

Diagnostic value of bikunin in two new cases of linkeropathy

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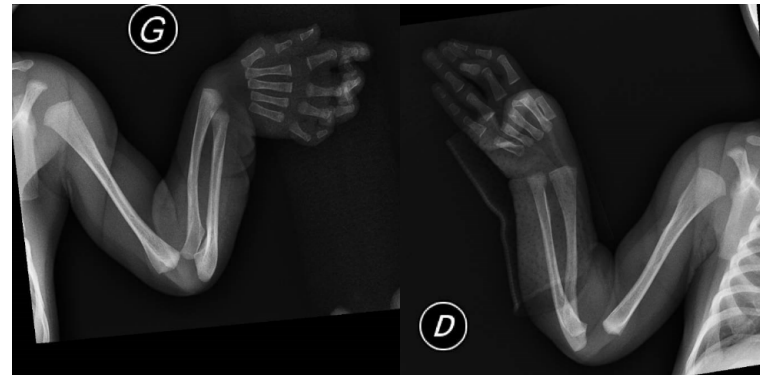
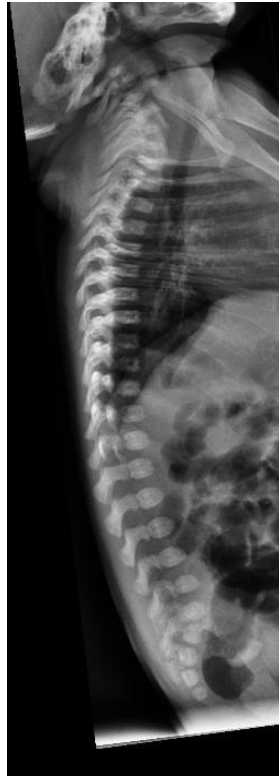
EUROGLYCAN-omics network meeting, Barcelona, 27-29 June 2022



First case report

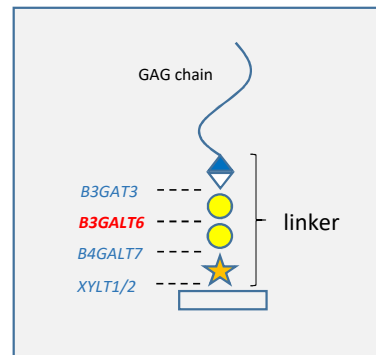
- 5-year-old male, consanguineous parents. Healthy older brother. 4 early miscarriages.
- increased nuchal translucency, fetal hypomobility, *talipes equinovarus*, arthrogryposis and hydramnios.
- birth weight, height and OFC were 2860 g (10th centile), 48 cm (15th centile), and 36 cm (75th centile).
- hypotonia, hypomobility, hypomimic face, *talipes equinovarus*, hands deformity, fingers laxity, contractures of elbows and knees.
- suspicion for severe *arthrogryposis multiplex congenita*. ES identified a homozygous missense VUS in *ADGR6* (*Adhesion G protein-coupled receptor G6*). Biallelic variants in *ADGRG6* were associated to “lethal congenital contractures syndrome 9” (OMIM 616503).
- He later required non-invasive ventilation at night, gastrostomy for feeding difficulties and brace for progressive kyphoscoliosis. At 2 y.o, distal femoral fracture, delayed gross motor development but constant progression in milestones. Able to walk at the age of 4 y.o. Mild speech delay, specialized educational center with physical and speech therapy.
- At 4 years + 9 m, height: 98 cm (-2 SD), weight: 11.4 kg (-3 SD) and OFC: 48 cm (-2.7 SD). Facial dysmorphism. Distal joints and fingers laxity, contractures with elbow deformity, kyphoscoliosis, hypotonia with low muscle mass, soft, doughy and hyperextensible skin, sparse hair, dental anomalies.





