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

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ABSTRACT – Benign infantile seizures (BIS) are usually a self-limiting condition, which may be associated with heterozygous mutations in the *PRRT2* gene at chromosome 16p11.2. Here, we report a boy with a deletion in 16p11.2, presenting with BIS and typical neurodevelopment in the first year of life, unexpectedly followed by severe autistic regression. 16p11.2 deletions are typically associated with intellectual disability, autism, and language disorders, and only rarely with BIS. This clinical report shows that the neurodevelopmental prognosis in BIS patients may not always be benign, and suggests that array CGH screening should be considered for affected infants in order to rule out deletions at 16p11.2 and long-term clinical follow-up.

Key words: benign infantile seizure, 16p11.2 deletion, PRRT2, autism, regression

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Benign infantile seizures (BIS) are a familial or sporadic, infantile-onset epilepsy syndrome, characterized by good response to antiepileptic drugs, spontaneous remission by age 2, normal neurodevelopmental outcome, and, sometimes, association with paroxysmal kinesigenic dyskinesia (PKD) (Vigevano, 2005). A recurrent frameshift heterozygous mutation (c.649dupC, p.Arg217Profs*8) in *PRRT2* (locus 16p11.2) underlies most BIS/PKD cases (Lee *et al*., 2012; Becker *et al*., 2013). Rarely, sub-microscopic 16p11.2 deletions, a well-established cause of neurodevelopmental disorders that includes cognitive/language delay and autism spectrum disorders (ASD) (Weiss *et al*., 2008), have also been detected in BIS/PKD (Dale *et al*., 2011; Weber *et al*., 2013). Why the same microdeletion results in different phenotypes (*i.e*. ASD or BIS) remains, however, unclear.

Here, we report a child harbouring a 16p11.2 deletion, presenting with BIS and normal early development, unexpectedly followed by cognitive and autistic regression.

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Case study

This 5-year-old boy was the second child of healthy, non-consanguineous parents. Birth and neonatal history were normal. At age 5 months, he displayed a first, afebrile seizure characterized by staring, eye deviation, and bilateral jerks, lasting about one minute and followed by post-ictal sleep. After 24 days, similar seizures recurred in clusters of two episodes per day, and remitted without therapy at age 6.5 months. At that time, the child came to our attention, and displayed normal psychomotor development based on standardized assessment (Bayley Scale of Infant and Toddler Development). Neurometabolic screening and EEG during wakefulness and sleep were normal, and a diagnosis of non-familial BIS was made. At age one, he was able to walk with support and, two months later, first words became evident. We observed a completely normal social and cognitive development up to 18 months, when stereotyped and repetitive behaviours, withdrawal, poor social gaze, and no response to his name became progressively evident, fitting the diagnostic criteria for ASD. Communicative gestures and language gradually disappeared, and a circadian rhythm sleep disorder and behavioural/emotional dysregulation clearly emerged. At age 3, cognitive testing (Griffiths Mental Development Scales) revealed mild-to-moderate intellectual disability (ID), and obvious receptive-expressive language impairments. EEG recordings, metabolic work-up, standard karyotyping, and brain MRI were normal.

Array-CGH testing, performed after informed consent, detected a 1.064-Mb 16p11.2 deletion (29,133,676-30,198,600) (*figure 1A*), encompassing about 35 genes. The deletion was inherited from the healthy mother, which differed from her child regarding the first distal oligo mapping in a region of segmental duplications (*figure 1 B*). The mean fluorescent log ratio of the deleted oligos was about -1, consistent with a non-mosaic deletion. Array-CGH in the father showed a 1.2-Mb 19q13.42 duplication (55,913,630-57,188,215).

Discussion

16p11.2 deletions, particularly the recurrent 600-kb deletion defined by breakpoints 4 and 5, havent been associated with up to 1% cases of autism and 1.5% cases of developmental and language delay, thus representing one of the most frequent known syndromic aetiologies for neurodevelopmental disorders and ASD (Weiss *et al*., 2008). Haploinsufficiency of genes at 16p11.2 may indeed play a role in the development of several brain functions, including language and social cognition (Hanson *et al*., 2015). However, whilst speech or language-related disorders are extremely common in the syndrome, only 18-25% of deletion carriers fit strict criteria for a diagnosis of ASD (Duyzend and Eichler, 2015; Hanson *et al*., 2015). Moreover, the degree of ID may be extremely variable, and sometimes carrier individuals may display normal cognitive phenotypes (Hanson *et al*., 2015). Only rarely, BIS may be the presenting symptom in patients with 16p11.2 deletions covering *PRRT2,* occurring either with a typical course (Weber *et al*., 2013) or with a milder seizure history (Dale *et al*., 2011), similar to our patienthttp://brain.oxfordjournals.org/content/138/12/3476.long - ref-102. Why most *PRRT2* heterozygous mutations lead to clinical seizures, while *PRRT2* deletion (as in 16p11.2 deletions) does not in most cases is, however, unclear. A dominant negative effect of the mutant *PRRT2* allele or the contribution of modifier genes within the deletion are possible explanations for this unsolved question.

