Ngly-1 deficiency is associated with reduced expression of the protein AQP1 and might explain the phenotype of alacrima in the patients.

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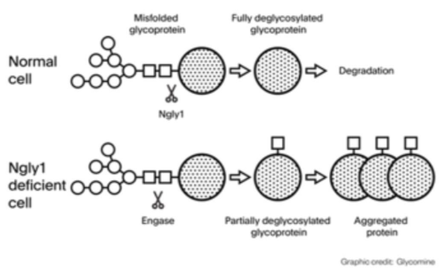
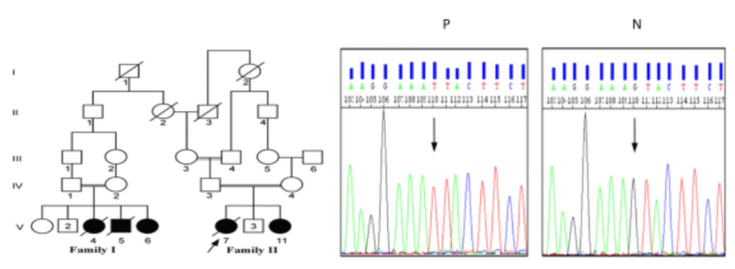
NGLY1 deficiency is a rare AR disorder. Less than 100 patients were reported worldwide. Affected individuals may present with : Intellectual disability and developmental delay ,movement disorders, seizures ,liver disease , Reduced sensitivity to pain and inability to produce tears (alacrima)

We aim To unveil the association between NGLY1 deficiency and AQP1 in our patients and to understand the unknown mechanism of alacrima.

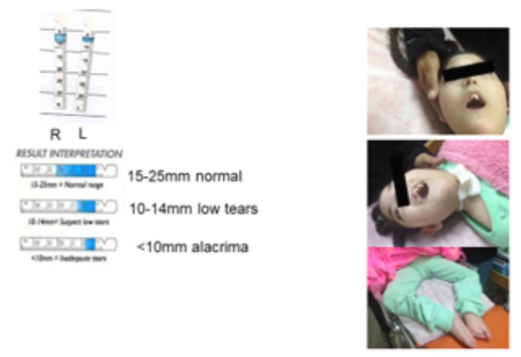
NGLY1 deficiency



A Druze founder variant(c.1294G>T, p.Glu432*)



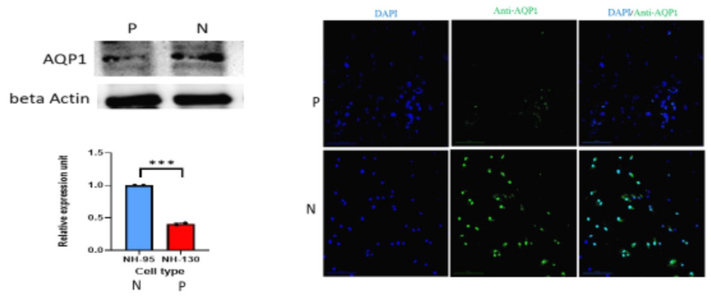
Schirmer's test and alacrima



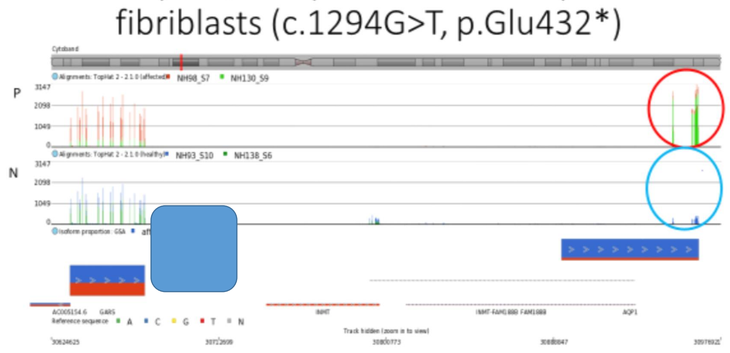
Dog AQP1 exasperation

Aquaporin 1 (AQP1) Expression in Healthy Dog Tears. *Animals* **2020**, .

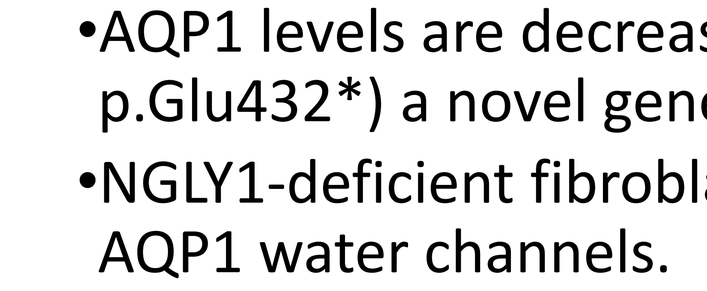
AQP1



RNAseq: AQP1 expression level in patients' fibriblasts (c.1294G>T, p.Glu432*)



Ngly1-Deficient Cells are Resistant to Hypotonic Stress



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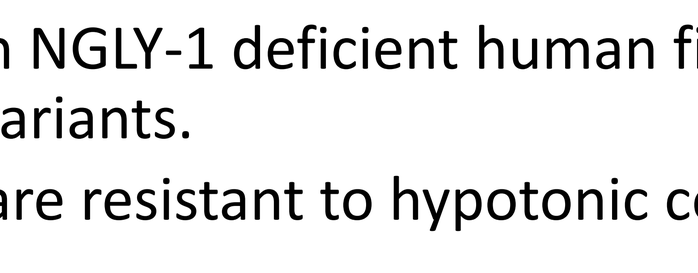
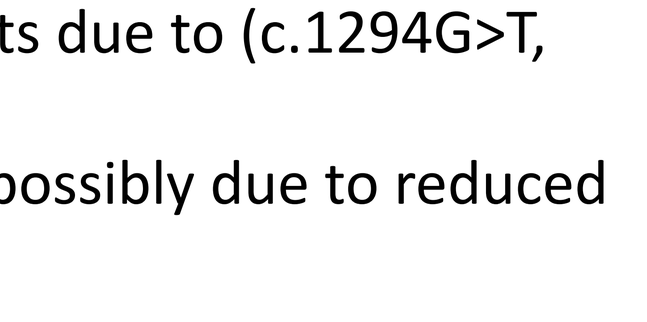


Correlation between AQP1 expression and pain insensitivity in the patients



Conclusions

- Patients with pathogenic mutations in NGLY1 cannot make tears and have global developmental delay.
- N-Glycanase 1 Regulates Aquaporin's transcription in addition to the Enzymatic Activity.
- AQPs are abundantly expressed and serve multiple functions in the eye and brain .
- We hypothesize that low AQP1 levels contribute to the phenotype of alacrima that is reported in all patients.
- AQP1 levels are decreased in NGLY-1 deficient human fibroblasts due to (c.1294G>T, p.Glu432*) a novel genetic variants.
- NGLY1-deficient fibroblasts are resistant to hypotonic cell lysis possibly due to reduced AQP1 water channels.