Genetics

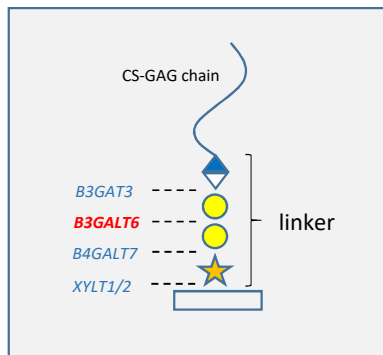
In the context of **ongoing pregnancy** and considering the clinical course of the disease, a re-analysis of the exome data was performed. A homozygous missense variant in **B3GALT6** was identified: c.290G>A, (p.Gly97Asp). Absent from control databases (dbSNP155, Exac, TopMed and GnomAD) and predicted **probably damaging and deleterious** (polyphen2: score 1 and SIFT score: 0.0); CADD score: 24.7



➔ Serum bikunin testing

Serum bikunin analysis

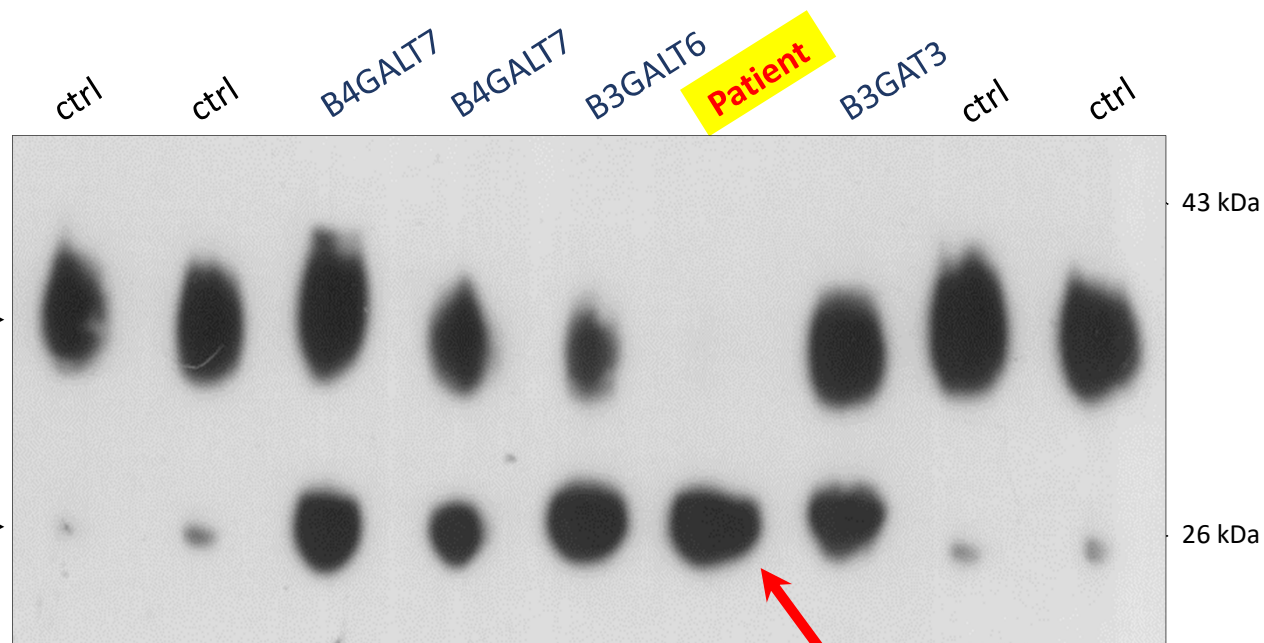
Western-blot



CS chain

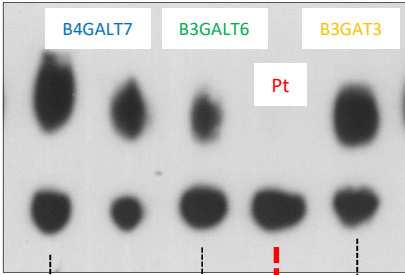
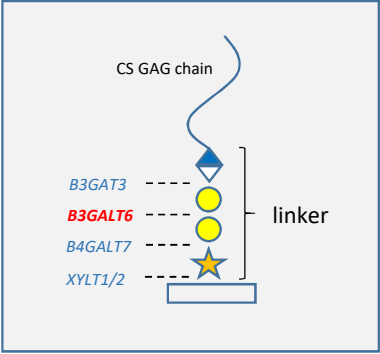
Bkn

Free Bkn

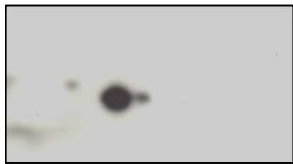
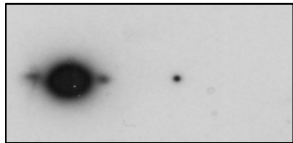
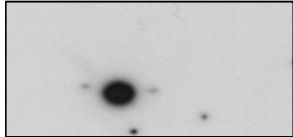
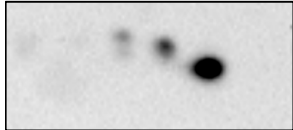


Bikunin analysis

2D electrophoresis



2D Western-blot



B3GALT6

Prenatal diagnosis

Second case report

2-years-old male

Pregnancy: slightly increased nuchal translucency, 1 thoracic hemi-vertebra, asymmetric cardiac chambers.

