A transferrin variant impairs the diagnosis of alcohol abuse and congenital disorders of glycosylation

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Introduction

1) CDT

- Carbohydrate-deficient transferrin (CDT) is a performant medical and forensic biomarker for chronic alcohol abuse diagnose [1]
- Transferrin carries two carbohydrate chains with sialic acid end groups
- Chronic alcohol abuse leads to the increase of deglycosylated transferrin [2]
- CDT presents higher specificity, sensitivity and predictive values compared to GGT and Mean Corpuscular Volume [3]

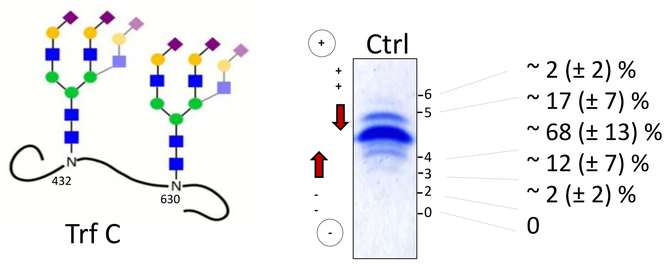
2) Case report

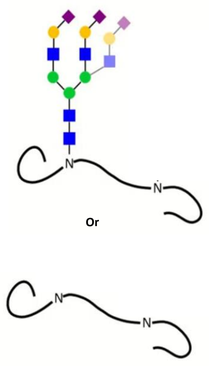
- A 39-year-old male of Tamil ethnicity living on the French island of La Réunion tested for CDT in the context of a driving license regranting
- CDT value > 20% twice by private laboratories using capillarys electrophoresis, unusually high (IFCC reference <2%) [4]
- Exchange between the biologist and the gastroenterologist : absence of symptoms + normal hepatic function
- Control of CDT using alternative immunonephelometric method [5]

→ Result : CDT 1.6%

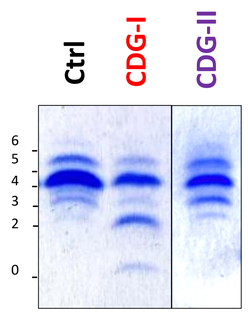
→ Glycosylation status study

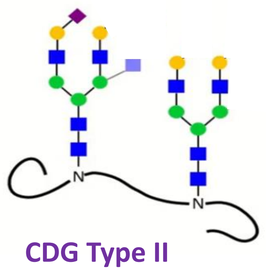
Isoelectric focusing (IEF) principle for the diagnosis of glycosylation defects [6]





CDG Type I





CDG Type II

Distribution of the patient's transferrin glycoforms

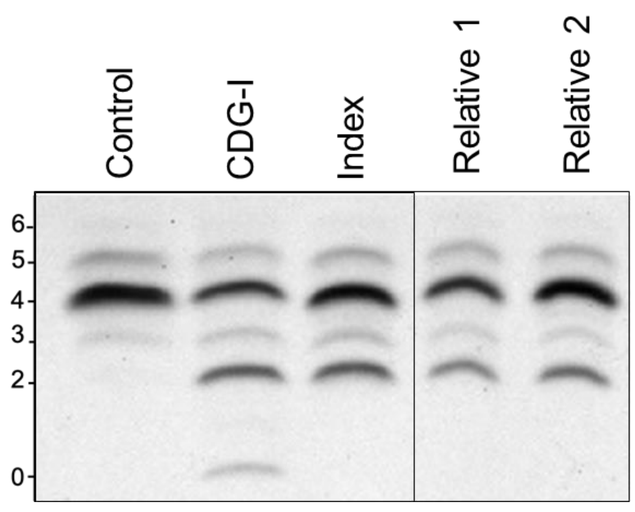
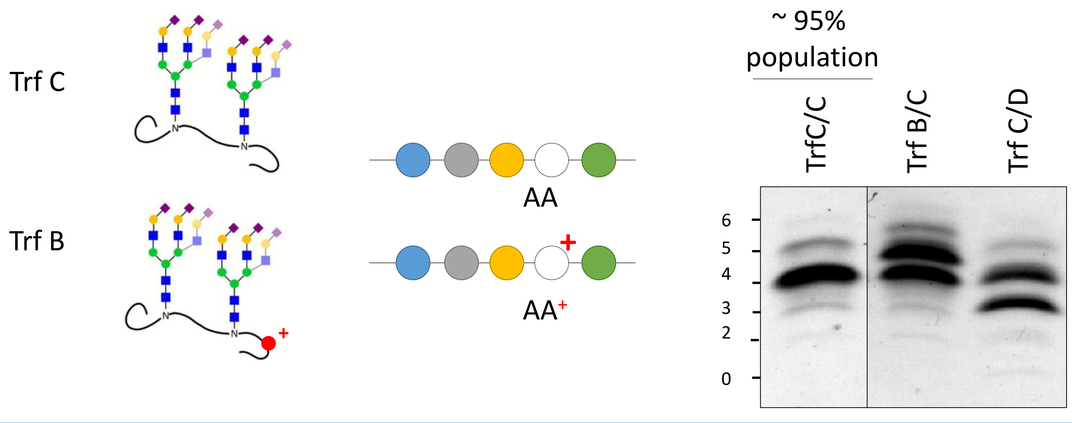


