Elucidating Genotype-Phenotype Connections in BCS1L Mutations

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Rare Disease Research at Calvin College

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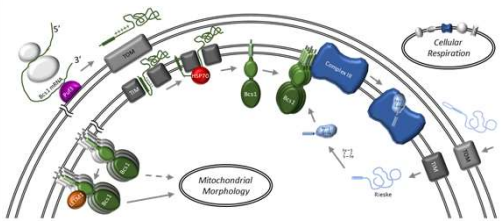
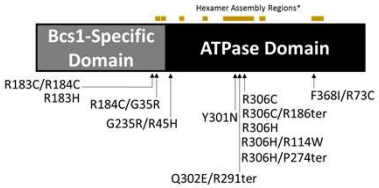
Role of BCS1L in the Mitochondria



- 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

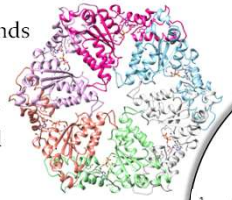
		GRACILE	Complex III	Leigh	Björnstad
Aural/Ocular	sensory-neural hearing loss/deafness	S	R	P	P
	hallucinations	-	-	++	-
	ocular abnormalities	-	-	P	-
Cognitive	encephalopathy	-	P	++	-
	atrophy	-	-	+++	-
	lesions	-	-	P	-
	complications	++	-	P	-
	regression	-	-	++++	-
	disabled	-	-	P	++
Facial/Hair	pili torti	-	-	-	P
	alopecia	-	-	-	P
	microcephaly	+++	++++	-	-
Kidney	tubulopathy	P	S	+++	-
	Faconi syndrome	P	-	++++	-
	dysfunction	-	-	P	-
Liver	elevated enzymes	++	++	++	-
	iron overload	P	-	-	-
	cholestasis	P	-	-	-
	failure/dysfunction	-	+++	P	-
	steatosis	P	-	-	-
	cirrhosis	P	-	-	-
	enlargement	++	-	-	-
Metabolism	lactic acidosis	P	P	P	-
	metabolism complications	P	-	-	-
	Kreb's intermediates	-	-	+++	-
	aminoaciduria	P	+++	-	-
	hypoglycemia	++	P	++++	-
Motor Function	psychomotor retardation/regression	-	P	++++	-
	seizures	-	R	P	-
	weak reflexes	++	-	-	-
	spasticity	-	-	P	-
	postural issues	-	R	++	-
Muscular	hypotonia	R	P	+++++++	-
	muscle wasting	-	-	P	-
	demyelination	-	-	P	-
	weakness	-	-	P	-
Oral/ Respiratory	feeding difficulties/phagia	-	++	P	-
	loss of appetite	-	-	P	-
	vomiting	-	++	P	-
	respiratory complications	-	-	P	-
Other	growth/developmental inhibition	P	P	P	-
	early death	P	S	++++	-
	failure to thrive	S	P	P	-
	skeletal abnormalities	-	-	++	-

Björnstad Syndrome



Observed with homozygous mutations in hexamer assembly contact regions

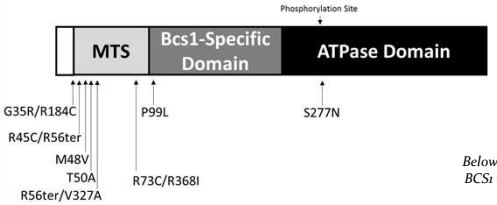
- Heterozygous patients with both a Björnstad mutation and an early termination also exhibit a Björnstad phenotype because only full length BCS1 can assemble.
- The severity of the disease depends on the particular amino acid change (Y301N is more severe than R183H) and whether the possibility for disulfide bond formation is introduced (R183H vs. R183C/R184C).



Chimera model of a hexameric assembly of the BCS1L ATPase domain

*Assembly Regions Not To Scale

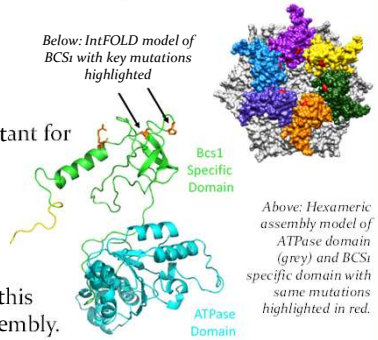
Complex III Deficiency



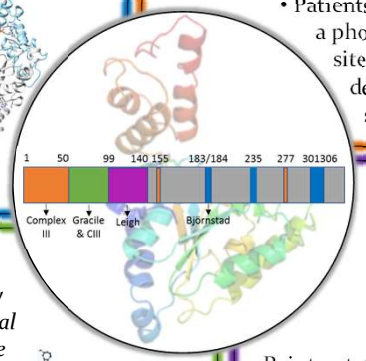
Observed with mutations primarily in or near the Mitochondrial Targeting Sequence

- 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.

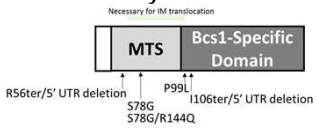
Below: IntFOLD model of BCS1 with key mutations highlighted



Above: Hexameric assembly model of ATPase domain (grey) and BCS1 specific domain with same mutations highlighted in red.

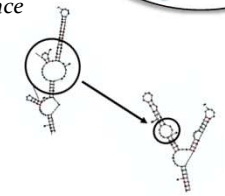


GRACILE Syndrome



Observed primarily in the Mitochondrial Targeting Sequence

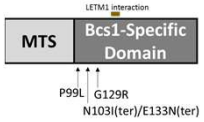
- Disruptions in or near the MTS exhibit a CIII deficiency/GRACILE phenotype, likely caused by lack of BCS1L in the mitochondria.
- Deletions in the 5' UTR inhibit BCS1L translation, also leading to GRACILE.
- Iron overload (characteristic of GRACILE) may be due to disruption of the Rieske interaction.



Deletions in the 5' untranslated region lead to changes in mRNA structure, causing a decrease in translation efficiency.

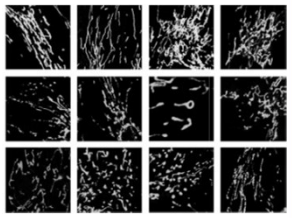
Gil-Borlado et al. (2009), "Pathogenic Mutations in the 5' Untranslated Region of BCS1L mRNA in Mitochondrial Complex III Deficiency."

Leigh Syndrome



Observed primarily in the BCS1 – Specific Domain

- Point or termination mutations near the LETM1 interaction site (important for mitochondrial morphology) present a Leigh phenotype.
- Documented Leigh mutations exhibit fragmented and punctate mitochondria, supporting a role of BCS1 in mitochondrial morphology.
- The characteristic muscular lesions may be linked to a BCS1L role in mitochondrial morphology.



Moran et al. (2010) "Cellular Pathophysiological Consequences of BCS1L Mutations in Mitochondrial Complex III Enzyme Deficiency."

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 R183C and R183H 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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