Amniocentesis: normal CGH array.

Birth weight, height and OFC were 2740 g (32th centile), 43 cm (0.5th centile), and 35 cm (80th centile) at 37+5 WG

Postnatally: association of 2 conditions with:

Oculo-auriculo-vertebral syndrome

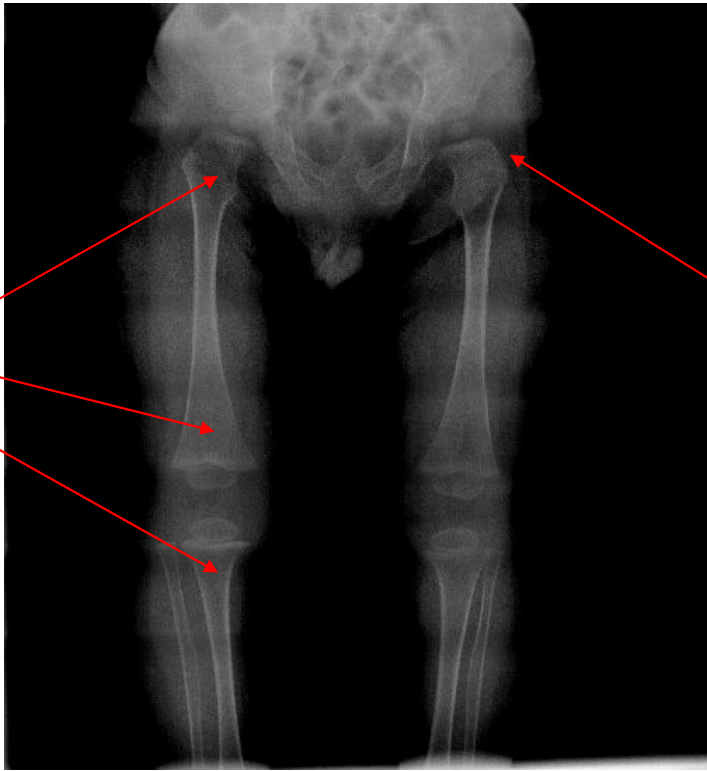
- Right chorioretinal coloboma
- Right outer ear dysplasia; right earing loss with with semi-circular canal malformation and right facial paralysis
- 1 hemi-vertebra (between T10 and T11)

Skeletal dysplasia (in the group of « **dysplasias with multiple joint dislocations** »)

- Short stature (H -3 SD, W -2,8 SD, OFC -0,4 SD) with short limbs
- Congenital left hip dysplasia with dislocation
- Joint laxity, especially knee recurvatum contrasting with elbow *flessum* (limited extension and supination)
- Slight right thoracic scoliosis
- Gross motor retardation (sitting at 14 months)
- Operated inguinal hernia; minor umbilical hernia
- Rather soft skin without hyperelasticity

14 months

Metaphyseal enlargements



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Genetics

Exome sequencing: Identification of **3 variants** in ***B4GALT7*** gene (not reported in HGMD-Pro)

*c.391C>T (**p.Leu131Phe**) maternal - absent from GnomAD

- predictions: probably damaging and deleterious (PolyPhen2 score: 0,957 and SIFT score: 0.01)
- CADD score 24.4

*c.585C>G (**p.His195Gln**) paternal - allele frequency 0.00001062 in GnomAD; no homozygous

- predictions: probably damaging and deleterious (PolyPhen2 score: 1 and SIFT score: 0)
- CADD score 24

*c.629A>T (**p.His210Leu**) paternal - allele frequency 0.00001069 in GnomAD; no homozygous

