Post axial Polydactyly: Isolated Symptom or Part of a Syndrome. A Case of BBS8 With Two Novel Molecular Anomalies.

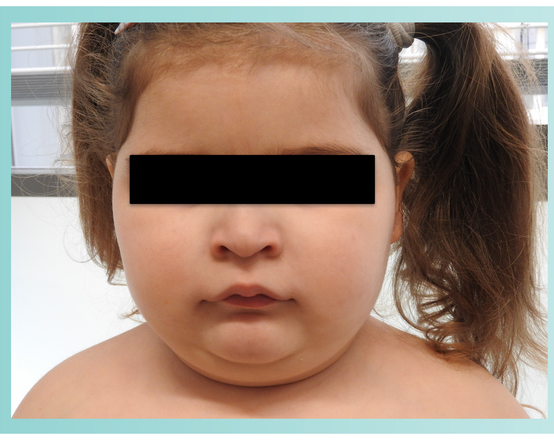
J. Harvengt [1], U. Schierloh [2], S.Bulk [1], G. Pierquin [1].

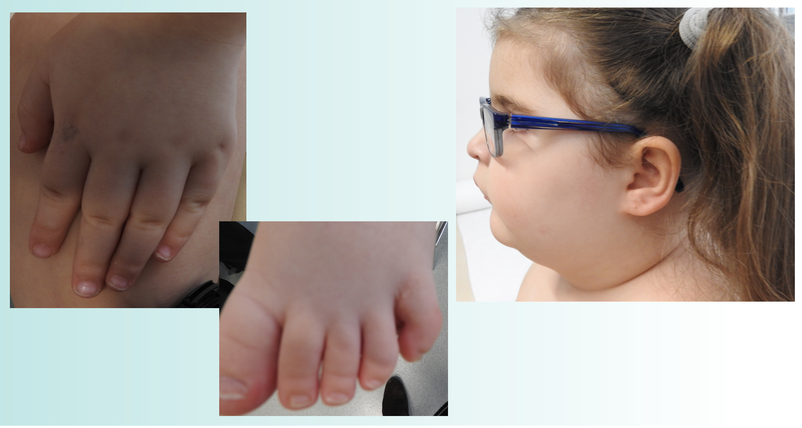
1. CHU Liège Sart Tilman, Human Genetic department, Liège, Belgium.
2. CHL KannerKlinik, Pediatric Endocrinology Department, Luxembourg, Grand Duché du Luxembourg.

Background.
Polydactyly constitutes the highest proportion among the congenital limb defects. Polydactyly can be an isolated symptom, but it may also be encountered in more than 300 different syndromes, mostly ciliopathies.

Methods. Case report.

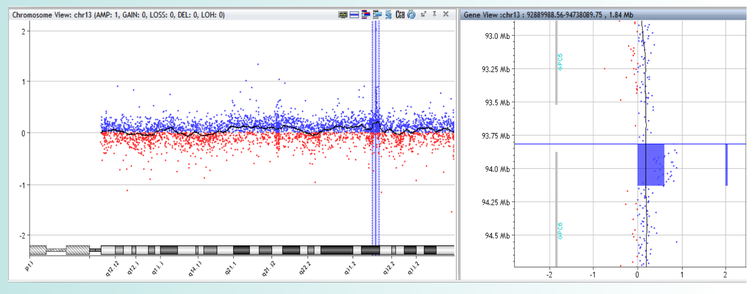
- A young Caucasian girl aged of 5 years
- Speech delay
- Precocious obesity
- Post axial polydactyly in the four limbs (surgical management at 2 years).
- Initially strabismus. Follow-up revealed retinitis pigmentosa.
- Dysmorphic features: full lips, a round face with a bitemporal narrowing, mild retrognathia, microdontia and brachydactyly.



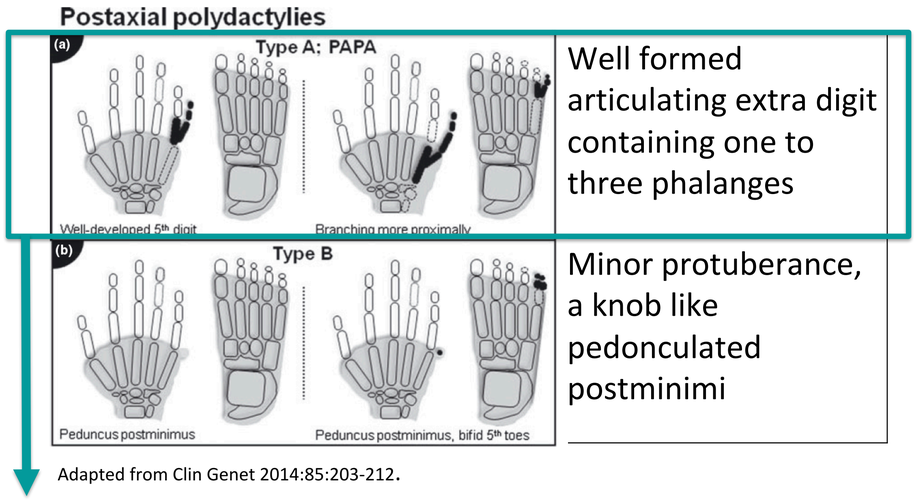


Results.
- Array CGH revealed a heterozygous duplication of uncertain significance in the 13q31.3 region. This duplication occurred *de novo*. This region includes 3 genes, one of them encoding for the GPC6 protein (exon 1 of the transcript ENST0000377047 of the gene *GPC6*, OMIM#604404).

