Author's response to reviews

**Title:** Paradoxycal Worsening Of Seizure Activity With Pregabailin In An Adult With Isodicentric 15 (IDIC-15) Syndrome Involving Duplications Of The GABRB3, GABRA5 And GABRG3 Genes.

**Authors:**

Alessandro Di Rocco (ALESSANDRO.DIROCCO@NYUMC.ORG)
Andrea Loggini (andrealoggini@gmail.com)
Maja Di Rocco (majadirocco@ospedale-gaslini.ge.it)
Pietro Di Rocco (pdi.rocco@libero.it)
Roger Rossi (RRossi@JFKHealth.org)
Giorgio Gimelli (giorgio.gimelli@gmail.com)
Carl Bazil (cwb11@mail.cumc.columbia.edu)

**Version:** 3  **Date:** 23 February 2013

**Author's response to reviews:**

February 14, 2013
Dr. Chantal Depondt
BioMed Central
Re: Manuscript # MS: 1802464444847671

Dear Dr. Chantal,

We thank the editorial office and the reviewers for the constructive comments. The manuscript has been revised incorporating the reviewers’ and the editor’s suggestions. All corrections, including bibliography additions, have been highlighted.

Specifically:

A) Regarding the comments of the First Reviewers:

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).

We believe that it is highly unlikely that the change in seizures severity could be due to any other cause. The change in seizure frequency, appearance of new seizures patterns, worsening in parallel to the dose escalation of pregabalin, and dramatic improvement after the drug was discontinued and lacosamide started, cannot have any more likely explanation. As per the trauma, it had occurred a year before pregabalin was introduced and the dramatic increase in seizure activity occurred. While the trauma and surgery did produce some increase in
frequency of her pre-existing complex partial seizures, it is unlikely that after a year these event could explain the sudden and dramatic change in seizure severity. We have provided a more detailed descriptions of the seizures (also requested by the other Reviewer) that we hope can better describe both the severity and change in seizure pattern and the temporal sequence of events.

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.

The background has been changed to include a more comprehensive description of the variants if chromosome duplication 15 syndrome.

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.

The sentence has been modified, and a reference to mutations of GABA receptors effect on epilepsy added.

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.

It is possible, as suggested by the other Reviewer, that other genes may be responsible for the unusual response to pregabalin. Among these is CHRNA7, the gene encoding the alpha 7 subunit of the nicotinic receptor, which can modulate GABA receptors’ function. This additional hypothesis has been added in the Discussion.

Minor Points/Revisions

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

The paragraphs have been restructured.

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.

The changes have been made in the abstract.
3. The description of the duplication gives the position of oligomers as “first deleted” and “last deleted”—should this instead state “duplicated”? The correction has been made in the text

B) Regarding the comments of the First reviewers:

1. The case description and the discussion of their findings can be significantly improved. In particular, description of seizure semiology and EEG findings during the clinical evolution of the patient would be useful.

A more accurate description of the seizures has been provided. We agree that an EEG would have been extremely useful in the evaluation of the seizures, especially as a complex and diverse pattern developed. The woman we report however, has significant intellectual disability, and she has been unable to cooperate in the past, not allowing adequate EEG recording.

2. Epilepsy worsening due to the use of some anticonvulsants is a well known phenomenon. The literature on this topic needs to be addressed more in detail. For instance, there is much literature on a derivative of pregabalin, i.e., gabapentin that may also induce life-threatening status epilepticus in some cases.

We have added the case indicated by the reviewer.

3. The 15q11–13 region that includes 2 GABA genes is of special interest. Notably, microdeletions at this position have been described in individuals with intellectual disability, autism spectrum disorder, and even epilepsy (Dibbens et al., Hum Mol Genet. 2009;18:3626-31). These data could improve the discussion of the genetic rearrangement found in the patient reported by Di Rocco et al.

The discussion on microdeletion has been added and appropriate reference included.

A) Regarding the comments of the Editor:

The title has been modified and the editorial requirements have been completed

Sincerely,

Alessandro Di Rocco, MD
Professor of Neurology,
Chief, Division of Movement Disorder
New York University School of Medicine
NYU-Langone Medical Center