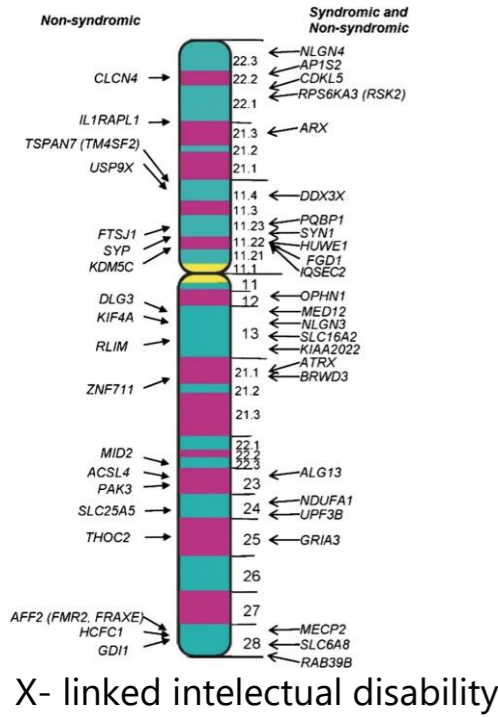




REVERSE PHENOTYPING AFTER NGS PANEL OF X-LINKED INTELLECTUAL DISABILITY UNRAVELS CREATINE TRANSPORTER (SLC6A8) DEFICIENCY

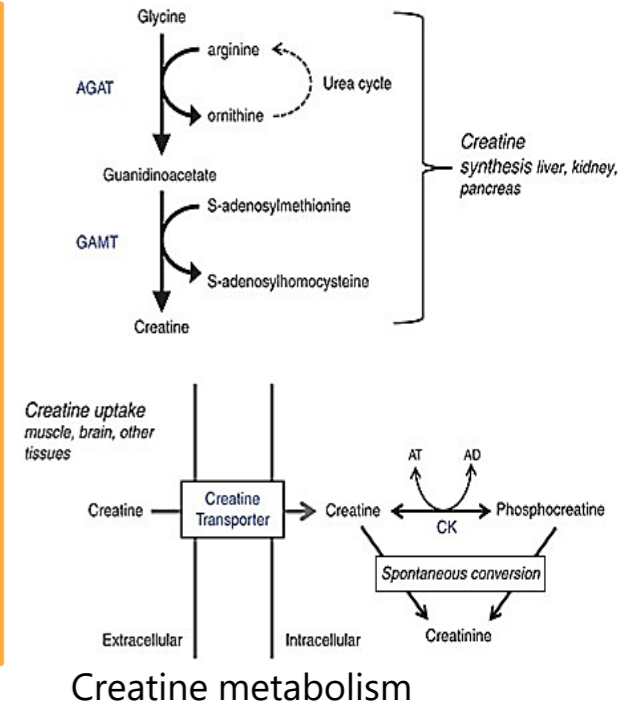
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BACKGROUND:

- X-linked intellectual disability (XLID) is characterized by extensive **genetic heterogeneity**.
- Next-generation sequencing (NGS) is a cost-effective **diagnosis approach**.
- Genetic findings often reveal variants unforeseen during clinical investigation, prompting the need for reevaluation - **reverse phenotyping (RP)**.
- X-linked creatine transporter deficiency (CTD) is a potentially treatable intellectual disability caused by **pathogenic variants in the SLC6A8 gene** leading to impaired creatine transport into the brain.



CASE REPORT

7 YO boy
Intellectual disability
Speech delay,
Hyperactivity
Epilepsy

FAMILY HISTORY
Mother with **learning difficulties**
Maternal uncle with **intellectual disability**

Genetic appointment

X-LINKED INTELLECTUAL DISABILITY (XLID) ???

