Sepiapterin Reductase and the Beery Twins: a Molecular Story From the CBM

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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 demonstrate 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 deficiency of the brain neurotransmitter dopamine. The symptoms matched those of her daughter. Shortly after, Noah's condition worsened. Both twins were treated with L-dopa (dopamine precursor) to vastly improve their condition. As the twins grew older, it became apparent that even this diagnosis was incorrect as their health began to further deteriorate.

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.

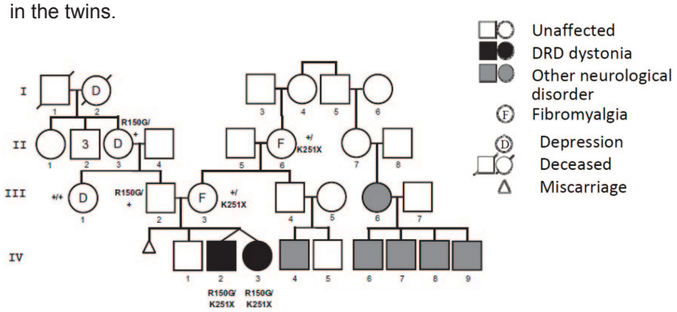


Figure 1. Pedigree of a Family[1]

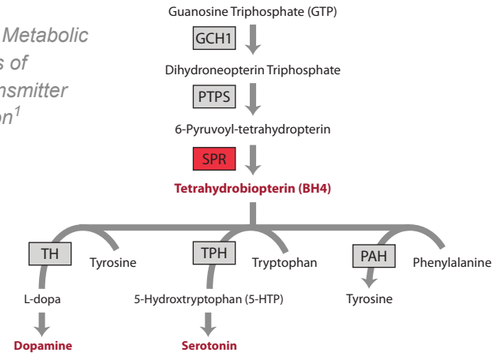
III. Whole Genome Sequencing

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.[1] 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.

IV. SPR's Role in Neurotransmitter Production

Sepiapterin reductase (SPR) is the final enzyme in the biosynthetic pathway of tetrahydrobiopterin, an important cofactor in the biosynthesis of many different neurotransmitters. Mutations in the SPR gene disrupts the production of both dopamine and serotonin.

Figure 2. Metabolic Pathways of Neurotransmitter Production[1]



V. Validation and Segregation of Two SPR Alleles

The Sanger sequencing traces showing the SPR genotype for each member of the Beery family are shown.

The Arg150Gly mutation is a A ⟶ G mutation on chromosome 2 at nucleotide 72,969,094 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 a A ⟶ T mutation on chromosome 2 at nucleotide 72,972,139 resulting in the conversion of a Lysine codon (AAG) to a STOP codon (UAG). 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 compound heterozygous (A/G and A/T) with a different pathogenic mutation at each allele.

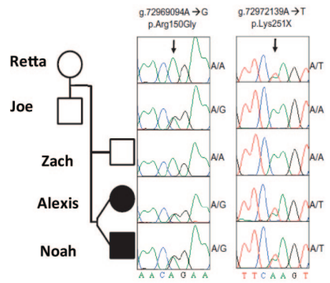


Figure 3. Pedigree and validation of two deleterious SPR Alleles[1]

VI. Sepiapterin Reductase - Based on 1sep.pdb

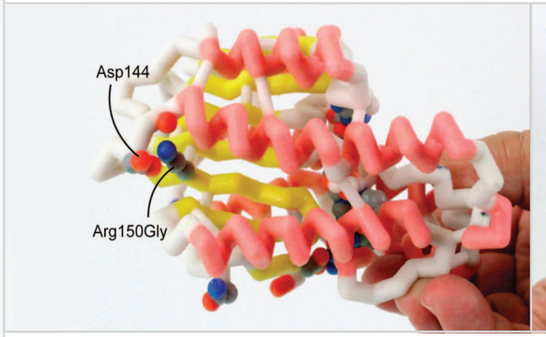


Figure 4. Missense Mutation

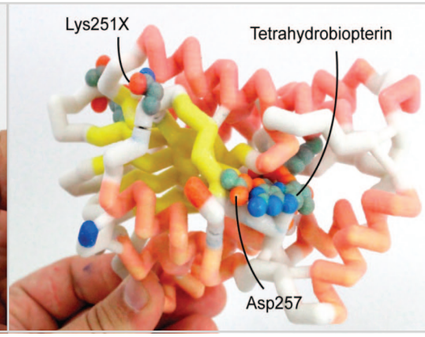


Figure 5. Nonsense Mutation

General Protein Structure:
- Select amino acids are displayed in spacefill and colored CPK.
- The C-terminus is indicated in red while the N-terminus is indicated in blue.

Secondary Structures:
- Alpha helices are highlighted in salmon and beta sheets are highlighted in yellow.

The Beery's Missense and Nonsense Mutations:
- Joe Beery's Arg150Gly missense mutation (Figure 3) 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 (Figure 4) results in a change from lysine at position 251 to a premature STOP codon, causing truncation of the enzyme.

VII. The Beery Family Today!

Based on the finding that both dopamine and serotonin biosynthesis were disrupted in Noah and Alexis, the precursor for serotonin, 5-HTP, was added to the L-dopa therapy that they had been taking. This new combination therapy made a huge difference in the health of both twins and they are now active teenagers leading relatively normal lives.

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!"

http://dystonia.thebeerys.com

References

1. Gibbs et al. (2011). Whole-Genome Sequencing for Optimized Patient Management. Science Translational Medicine. 3(87):1-6

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.

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