-verbal, can crawl but not walk, and relies on his caregivers for activities of daily living

Evalutions

Previous key evalutions

As BOB DOE came into the UDP, a unifying diagnosis had not been made despite extensive evaluations that included the following key investigations:

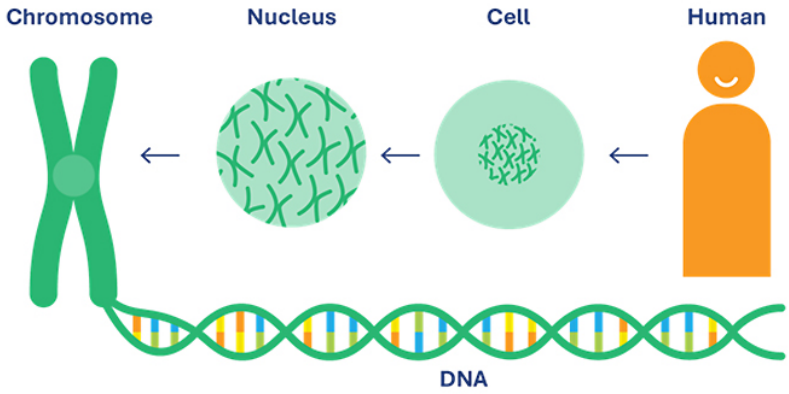
Blood lactate	**2013-11-07**
Serum biotinidase	**2013-11-07**
VLCFA	**2013-11-07**
SNP microarray	**2013-11-07**
Whole genome sequencing	**2015-01-15**

Family history

A three-generation family history shows the following:
no known history of congenital anomalies, developmental delay or seizures.

Test Results and Discussion

Your conclusions regarding the patient
After discussing **BOB DOE** history and signs/symptoms in detail, the team decided to proceed with: **reanalysis of existing whole genome sequencing data**
Based on this new testing and discussion within our team, we now believe we have identified the likely cause of **BOB DOE** condition – a change in a/changes in SINGLE GENE described as: ABC123
The **SINGLE GENE** is one of the approximately 20,000 that are present in the cells of our body.
Each gene comes in two copies and has a very specific job. To do that job, our genes make proteins that make everything in the body work, grow and function properly.
A gene is made up of a long string of many letters (A, C, G and T) that act as an instruction manual for how to make a specific protein. If there are any spelling mistakes in that instruction manual (called a variant), it can cause the gene to make either an abnormal protein or no protein at all, which can cause genetic conditions. Sequencing is the process where the lab reads through the letters of a gene and looks for any changes that may affect how the gene works.



Change/s in the SINGLE GENE

Predicted Class/s	Genes	Chromosome	Nucleotide Change	Protein Change	Zygosity	Effect	Inheritance
Likely pathogenic	ABC123	16	c.412G>C	p.Ala138Pro	heterozygous	missense	de novo

What is known about the function of the SINGLE GENE?

Changes in this gene are associated with a variety of signs/symptoms including:
• developmental delays, some quite profound (e.g., no language), some milder
• epilepsy of different types, including generalized tonic-clonic seizures, partial seizures, or infantile spasms
• microcephaly (smaller sized head)
• other findings were reported, but none in more than one child—these include a degree of muscle weakness, low tone, thickened heart muscle (left ventricular hypertrophy).

Effect of change on protein

Because this gene codes for a protein, the spelling change causes the protein to be made differently.
Although the other copy of Bob's ABC123 gene is working normally, the altered protein is not able to function in the usual way.

Future actions

Why did this happen?

Bob's gene change is 'de-novo' or 'new', meaning it happened for the first time in him – neither parent is a carrier, so neither parent passed it on. This is typical in children with ABC123-related conditions. This information has three important implications.

• First, there is nothing that parents did or did not do that caused the change in Bob. Changes in genes happen fairly frequently, and their cause is largely unknown.

• Second, because neither parent is a carrier, the recurrence risk in future pregnancies of parents is very low, likely much less than 1%.

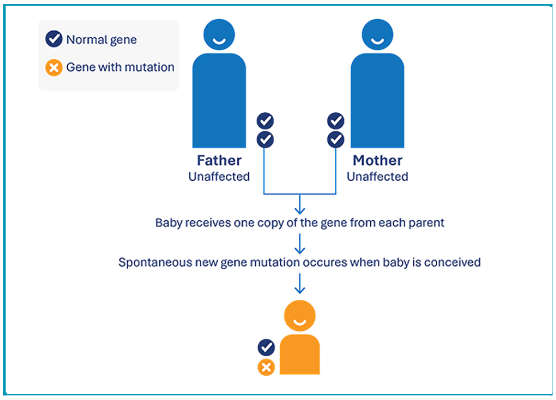
• Third, because the change is 'de-novo' in Bob and his siblings show no signs/symptoms, they are not at increased risk of having children with Bob's condition.