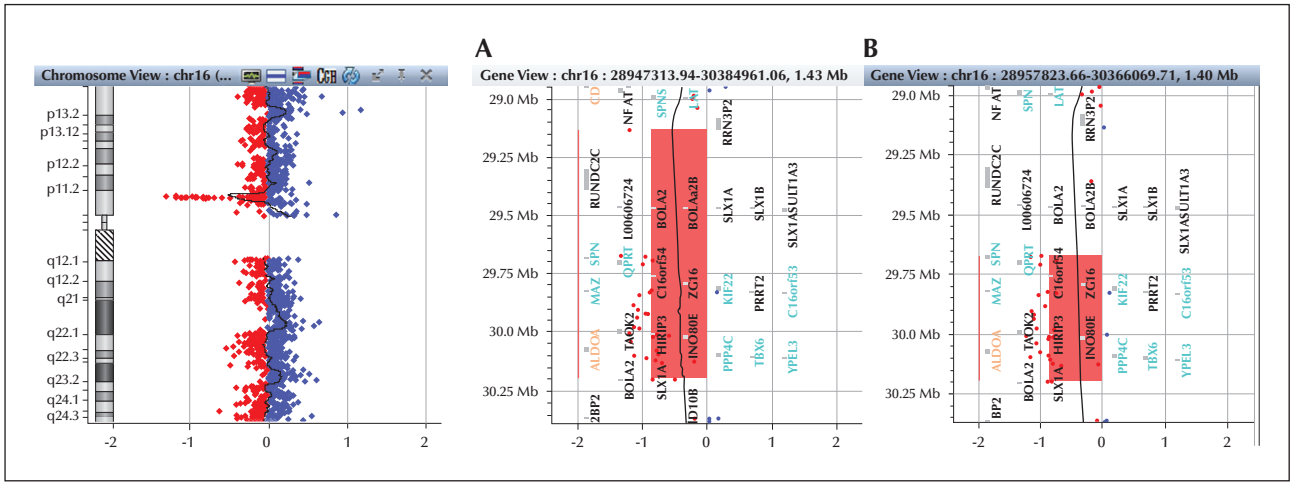

Figure 1. Array CGH profile showing the 16p11.2 deletion (arrow) (UCSC genome Browser; http://genome.ucsc.edu/; hg 19 release), with enlargement of the deleted region in the child (A) and his mother (B).

Table 1. Main candidate genes implicated in the neurological phenotype of the reported patient, including a description of function and potential disorders related to altered gene dosage.

Gene	Protein	Function	Potential disorders related to altered gene dosage	References
SEZ6L2	Seizure 6-like protein 2 (seizure-related protein)	Contributes to specialized functions of the endoplasmic reticulum in neurons	Seizure disorders Adjunctive risk factor for ASD	Orita *et al.,* 1995 Kumar *et al.,* 2009
QPRT	Nicotinate-nucleotide pyrophosphorylase (carboxylating)	Regulation of the catabolism of quinolinate, an intermediate in the tryptophan-nicotinamide adenine dinucleotide pathway	Seizure disorders Neurodegenerative disorders	Feldblum *et al.,* 1988 Németh *et al.,* 2005
PRRT2	Proline-rich transmembrane protein 2	Regulation of synapse exocytosis and neurotransmitter release by interaction with SNAP25	BIS, PKD, ID, familial hemiplegic migraine, adjunctive risk factor for ASD	Lee *et al.,* 2012 Schubert *et al.,* 2012
MIR 3680-2	No post-translational modifications	Regulation of translational-dependent processes that occur during brain maturation	Translational dysregulation leading to altered neuronal circuitry development	Vaz *et al.,* 2010 Ghahramani Seno *et al.,* 2011

ASD: autism spectrum disorder; BIS: benign infantile seizure; PKD: paroxysmal kinesigenic dyskinesia; ID: intellectual disability.

Here, we report a child with a 1.064-Mb 16p11.2 deletion, presenting with BIS and normal neurodevelopment followed, at the age of 18 months, by a regression leading to ASD, ID, and language impairment. It is hard to know why, despite the good outcome of seizures, this patient underwent such a severe developmental trajectory. In contrast to single-gene *PRRT2* mutations leading to BIS, which do not play a major role in ASD susceptibility (Huguet *et al*., 2014), the haploinsufficiency of several likely genes included in the deletion may account for a more severe impairment of brain development and function (*table 1*). However, why the phenotype in this child differed so strongly from that of his asymptomatic mother remains an open issue, possibly due to an increased risk of disease in males with respect to females (Duyzend and Eichler, 2015), inherited versus *de novo* deletions (Moreno-De-Luca *et al*., 2015), or incomplete penetrance of 16p11.2 deletions (Rosenfeld *et al*., 2013). The coding genes in the non-deleted region in the mother (*BOLA2*, *BOLA2B*, *SLX1B*, *SLX1A*, *SULT1A3*, and *SULT1A4*) are not known to be relevant to the phenotype, and are therefore unlikely to contribute to clarifying genotype-phenotype correlations. In addition, the question of whether seizures in our patient may have acted as an epigenetic mechanism which led to gene expression changes, triggering otherwise silent gene imbalances in the deleted region, remains unresolved.

Despite several unresolved issues, this report suggests, however, that the neurodevelopmental prognosis in BIS patients might not be as benign as expected (Becker *et al*., 2013). It is well established that patients with epilepsy have an increased burden of genomic rearrangements, particularly when associated with ID or other neuropsychiatric problems (Striano *et al*., 2012). Accordingly, we suggest that infants with BIS, in the absence of mutations in *PRRT2*, should also be screened for copy number variants in order to rule out 16p11.2 deletions and should be provided with a neurodevelopmental prognosis with caution, with careful clinical follow-up. □

Supplementary data.
Summary didactic slides are available on the www.epilepticdisorders.com website.

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None of the authors have any conflict of interest to declare.

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TEST YOURSELF

(1) Are benign infantile seizures (BIS) the only manifestation resulting from mutations in *PRRT2*?

(2) Is the neurodevelopmental prognosis of BIS always benign?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".