Elucidating Genotype-Phenotype Connections in BCS1L Mutations
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Role of BCS1L in the Mitochondria

- Review and document mutations and respective phenotypes from all published cases
- Optimize comprehensive disease descriptions
- Develop BCS1L structural models
- Identify links between particular mutations and phenotypic outcomes

GRACILE Syndrome

- Observed primarily in the Mitochondrial Targeting Sequence
- Disruptions in or near the MTS exhibit a CIII deficiency/GRACILE phenotype, likely caused by lack of BCS1L in the mitochondria.
- Deletions in the 5' UTR inhibit BCS1L translation, also leading to GRACILE.
- Iron overload (characteristic of GRACILE) may be due to disruption of the Rieske interaction.

Complex III Deficiency

- Structural modeling suggests key CIII mutations may occur in regions important for the translocate of Rieske by BCS1L.
- Patients with a mutation on a phosphorylation site (S277N) show CIII deficiency, suggesting this site is key for CIII assembly.

Conclusions & Future Directions

- Reassigning the case diagnoses using optimized disease descriptions was essential for identifying patterns in the relationship between genotype and phenotype.
- Future questions and experiments based on our analysis:
  - Björnstad: Create R85C and R85H mutations to determine the possible role of disulfide bond formation in disease severity.
  - GRACILE Syndrome: Measure iron overload resulting from GRACILE-associated mutations.
  - Complex III Deficiency: Use reactive oxygen species assays along with native gels to determine the severity of Complex III assembly disruption for a particular mutation.
  - Leigh Syndrome: Construct mutations in the Leigh region and use confocal microscopy to analyze the impact on mitochondrial morphology.

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