• A change in only one of the two copies of the ABC123 gene is required for a person to be affected, which is known as autosomal dominant inheritance. There is therefore a 1 in 2 chance of Bob passing on the condition if he were to have his own childrend in the future. Genetic counselling is recommended.

Relevant option/s

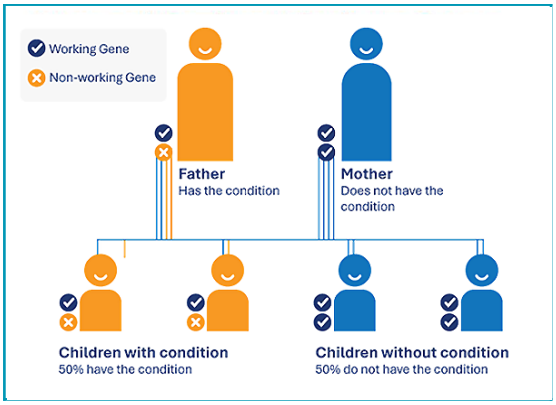
De novo

Testing of **BOB DOE** parents has shown that the **SINGLE GENE** change/s happened as a spontaneous (de novo) event.



Autosomal dominant (parent affected)

Testing has shown that the **SINGLE GENE** has/have occurred in one of the chromosome/s pair/s. This inheritance pattern is called autosomal dominant.



What about the future?

BOB DOE has a very rare condition so while some information is available, it is still relatively scarce. It is likely that individuals with **SINGLE GENE** -related disorder will be increasingly diagnosed, so we expect that over time more information about health issues and long-term outcomes will become available.

What can be done?

Based on our discussion, we have the following recommendations for **BOB DOE** moving forward:

Ongoing care management and coordination:
Manage his complex care in a coordinated way though his current care team or the Complex Care Team at XYZ Hospital. We would be happy to arrange a referral to this service.
• Continue working with Dr. Robert (Pediatric Neurology) to track Bob's progress, control seizures, ensure that his needs are met as well as follow the latest information about the condition.
• Continue working with developmental therapies such as physical therapy, occupational therapy and speech therapy to maximize Bob's potential.

Consider sharing your story with other families and researchers, as it is through these networks that information can be gathered more quickly, for the benefit of everyone. We are happy to help with sharing de-identified information within the network of doctors and researchers doing work on this gene, should you choose to do so.

Addendum

Additional findings from Whole Genome Sequencing

Variants of uncertain significance:
Bob carries two changes in the HFE gene, one from mum and one from dad. Changes in the HFE gene can increase a person's risk for a condition known as haemochromatosis, which causes increased amounts of iron in the blood. Not all people who have two changes in the HFE gene develop haemochromatosis. However, it is important to know as the iron accumulation can lead to certain medical complications in some people. Monitoring of Bob's iron levels will be important in adulthood, treatment is available if appropriate.

BOB DOE has a few differences called 'pharmacogenetic variants', which may influence the way they respond to certain medications. These are the specific variants detected:

CYP2C9, Intermediate Metabolizer
UGT1A1, Intermediate Metabolizer

The lab did not identify any other disease-causing changes in the genes defined as medically actionable by the American College of Medical Genetics.
Home (acmg.net)
ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing

The Food and Drug Administration (FDA) regularly updates a list showing possible interactions between specific variants and medications. BOB DOE health care providers may find this information useful if certain medications are required in the future . Please refer to Table of Pharmacogenetic Associations published by FDA:
https://www.fda.gov/medical-devices/precision-medicine/table-pharmacogenetic-associations

Resource and support links

After the journey to find an answer, receiving a rare diagnosis can be a time of mixed feelings and more questions. Although information and support specific to the diagnosis is often limited, general resources can help with many aspects of daily life as well as moving forward.

Family wellbeing

Rareminds | Mental Health Services for the Rare Disease Community
Your Health and Wellbeing
YoungSibs
Parent feelings: children with disability, autism or other additional needs

Rare disease information and support

Oprhanet - Patient Organisations
Home - Rare Is Everywhere
Extraordinary! A Book for Children with Rare Diseases
Raising Children with Disability | Raising Children Network
Children with Multiple Disabilities, Rare Conditions or are Undiagnosed Navigate Life Texas