I. The Beery Family History
Soon after Alexis and Noah Beery were born it was obvious to their parents, Joe and Retta, that the twins were different from their older brother, Zach. They demonstrated poor muscle tone, cried nonstop, vomited frequently and missed developmental milestones. Physicians diagnosed the twins with cerebral palsy. By age 5, Alexis was having difficulty swallowing and was wasting away, symptoms not consistent with cerebral palsy. Retta came across an article about a rare disorder, dopa-responsive dystonia (DRD), which is caused by a mutation in the sepiapterin reductase (SPR) gene. Joe Beery was hired by Life Technologies (a subsidiary of Thermo Fisher Scientific) where he arranged to have the twins' genomes sequenced as part of a project to understand the molecular basis of their disease and informed a change in their medical treatment.  Joe and Retta’s decision to have the twins’ genomes sequenced was driven by their passion to share their story. According to a recent blog post, "It’s our hope and prayer that people will use their voices in their medical care or any other area of their lives, and never, ever give up hope - no matter how dire the situation may seem. Because hope is unlimited and has no boundaries!"

II. The Beery Family Pedigree
Further examination of the Beery Family pedigree shows a family history of depression on the paternal side and a history of fibromyalgia and undisclosed neurological disorder on the maternal side, in addition to DRD in the twins.

III. Whole Genome Sequencing
In the case of the Beery twins, whole genome sequencing led to a more complete understanding of the molecular basis of their disease and informed a change in their medical treatment. Joe Beery was hired by Life Technologies (a biotech company involved in NextGen DNA sequencing) where he arranged to have the twins’ genomes sequenced by the Baylor College of Medicine. Various bioinformatic filters were applied to eliminate variants that were not thought to be responsible for their condition. Only three variants remained as candidate genes. One of these was sepiapterin reductase (SPR).

IV. Validation and Segregation of Two SPR Alleles
The Sanger sequencing traces (below) show the SPR genotype for each member of the Beery family.

- The Arg150Gly mutation is an A→G mutation on chromosome 2 at nucleotide 72,969,694 leading to the replacement of Arginine with Glycine. The unaffected father is heterozygous (A/G) for the pathogenic Arg150Gly allele at the first locus and homozygous (A/A) for the wild-type allele at the second locus.
- The Lys251X mutation is an A→T mutation on chromosome 2 at nucleotide 72,972,139 resulting in the conversion of a Lysine codon (AAG) to a STOP codon (UGA). The unaffected mother is homozygous (A/A) for the wild-type allele at the first locus but heterozygous (A/T) for the pathogenic Lys251X allele at the second locus.

Each affected twin is a compound heterozygote - (A/G and A/T) with a different pathogenic mutation at each allele.

V. Mapping the Mutations to a Physical Model of Sepiapterin Reductase
- Joe Beery’s Arg150Gly missense mutation (left image) results in a change from a positively charged basic arginine amino acid at position 150 to an uncharged glycine. This would disrupt a salt bridge interaction with the negatively charged aspartic acid at 144 in the functional enzyme.
- Retta Beery’s Lys251X nonsense mutation (right image) results in a change from lysine at position 251 to a premature STOP codon, causing truncation of the enzyme.

VI. The Biosynthesis of Two Neurotransmitters
Sepiapterin reductase is the final enzyme in the biosynthetic pathway for tetrahydrobiopterin — a cofactor used by other enzymes in the synthesis of the neurotransmitters dopamine and serotonin.

In the case of dopamine biosynthesis, the enzyme tyrosine hydroxylase uses tetrahydrobiopterin as a cofactor to convert tyrosine to L-DOPA. In the case of serotonin, the enzyme tryptophan hydroxylase uses tetrahydrobiopterin to convert tryptophan to 5-hydroxytryptophan (5-HTP). In a second reaction in each pathway, aromatic L-amino acid decarboxylase (AAAD) converts both L-DOPA to dopamine and 5-HTP to serotonin, the active neurotransmitters.

What can go wrong?
Mutations in the gene for sepiapterin reductase results in a deficiency in the cofactor tetrahydrobiopterin — which in turn results in deficiencies in dopamine and serotonin.

How can we fix it?
Neurotransmitter levels can be boosted in individuals with a defective sepiapterin reductase enzyme with daily doses of both L-DOPA and 5-HTP. Both of these precursors are downstream of the biosynthetic step that is catalyzed by an enzyme that requires tetrahydrobiopterin.

VII. The Beery Family Today!
Noah and Alexis have a passion to share their story. According to a recent blog post, “It’s our hope and prayer that people will use their voices in their medical care or any other area of their lives, and never, ever give up hope - no matter how dire the situation may seem. Because hope is unlimited and has no boundaries!”

References
2. Huber et al. (1997). The 1.25 A crystal structure of sepiapterin reductase reveals it binding mode to pterins and brain neurotransmitters. The EMBO Journal. 16(24): 7219-7230