NGS PANEL

c.880_881Del
(p(Lys294AlaFS*2)) IN THE
SLC6A8 GENE IN
HEMIZYGOSITY

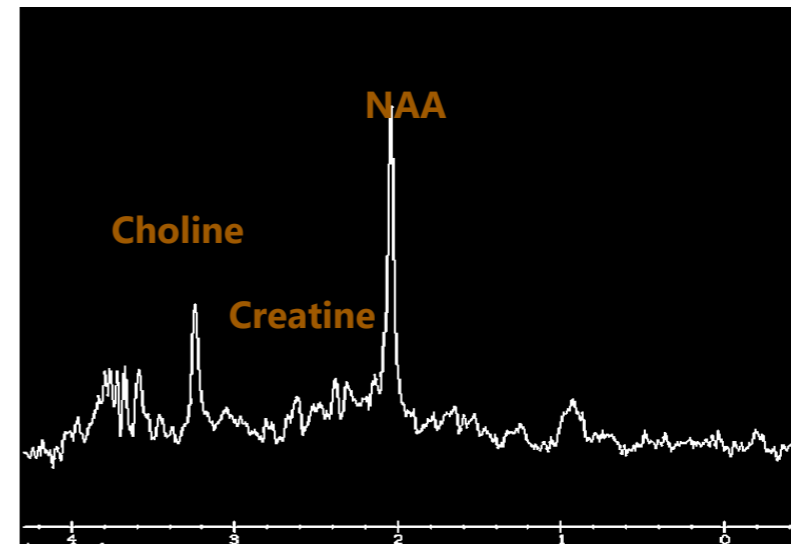
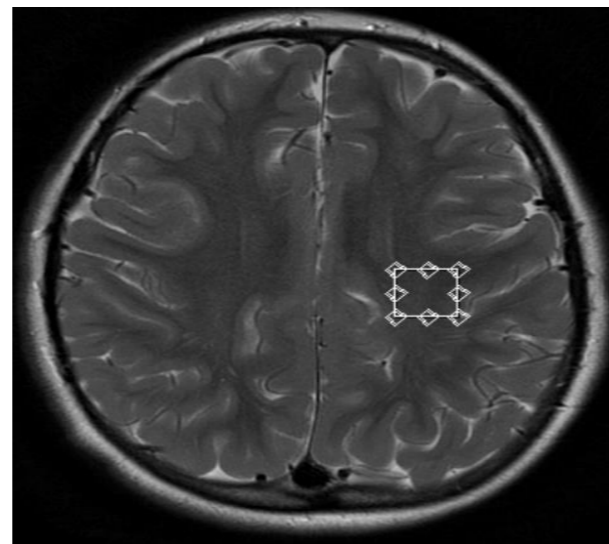
X-LINKED CREATINE TRANSPORTER DEFICIENCY (CTD)

REVERSE PHENOTYPING

Biochemical Test

- **Creatine-Creatinine ratio 2.17** (RV 0,04-1.07);
- **Guanidinoacetate acid 67 micromol/mmol creat** (RV 18-130)
- **Creatine 11060 micromol/L** (RV 146-8560)

MRI with Spectroscopy



Absence of creatine peak

TREATMENT

Creatine-monohydrate 240mg/kg/day
L-Arginine 366mg/kg/day
Glycine 150mg/kg/day



Risperidone 2mg/day
Valproic acid 11mg/kg/day

FOLLOW-UP

Efficacy	How often
Outcome	
Outcomes directly related to brain creatine content	
Primary outcome	
Brain creatine content	Every 6–12 mo
Secondary outcomes	
Epilepsy	Every 6 mo
Global development/intelligence	Every 12 mo
Adaptive function	Every 6 mo
Receptive & expressive language	Every 6 mo
Early academic achievement	Every 6 mo
Emotional/behavior	Every 6 mo
Visual motor skills	Every 6 mo

Based on Treatment of X-linked creatine transporter (SLC6A8) deficiency: systematic review of the literature and three new cases

KEY TAKEAWAYS

- ✓ **NGS panels can uncover unexpected diagnoses in XLID cases**
- ✓ **Reverse phenotyping bridges genetics and clinic validation**
- ✓ **Early detection of CTD enables targeted therapeutic interventions**

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