Reviewer's report

**Title:** Duplication involving GABA receptor genes accounts for paradoxical response to antiepileptic drugs in Isodicentric 15 syndrome.

**Version:** 2  **Date:** 4 January 2013

**Reviewer:** Amber Hogart Begtrup

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This case report presents an adult patient with a supernumerary isodicentric chromosome 15. The Idic(15) chromosome in this patient includes approximately 8 Mb spanning 15q11-13.1, and results in 4 copies of the 21 genes found within this genomic interval. The case report focuses on management of seizures in this patient, with an emphasis on an adverse reaction to the administration of pregabalin. The conclusions drawn in this case report suggest that this patient’s worsening seizures are due to an abnormal GABAergic response to pregabalin. Despite this claim, the authors state that pregabalin does not bind GABA-A or GABA-B receptors, or affect GABA uptake or degradation. Furthermore, increasing seizure activity also is reported in patients without chromosomal abnormalities, upon taking other GABAergic drugs. These facts present major challenges in making general conclusions about the management of seizures more broadly in individuals with chromosome 15q duplication syndrome.

**Major Compulsory Revisions:**

1. Could the adverse outcome in this individual be related to a change in her brain resulting from trauma and surgery, and less an issue from her abnormal dosage GABA receptors? If the authors view this as unlikely please provide some evidence to support why the adverse response is specific to her Idic(15).

2. The authors should expand the first paragraph of the background to include more information about the variants of chromosome 15 duplication syndrome, of which Idic(15) is one. (i.e. interstitial duplications versus isodicentric supernumerary chromosomes and small heterochromatic duplications versus larger gene-containing duplications). This distinction is important as the dosage of genes predicts the phenotype of the patients.

3. The statement that “In IDIC-15 both the intellectual disability and seizure disorder are related to abnormal GABA receptor morphology and function” is speculation. This sentence should be altered to say that it “may be related to abnormal GABA receptors”. Additional citations demonstrating that alterations in these genes have phenotypic effects (i.e. the mouse deletion models of Gabrb3, or studies of human mutations in seizure disorder) would strengthen this statement and should be included.

4. In the discussion the authors state that “there may be other reasons that could explain the severe exacerbation of the seizure disorder”, however do not include
specific examples. This paragraph should be expanded to discuss some alternative possibilities given the unclear effect that pregabalin has on GABA receptors.

Minor Points/Revisions

1. Paragraphs should consist of multiple sentences, therefore restructuring of single paragraph sentences is needed throughout.

2. Abstract—Idic(15) is one of the more common chromosomal abnormalities, therefore “rare” should be removed. Modify “partial duplications of chromosome 15 typically includes” to “may include” as the smaller duplications/Idic (15) supernumerary chromosomes are common. Additionally, the intellectual disability and behavioral disorders “may” be related to abnormal GABA receptor function, but may also be related to other genes within the interval.

3. The description of the duplication gives the position of oligomers as “first deleted” and “last deleted”—should this instead state “duplicated”?

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.