Recent research
-
A new form of syndromic CHI?

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Alina, medical history

- Born at 38 weeks, (bw 2985g, l 47cm, hc 31.8cm), healthy non-consang. parents
- Cardiac malformation (atretic tricuspid valve, septal defect, hypoplastic aortic arch)
  - Multiple cardiac surgeries, resulting in Fontan circulation
- Choanal stenosis, facial dysmorphism
- Congenital Hyperinsulinism, diagnosed at age 5d
  - Insulin of 22 and 35µU/l at BG 43 and 50mg/dl, hypoketotic
  - Diazoxide responsive (<5mg/kg/d), nutritional support with PEG feedings

- 6 months inpatient treatment

Genetic tests so far were all unremarkable…

- Chromosomal analysis
- Array CGH → loss in 18q22.3, unclear significance
- DIS3L2 (Perlman syndrome), USP9X
- CHARGE syndrome/CHD7, 23q11 deletion
- INS, INSR, SLC16A1, HADH, GLUD1, ABCC8, KCNJ11
- Cornelia de Lange syndrome - NIPBL, RAD21, HDAC8, ANKRD11, SMC1A, SMC3

Alina, at 4.5 years of age

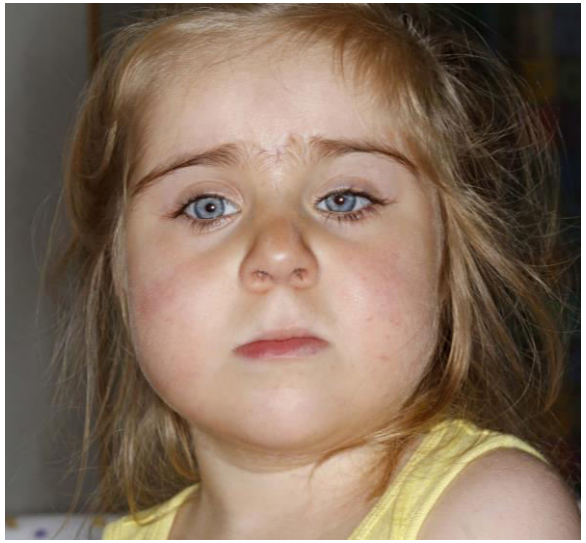
- Developmental delay
- Small stature
- Microcephaly
- Still on PEG feedings, no hypoglycemia with Diazoxide 2.5mg/kg/d

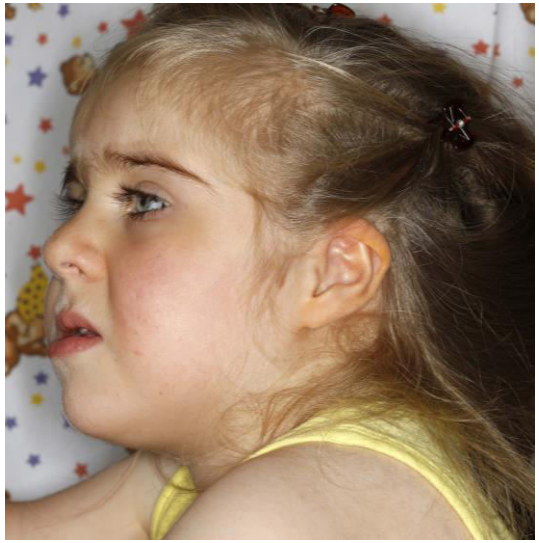
- Withdrawal of diazoxid unsuccessful (→ fasting tolerance <6h)

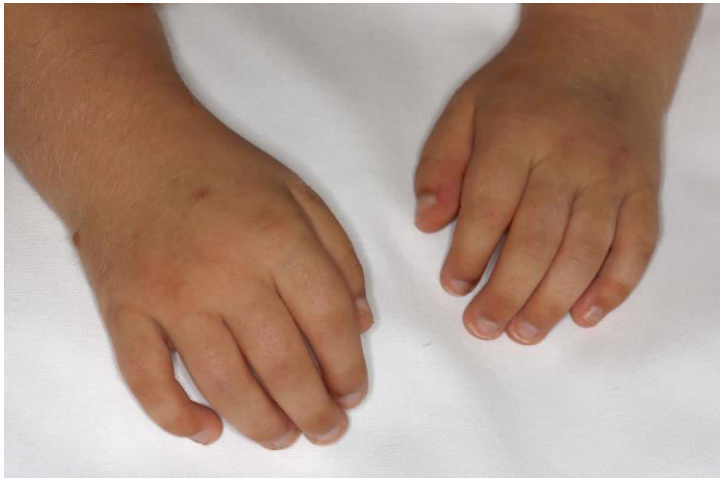
- Re-start of diazoxide 5mg/kg/d → FT >15h

  No need for further PEG feeding

Alina, at 4.5 years of age







- Ptosis, interm. strabismus
- Broad nose bridge
- High philtrum
- Narrow upper lip
- Dysplasic ears
- atactic gait pattern
- Microcephaly (-4,5 SDS)
- Small stature (-3,2 SDS
- Coarse wrists

Alina, at 4.5 years of age → genetics?