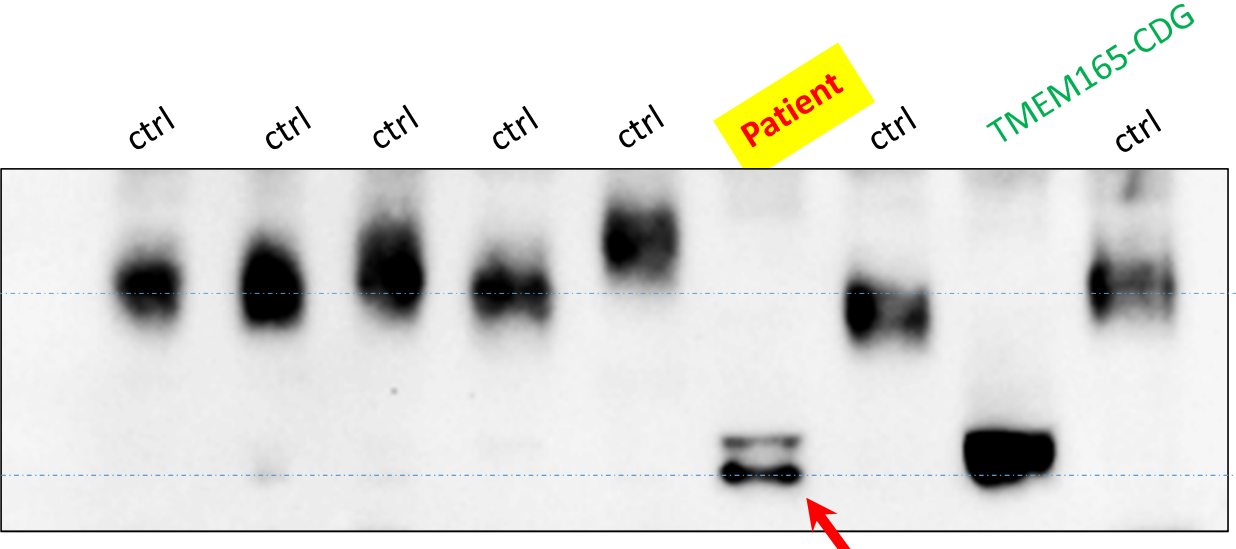
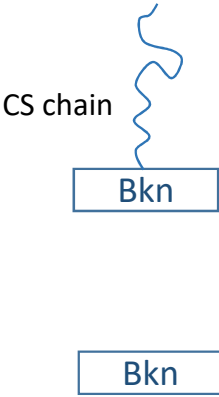
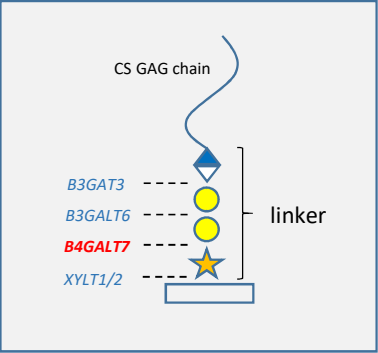
- predictions: benign and deleterious (PolyPhen2 score: 0.181 and SIFT score: 0)
- CADD score 26.6

➔ **Bikunin testing** in order to assert the diagnosis (and for genetic counselling)

- Compatible clinical date, but young age
- Few and slight radiological abnormalities (at young age)
- Not reported variants in HGMD Pro



Serum bikunin analysis

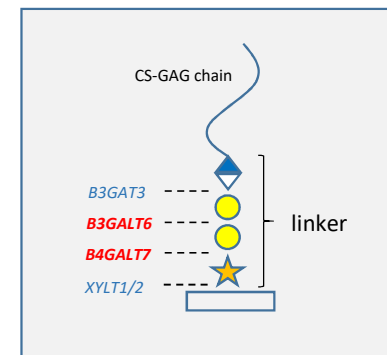
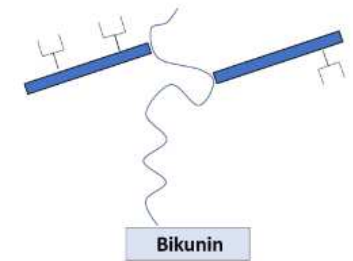


2-DE will be performed...



Conclusions

- Two new cases of linkeropathy (B3GALT6; B4GALT7)
- Unspecific clinical symptoms leading to an initial erroneous diagnosis; crucial need for multidisciplinary medical consultations and specialized professionals
- High interest of serum bikunin analysis for the quick and confident assertion of the pathogenicity of *B3GALT6* and *B4GALT7* gene variants.
- As for bikunin towards linkeropathies, major interest of disposing of simple and robust blood biomarkers in ultrarare IEM.



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