-A multi-gene panel test for Bardet Biedl Syndrome (BBS) revealed a new maternally inherited pathogenic splice site mutation in intron 13 of the TTC8 gene (NM_198309.3: c.1317+1G>A) and a likely pathogenic splice site variant in the exon 5 of the *TTC8* gene inherited from the father (NM_198309.3: c.459G>A (p.Thr153Thr)).



Types of postaxial polydatyly.



Adapted from Clin Genet 2014:85:203-212.

Polydactyly as a part of a syndrome : BBS.

- BBS is a ciliopathy with a wide spectrum of clinical feature : retinitis pigmentosa, renal impairment, polydactyly, obesity, hypogenitalism and cognitive impairment.
- At least 20 genes are currently known to be associated with BBS, with an autosomal recessive transmission. *TTC8* accounts for 1.2 % of the BBS.

New splice site variant in the intron 13 of *TTC8*.

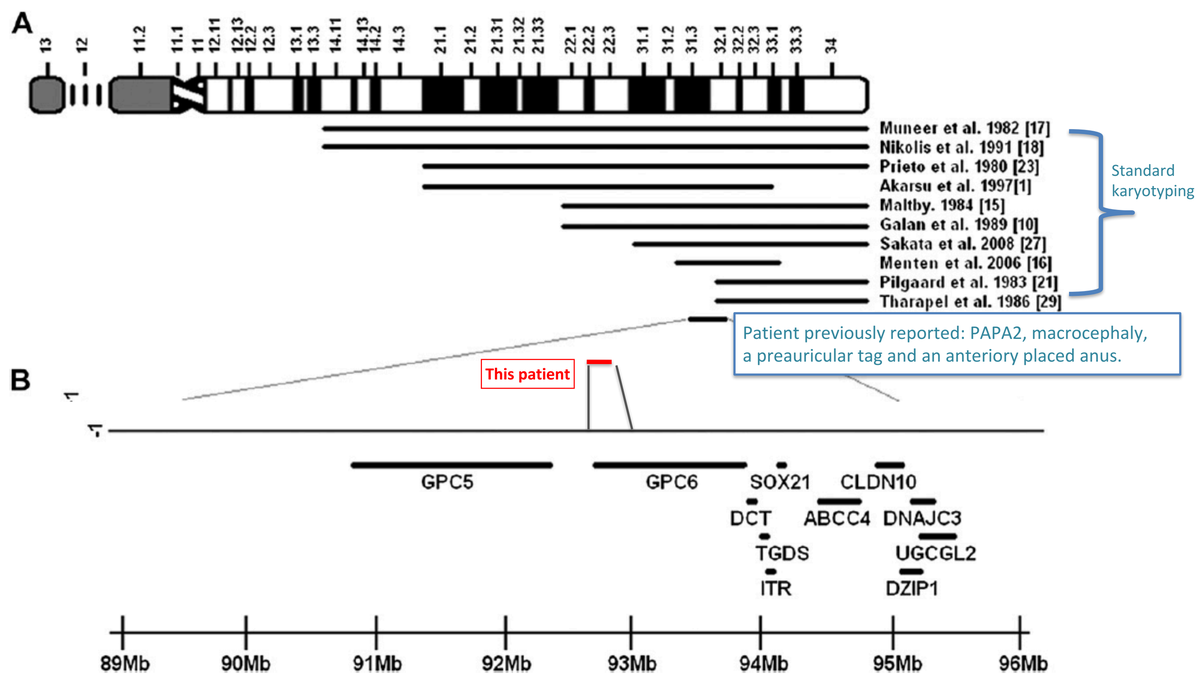
- The variant c.1317+1G>A has never been published in the literature or databases so far.
- According to the algorithms, the variant leads to a complete loss of the natural splice site. This may lead to exon skipping, inclusion of intronic sequences or usage of a cryptic splice site. No functional studies have been performed.

Rare splice site variant in the exon 5 of *TTC8*.

- The variant c.459G>A affects the last base pair of exon 5 and can be relevant for a correct splicing processes. According to the algorithms, the variant is predicted to abolish or to reduce the splice site efficiency of the exon 4, therefore affecting the amount of functional protein.
- The frequency of the variant (<2/10000) is low enough to be consistent with a recessive carrier frequency.
- The substitution was reported to segregate with BBS in one North-African family (Stoetzel et al. 2005, J Human Genet 51:81) but no functional studies have been published.

GPC6 as a candidate gene.

-Type 2 Post axial Polydactyly A (PAP-A2) is associated with duplication of the long arm of the chromosome 13, based on genetic linkage analysis.
-Dose dependency for digital malformation was observed in this region: deletions result in oligodactyly and duplications in polydactyly.
-*GPC6* is postulated in literature to be a candidate gene in the pathogenesis of PAP-A2.



Adapted from Eur J of Med Gen, 53, 2010, 45-49.

Conclusion.
We describe a girl with a BBS8 with a new pathogenic variant of the intron 13 of *TTC8* and a rare splicing mutation in the exon 5 of *TTC8*. Moreover, CGH array revealed a duplication including *GPC6*, a gene described as a candidate in the pathogenesis of PAP-A2. The patient's polydactyly is a feature of BBS, but the duplication of *GPC6* has probably influenced the particular expressivity of the phenotype, with polydactyly of all four limbs of our patient.
In case of post axial polydactyly associated with other features or malformations, etiological investigations are indicated. However, post axial polydactyly can sometimes be the only initial clinical finding in case of ciliopathy. This highlights the necessity to maintain a careful follow up of these particular cases.

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Contact
Julie.Harvengt@chuliege.be
Genetic Department CHU Liège

www.chuliege.be