Exploring the Landscape of Mutations in the Gene PTPN11

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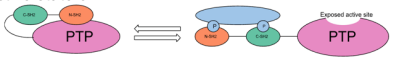
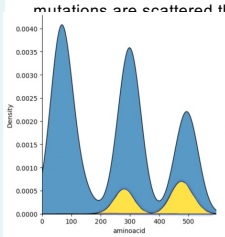
Introduction

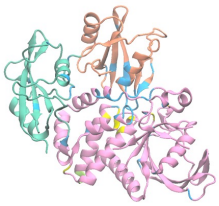
- PTPN11 mutations are associated with various genetic diseases
- The aim of this project is to determine classifiers to identify whether a mutation will result in Noonan's Syndrome(NS) or LEOPARD's Syndrome(LS)

- The SH-2 region folds into the PTP region to form the inactive state of PTPN11



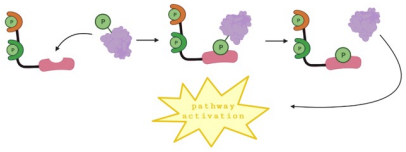
- LS mutations are confined to the PTP domain while NS mutations are scattered throughout the gene



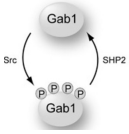


Origins of PTPN11 RASopathies

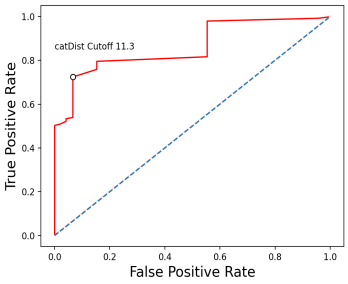
- The gene PTPN11 encodes the protein SHP2 which dephosphorylates signal proteins leading to pathway activation
- LEOPARD's Syndrome and Noonan's Syndrome both favor the open state of SHP2

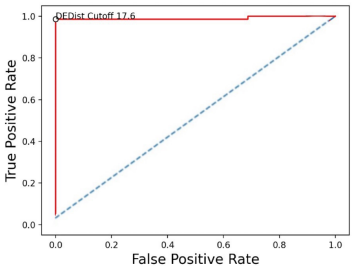


- LEOPARD's Syndrome has a change of specificity and preferentially binds GAB1
- Both NS and LS result in increased activity and similar clinical presentations
- Both NS and LS are associated with cardiac defects in utero
- Early diagnosis is critical in treatment interventions



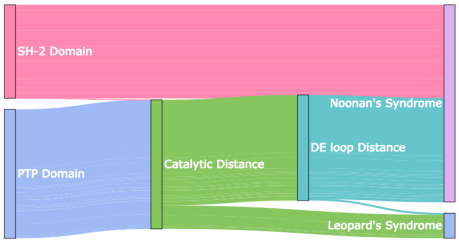
Results

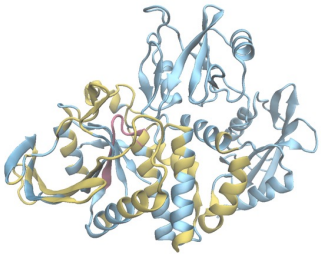




- Logistic regression on PTP domain mutations revealed the distance from the catalytic site as statistically significant
- A ROC curve was used to determine the most accurate cut off point
- Mutations within 11.3 Angstroms from the catalytic site were classified as LEOPARD's Syndrome
- Another logistic regression was run on the remaining mutations and the D'E loop was statistically significant
- Using a ROC curve a classifier for the D'E loop was revealed
- Mutations within 17.6 Angstroms of the D'E loop were concluded to be LEOPARD's Syndrome

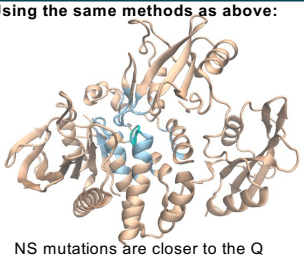
Filtering by Mutation



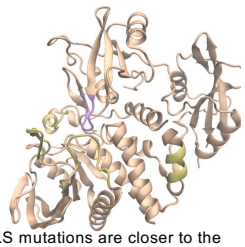


Comparison to Benign PTPN11 Mutations

Using the same methods as above:



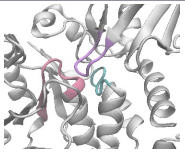
NS mutations are closer to the Q loop than benign mutations



LS mutations are closer to the D'E loop than benign mutations

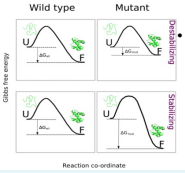
- This confirms that these mutations are being selected for based on their positions near certain functional sites of the protein
- A possible caveat is that mutations near the catalytic site may cause loss of life and are absent from datasets

Features That May Determine Disease



- Catalytic Site: binds with the substrate so dephosphorylation may occur
- D'E Loop: interacts with catalytic cleft and blocks substrate access (closed position)
- Q Loop: aids in catalysis and stabilizing WPD loop

- SAS: surface area that is accessible by a solvent (represented by rolling a ball across the surface)



- DDG: measures the change in energy between native and mutated proteins

Conclusions and Continuations

- LEOPARD Syndrome mutations cluster near the catalytic domain leading to change in specificity
- LEOPARD Syndrome mutations that are further than the cutoff for the catalytic domain are near the D'E loop, which is responsible for the closed PTPN11 conformation
- To confirm these results proteins should be synthesized with mutations within 11.3 Angstroms of the catalytic site and placed in an assay so their dephosphorylation rates may be measured
  - If the enzyme activity is consistent with LEOPARD's Syndrome our results will be confirmed

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