Clinical commentary

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Benign infantile seizures followed by autistic regression in a boy with 16p11.2 deletion

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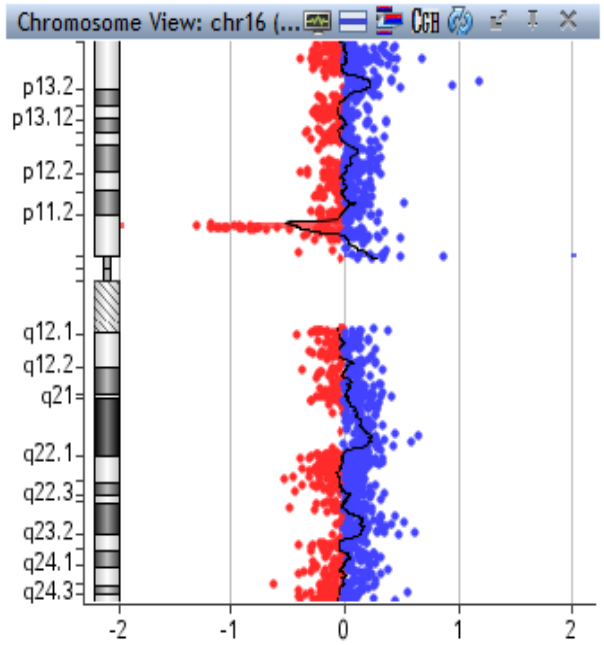
- Benign infantile seizures (BIS) are usually a self-limiting epilepsy syndrome consisting of infantile-onset seizures, good response to antiepileptic drugs, spontaneous remission by age two, and normal neurodevelopmental outcome. BIS may be familial or sporadic, and are sometimes associated with paroxysmal kinesigenic dyskinesia (PKD) [Vigevano, 2005].

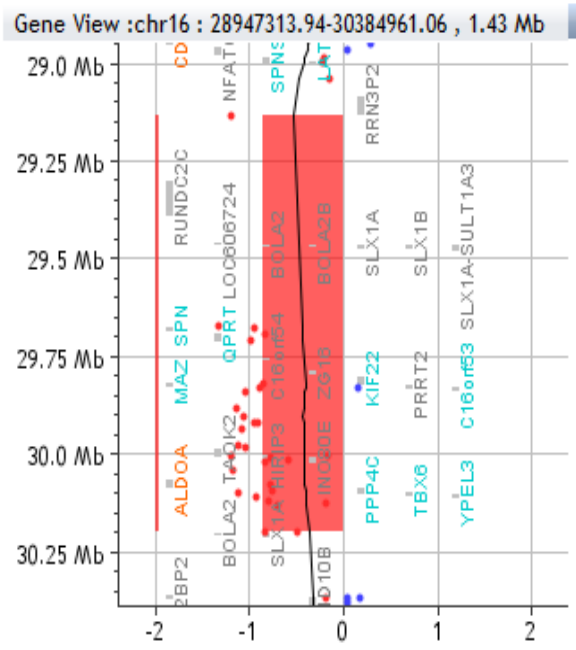
- A recurrent frameshift heterozygous mutation (c.649dupC, p.Arg217Profs*8) in the *PRRT2* gene (locus 16p11.2) underlies most BIS/PKD cases [Lee et al., 2012; Becker et al, 2013].

- Sub-microscopic deletions in 16p11.2, encompassing *PRRT2*, are an established cause of cognitive/language delay and autism spectrum disorders (ASD) [Weiss et al., 2008], but have been only rarely associated with BIS/PKD [Dale et al., 2011; Weber et al., 2013].

- Why most *PRRT2* mutations lead to BIS, while *PRRT2* deletion (as in 16p11.2 del) does not in most cases is unclear. Possible explanations may be a dominant negative effect of the mutant *PRRT2* allele or the contribution of modifier genes within the deletion.

- We report on a child harbouring a 16p11.2 deletion, and presenting with BIS and normal early development. Despite a good outcome of seizures, he displayed, at the age of 18 months, an unexpected regression leading to ASD, intellectual disability, and language impairment.





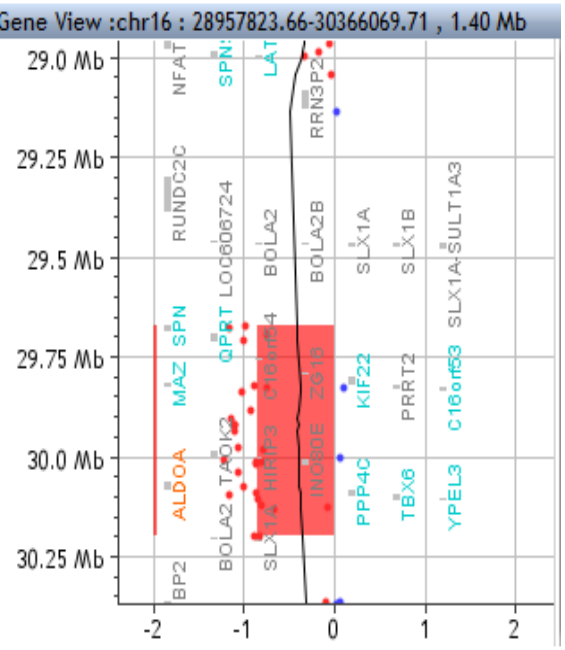


Figure 1

A

B

- The array-CGH (Figure 1) shows the deletion in the child (A) and (smaller) in the healthy mother (B).

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Possible mechanisms for the different phenotypes in the child and his asymptomatic mother are:

- An increased risk of disease in males with respect to females [Duyzend and Eichler, 2015], or inherited versus *de novo* deletions [Moreno-De-Luca et al., 2015]
- Incomplete penetrance of 16p11.2 deletions (Rosenfeld et al., 2013)
- Role of the seizures as an epigenetic mechanism leading to gene expression changes, triggering otherwise silent gene imbalances in the deleted region

CONCLUSIONS

- The neurodevelopmental prognosis of BIS patients may be less benign than expected.
- Infants with BIS, in the absence of mutations in *PRRT2*, should be screened for copy number variants to rule out 16p11.2 deletions.
- A cautious neurodevelopmental prognosis and careful long-term, clinical follow-up is recommended for infants presenting with BIS.

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