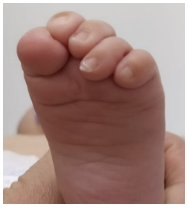
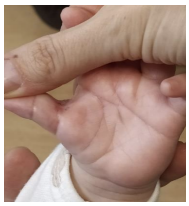
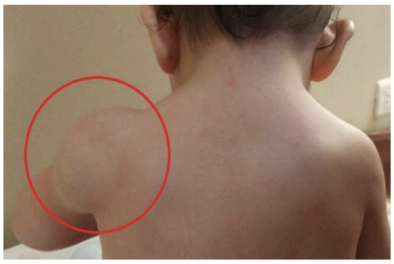
**Case Background**

A baby is born and within the first hours of life, he presents with tachypnea (rapid breathing). Additionally, due to the presence of a heart murmur, an echocardiogram is taken which reveals a slightly thickened pulmonary valve. This results in the use of oxygen for one month.

At two months, growth defects are observed, including a short neck, depressed nasal bridge, abnormal distribution of the hand crease, and overlapping toes. After a geneticist is consulted, Noonan syndrome is suggested as a possible explanation for the growth defects. Noonan syndrome is a common genetic disorder that affects the receptor tyrosine kinase pathway and leads to distinctive facial features, short stature, and congenital heart defects.







At four months, a smooth mass was found in the left shoulder that was determined to be compatible with lymphedema (protein-rich fluid accumulation).

**Biochemistry**


An Epidermal Growth Factor Receptor (EGFR) is a tyrosine kinase that impacts cellular growth and development. Noonan syndrome is caused by a missense mutation in the SOS1 gene. In wildtype cells, the Ras/Sos complex has self-inhibition activity (not shown on the diagram) that regulates the level of the GTP switching. The missense mutation disrupts this self inhibition of the Ras/SOS activity.

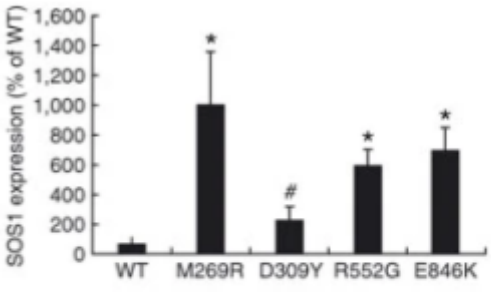
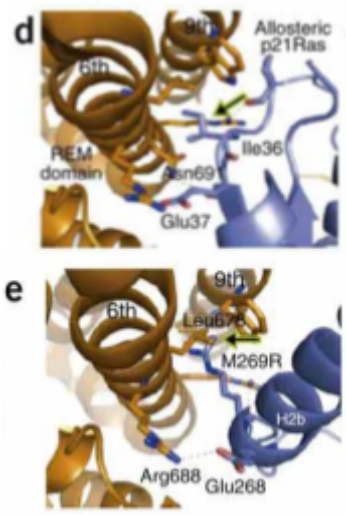



Figure 1. M269R, D309Y, R552G, and E846K are mutant SOS1 proteins. There is a 3-4 fold increase in SOS1 activity for these mutations.

**Question One:**
Does the mutation in SOS1 result in an increase, decrease, or no change in the amount of RasGTP? What are the effects of this mutation on the activity of the EGFR signaling pathway (increased/decrease/no change activity)?

**Question Two:**
The structures on the right are predicted structures of the REM (yellow) and DH (blue) domains of SOS1 which are known to be involved in autoinhibition activity of the SOS/Ras complex. Ras binds allosterically and is not shown in the structures. Image D is the wild-type structure of the REM and DH domains during Ras binding and image E is the mutant REM and DH domains during Ras binding. What do the structures indicate occurs in the mutant SOS1 protein? (Hint: Think broadly about the differences between the WT and mutant structures, not individual amino acids.)




**Question Three:**
What symptoms can be explained by the change in activity of the EGFR pathway? (Rapid breathing, heart murmur, and other growth defects)

**Question Four:**
Mutations in TKR receptors are often present in many kinds of cancer. A common treatment for these cancers is the use of a Tyrosine Kinase Inhibitor (TKI). TKIs disrupt the signal transmission by binding to and inhibiting the activity of the TKR. Why would this treatment not work in the case of Noonan Syndrome?

**Works Cited:**

Nájera, A.; Granda, D.; Arteaga Espinosa, M. E. Síndrome de Noonan Asociado a Mutación Del Gen SOS1. Revista Ecuatoriana de Pediatría 2021, 22 (3). https://doi.org/10.52011/93.

Roberts AE, Araki T, Swanson KD, Montgomery KT, Schiripo TA, Joshi VA, Li L, Yassin Y, Tamburino AM, Neel BG, Kucherlapati RS. Germline gain-of-function mutations in SOS1 cause Noonan syndrome. Nat Genet. 2007 Jan;39(1):70-4. doi: 10.1038/ng1926. Epub 2006 Dec 3. PMID: 17143285.