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Bowen-Conradi Hutterite Syndrome is due in part to a loss of protein-protein interactions

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Background:

Bowen-Conradi Syndrome (BCS) is a developmental disorder in the Hutterite population. It is due to a D86G mutation in the ribosome assembly protein Emg1 making it a ribosomopathy. The BCS mutation is suggested to structurally perturb Emg1, which may alter its protein-protein interactions (PPIs), which are between Emg1 and the ribosome assembly protein Utp2. This later interaction is likely required for import of Emg1 to the nucleolus, the site of ribosome assembly.

Objective:

Our objectives are to create and validate a yeast model system of BCS to use in further understanding the molecular pathogenesis of the disease and to examine changes in the disease's PPIs.

Methods:

Using Saccharomyces cerevisiae, we have created a yeast model system of BCS by placing endogenous Emg1 under the control of a conditional promoter, allowing for genetic depletion of the wild-type protein, and expressing yeast and human wild-type and BCS Emg1 from a plasmid. We examined PPIs between Emg1 and Utp2 using the yeast-two hybrid (Y2H) system, and are currently validating these by co-immunoprecipitation (co-IP).

Results:

Our growth curve shows a distinct growth defect, a hallmark of ribosome mis-assembly, between wildtype and BCS mutant Emg1 from both yeast and humans. This is being further characterized by pre-rRNA processing northern. Antibiotic sensitivity assays suggest that BCS mutant ribosomes may be structurally and thus translationally altered. Through our comprehensive Y2H assay, we show that both yeast and human Emg1 and Utp2 exhibit strong PPIs, which are abolished in the presence of the BCS mutation.

Conclusion:

We have constructed and partially validated a yeast model system of BCS, showing that the mutation causes a growth defect that is likely to perturb the structure and thus the translational fidelity of the ribosome. We also show that the mutation changes the Emg1's PPIs and that these may be an underlying cause of the disease.