Cockayne Syndrome (CS) is a rare, autosomal recessive, neurodegenerative disorder where patients exhibit sensitivity to light and premature aging. CS Type II, the congenital form of the disease, is caused by mutations in the ERCC6 gene [1]. ERCC6 regulates the transcription coupled nucleotide excision repair process and because DNA lesions are the result of UV radiation, loss of ERCC6 leads to an increased sensitivity to light. ERCC6 is also thought to play a role in repairing DNA damage caused by oxidative damage[2]. In order to determine how mutated ERCC6 leads to a premature aging phenotype in Cockayne Syndrome patients, the role of ERCC6 in repairing oxidative damage in mice must be determined.

Aim 1: Identify which ERCC6 protein domains are important for managing oxidative stress using a loss of function method.

**Approach:** I will use SMART and Pfam to identify known protein domains in the ERCC6 protein. I will then screen through known CS-associated ERCC6 mutations and find mutations that are within identified protein domains. Using CRIPSR/Cas9, I will create mice that have induced mutations in one ERCC6 protein domain, and I will do this for all identified protein domains. This will give me different lines of CS mice, where each line is defective in one unique protein domain. I will induce oxidative stress in the skin cells of each mouse line, and will determine the cellular response indirectly by measuring levels of 8-hydroxydeoxyguanosine (8-OHdG), an oxidative derivative of guanosine, using the Cell Biolabs 8-OHdG RNA Damage ELISA [3,4].

**Rationale:** CSB has two major protein domains: a SNF2\_N domain and HELICc domain, which have different functions. Deducing which domain helps mitigate oxidative damage levels will help clarify how the protein interacts with oxidative damage.

**Hypothesis:** I hypothesize that because helicase domains can play an integral role in DNA repair, a knockout of the ERCC6 helicase domain will result in the most accumulated oxidative damage.

References

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