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STUDYING THE GENE DOSAGE AND GENETIC INTERACTIONS OF THE BOWEN-CONRADI SYNDROME PROTEIN EMG1

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Background:
Bowen-Conradi Syndrome (BCS) is a ribosomopathy exclusively found in the Hutterite population of the Canadian Prairies. It presents with severe growth retardation and developmental delay, with death in early childhood. BCS is due to a D86G mutation in the ribosome assembly and SSU processome protein Emg1. The mutation causes a hypomorphic allele, with likely localized unfolding of Emg1, leading to the loss of protein-protein interactions , cellular mislocalization, decreased protein stability and abundance.

Objective:
We are exploring the gene dosage and genetic interactions of Emg1 in a yeast model system of BCS using a variety of strategies. This includes the creation of a pseudo-diploid system mimicking the heterozygous/carrier situation, allowing us to identify possible interactions between WT and BCS alleles along with gene dosage effects. We are also examining gene dosage effects using low and high copy-number plasmids with different promoter strengths. Of Emg1's known genetic interactions, we are determining the molecular basis of the positive epistatic interaction between Emg1-snR35, where deletion of the snoRNA rescues the lethal phenotype of the Emg1 depletion. Lastly, we will determine if over-expression of Emg1's only known protein-protein interacting partner, Utp2, can partially restore nucleolar levels of the Emg1-BCS variant.

Methods:
Using a yeast model of BCS we are expressing WT and BCS-Emg1 using a plasmid system and monitoring for rescue of growth defects.

Results:
Results suggest that increased expression of the BCM-Emg1 rescues the growth defects. Similarly, over-expression of Emg1's binding partner Utp2 also rescues the growth defects.

Conclusion:
This will contribute to furthering our understanding of the molecular function of Emg1 in ribosome assembly, how it is perturbed in BCS, and may identify potential therapeutic strategies in the management and treatment of BCS.