Figure 1: Distribution of Tf glycoforms using Tf isoelectric focusing of the patients compared to control and a common Tf variant [7] (a) Normal serum (b) CDG-I (MPI-CDG) (c) Index case (d) Brother of the index case (e) Cousin of the index case. Left of the figure are the numbers of sialic acid residues present on the Tf

→ 3-sialo↘ ,2-sialo↗, no 0-sialo ↗

Transferrin most common variants [8]



Transferrin isoelectrofocusing of the patient after neuraminidase

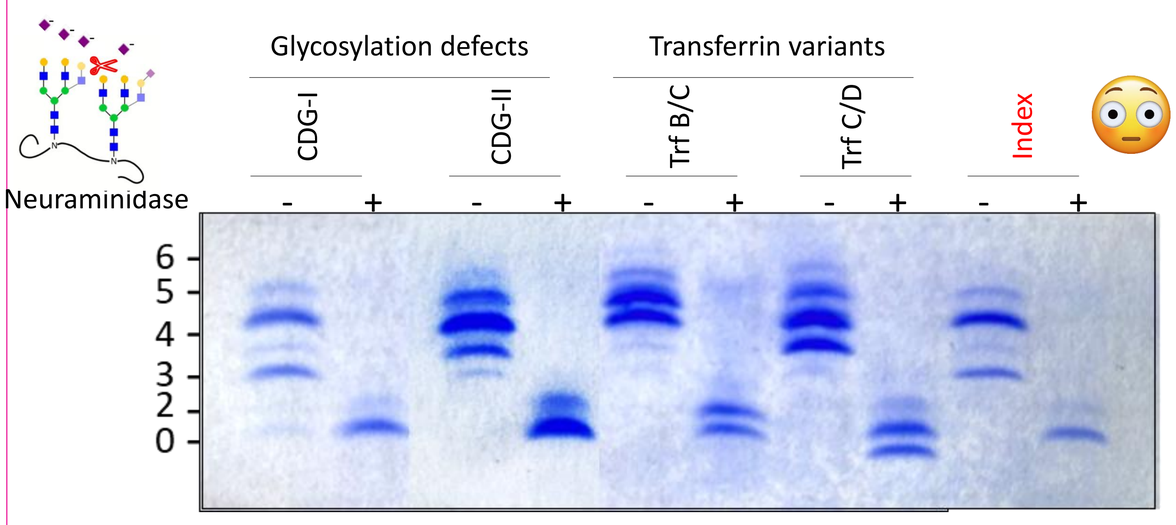


Figure 2: Tf isoelectric focusing profiles before and after neuraminidase incubation [9-14] (a) CDG-I profile (b) Tf heterozygous variant BC (c) Tf heterozygous variant CD (d) Index case. Patients lanes a and are homozygous for Tf CC. Left of the figure are the numbers of sialic acid residues present on the Tf.

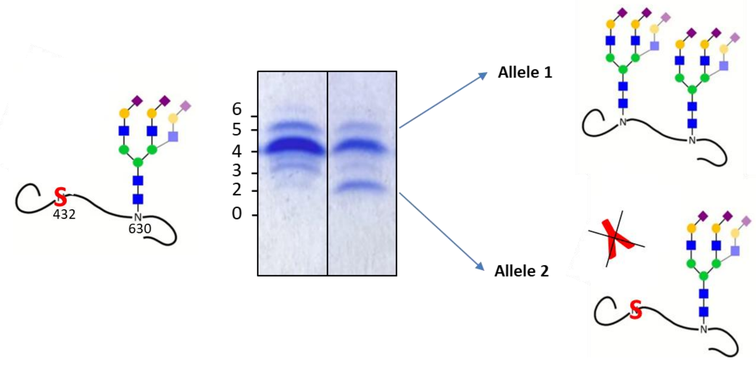
→ 1 band

Case resolution

Genetic analysis using WGS:

- Including *TF* and genes involved in glycosylation

→Heterozygous missense variant NM_001063.4(TF):c.1295A>G in *TF* → p.Asn432Ser



Antibody unable to recognize the site

→ Variant affecting 1 glycosylation site

Conclusion

- The variant explains the results observed in capillary electrophoresis, nephelometry, transferrin isoelectric focusing
- Genetic report to the physician contra-indicating the use of capillary electrophoresis for CDT measurement for the family
- Nephelometry is not optimal: reflects only 75% of the real value
- Recommandation: unusually elevated CDT (> 15%)
- → importance of contacting a specialized laboratory in glycobiology +++
- → use of direct markers of alcohol metabolism [3] (ethylglucuronide + phosphatidylethanol)

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