- Next-gen sequencing
  - Some known CHI genes not examined so far (GCK, HNF1A, HNF4A, CDG-syndromes, UCP2 etc.)
  - Syndromic CHI (Kabuki, Costello, etc.)
  - Neonat. Diabetes, MODY- genes

→ nothing….

- Readjusted filtering of NGS data to include
  - syndromes with cardio-facial abnormalities
  - syndromes with facial dysmorphia and developmental delay

→ Heterozygous variant in ***EP300*** c.4505C>T, p.(Pro1502Leu)

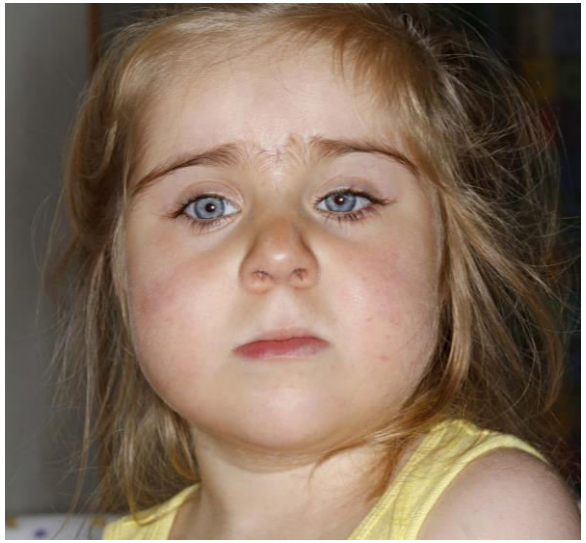
Prediction: 9/10 suggest pathogenicity

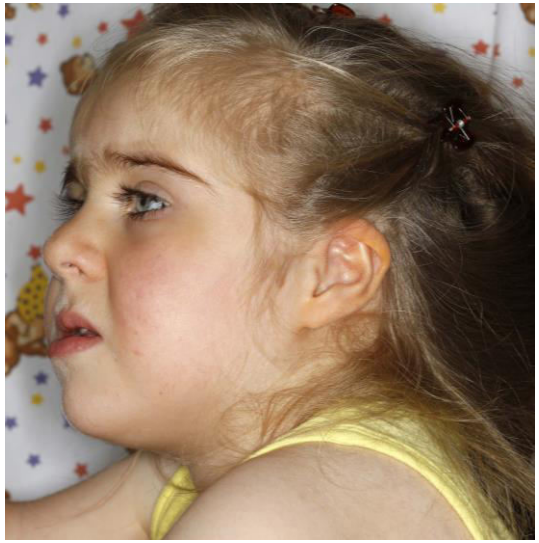
No frequency in any database

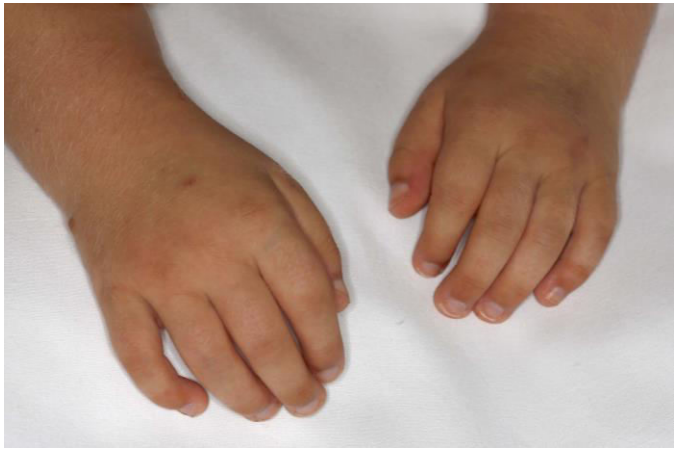
segregation: de novo variant.

mutations in EP300 cause **Rubinstein Taybi syndrome type 2**

Reverse phenotyping







- Ptosis, interm. strabismus
- Broad nose bridge
- High philtrum
- Narrow upper lip
- Low-set, dysplasic ears
- atactic gait pattern
- Coarse wrist
- Full eyebrows
- Microcephaly (-4,5 SDS)
- Small stature (-3,2 SDS)
- Developmental delay
- Cardiac malformation

Rubinstein Taybi syndrome

- Majority caused by mutations in *CREBBP*
- EP300-related RSTS: ~50 published cases [1]

- So far not shown to be associated with CHI [1]

  coincidence?

EP300:

- Histone acetyltransferase → transcriptional regulation
- No obvious/known interaction with CHI-related cellular pathways

[1]Fergelot 2016 Am J Med Genet

- If anybody knows a CHI patient with these features

  → please do *EP300* and *CREBBP* seq

  → and send me an email ☺

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