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**Specific Aims**

Noonan syndrome (NS) is a genetic disorder associated with unusual facial characteristics, short stature, heart thickening, bleeding problems, developmental delays and rib cage bone malformations (1). The physiological symptoms of NS are caused by mutations in the **PTPN11/SHP2** gene which is a tyrosine phosphatase involved in cell signaling. In Noonan Syndrome, PTPN11/SHP2 mutants lack autoinhibitory functionality, rendering them constitutively active. It has been suggested that the role PTPN11/SHP2 plays in epidermal development is connected to its role in forming epidermal growth receptor complexes (2). However, the role of PTPN11/SHP2 in epidermal and facial development is not clear.

The goal is to determine the role of PTPN11/SHP2 in regulating epidermal cell growth and facial development. The **hypothesis** is that PTPN11/SHP2 interacts with proteins that control skin development during embryogenesis.

The **long-term goal** of this project is to determine how PTPN11/SHP2 functions in signal transduction during embryonic growth and development. The following specific aims will be used to test our hypothesis and direct our project toward its long term goal:

1. **Identify PTPN11/SHP2 interacting proteins that control epidermal development in zebrafish:** **Approach-** Interacting proteins will be identified using tandem affinity purification (TAP). Identified proteins will be sorted using Gene Ontology (GO) for factors that regulate epidermal cell growth and regulate the formation of epidermal growth receptor complexes. Additionally, conserved factors that are potential epidermal growth factors will be identified using STRING and GO in zebrafish. Mutant PTPN11/SHP2 will be generated with CRISPR. **Rationale-** By examining protein complexes involved with epidermal growth, protein interactions will be identified that are related to skin development. Then, by analyzing the effect of mutated PTPN11/SHP2 and mutated interacting proteins, their role in skin development will be determined and can then be targeted by chemical compounds.
2. **Identify chemical compound that regulates the activity of mutant PTPN11/SHP2:**  **Approach -** The pubchem database will be used to search for inhibitors that affect mutant PTPN11/SHP2 and/or proteins affected by mutant PTPN11/SHP2. **Rationale -** If a compound can be found that can inhibit the activity of mutant PTPN11/SHP2, it will be possible to reverse its effects on skin development. Compounds found will then be tested for their efficacy using phosphoproteomics.
3. **Determine effect of chemical compounds on the activity of mutant PTPN11/SHP2: Approach -** Phosphorylation of proteins that interact with mutant PTPN11/SHP2 will be measured using tandem mass spectrometry. **Rationale** - Since PTPN11/SHP2 has phosphatase activity, by measuring the phosphorylation of PTPN11/SHP2 interacting proteins, the chemical activity of the chosen chemical compounds will be determined.

[References:](http://www.ncbi.nlm.nih.gov/pubmed/14560030)

1. <http://www.ncbi.nlm.nih.gov/pubmed/21396583>
2. <http://www.ncbi.nlm.nih.gov/pubmed/11432805>