# Immunotherapy Responsive Recurrent Post-Infectious Ataxia Associated with Recurrent ATP2B2 Gene Variant

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Introduction/Objectives: Acute cerebellar ataxia is a rare, para-infectious or post-infectious, phenomenon occurring in both children and adults. In the past two decades, a variety of genetic, infectious, and antibody-mediated causes of acute cerebellar ataxia have been identified[1]. Although rare, recurrent cases of acute cerebellar ataxia have been reported but little is known about the mechanisms of disease in such cases. This case report details a case of recurrent para-infectious cerebellar ataxia in a young girl with a likely pathogenic gene variant in the *ATB2B2* gene.

Method: The patient was identified after her second hospitalization for post-infectious cerebellar ataxia. Given the atypical nature of recurrent ataxia, whole-exome sequencing (performed using the Illumina HiSeq platform and analyzed in the GENESIS platform) and in silico analysis (by an Invitae panel) were completed after discharge.

Results/Case Description: An 11-year-old girl with one prior episode of self-resolving para-infectious acute cerebellar ataxia at age four years presented with acute-onset ataxia, dysarthria, and gait instability in the setting of influenza A infection. Admission workup was notable for CSF pleocytosis (WBC 78, Lymphocyte predominant) but negative influenza PCR and antibody detection in the CSF (**Table 1**). Because of clinical deterioration, she received empiric IV methylprednisolone without improvement. She was subsequently administered IVIg and improved dramatically over the subsequent seven days. After discharge, patient was found to have a rare de novo *ATP2B2* gene (c.3028G>A, p.(Glu1010Lys)), which was initially reported as a variant of unknown significance (**Figure 1**). The variant was analyzed to have a Combined Annotation Dependent Depletion score of 33 and Polyphen-2 score of 1.0 and was determined to be likely pathogenic according to American College of Medical Genetics PP3 and PM2 criterion[2].

Discussion: Recurrent episodes of cerebellar ataxia are an especially rare occurrence, and genetic testing may be warranted in these individuals. This is the first known case of recurrent cerebellar ataxia associated with the *ATP2B2* (c.3028G>A) gene variant, expanding the broad spectrum of neurodevelopmental and cerebellar manifestations in this condition. We speculate that a heterozygous gene variant in ATP2B2 may not be sufficient to produce neurologic disease during physiologic homeostasis: that is, second hits may be required for *ATP2B2* variant–mediated ataxia. This is partially supported by the observation of five individual heterozygous carriers for this variant identified from the gnomAD version 4.1.0 control database[3]. When stressed in the setting of infection (second hit), the energy-dependent export of Ca2+ out of the cell may fail and cause cellular injury[4], activating central immunologic cascades and explaining the patient's abnormal CSF findings[5]. Although strictly hypothetical, augmentation of the immune response to cell injury may explain some of the patient's clinical response to immunotherapy. Given this patient's remarkable clinical response to immunotherapy, the authors propose that

immunotherapy may be considered a viable treatment option for patients with symptomatic ataxia presumed secondary to *ATP2B2*, particularly when clear evidence of para-infectious disease is present on neuro-diagnostic studies.

| **1st Admission Data** | | **2nd Admission Data** | | | | |
|---|---|---|---|---|---|---|
| **CBC** | | | **CSF** | | | |
| *WBC* | 7.00 | 7.81 | *CSF Appearance* | Clear | *MyelinBasProt C* | <2.0 |
| *RBC* | 5.70 (H) | 5.82 (H) | *CSF Color* | Colorless | ***Oligo Bands CSF*** | **PRESENT** |
| *HGB* | 12.2 | 12.5 | ***CSF WBC*** | **78 (H)** | *Synth RateIgG C* | +0.7 |
| *HCT* | 40.5 (H) | 41.0 (H) | *CSF RBC* | 1 | *IgG Index* | 0.61 |
| *MCV* | 71.1 (L) | 70.4 (L) | *CSF Cells Seen* | 100 | *Albumin CSF-SO Q* | 19.5 |
| *MCH* | 21.4 (L) | 21.5 (L) | *CSF Lymph %* | 95 (H) | *Albumin S-SO Q* | 3.5 (L) |
| *MCHC* | 30.1 (L) | 30.5 (L) | *CSF Mono/Macro %* | 5 (L) | | |
| *Platelets* | 275 | 300 | *Glucose* | 60 | | |
| *MPV* | 10.5 | 10.4 | *Protein* | 32 | | |
| *RDW-CV* | 10.9 (H) | 10.4 (H) | **Paraneoplastic/Enceph Eval, CSF** | | | |
| **Differential Automated** | | | *IFA Notes CSF-PCDEC* | None | *LGI1-IgG CBA, C* | Negative |
| *Seg/Band%* | 51.8 | 87.0 (H) | *Anti-Neuronal Nuclear Ab Type 1, C* | Negative | *mGluR1 Ab IFA, C* | Negative |
| *Lymph %* | 41.1 | 4.1 (L) | *CASPR2-IgG CBA, C* | Negative | *NMDA-R Ab CBA, C* | Negative |
| *Mono %* | 5.6 | 8.2 | *DPPX Ab IFA, C* | Negative | *NMO/APQ4-IgG FACS, C* | Negative |
| *Eos %* | 0.9 | 0.0 | *GABA-B-R Ab CBA, C* | Negative | *Purkinje Cell Cytoplasmic Ab Type Tr, C* | Negative |
| *Baso %* | 0.3 | 0.1 | *GAD65 Ab Assay, C* | 0.00 | *Neurochondrin IKA, CSF* | Negative |
| *IG %* | 0.3 | 0.6 (H) | *GFAP IFA, C* | Negative | | |
| **Other** | | | **Infectious Disease, CSF** | | | |
| *Sed Rate* | 44 (H) | | *Bacterial Culture, CSF* | Negative | *Influenza A Ab, CSF* | <1:1 |
| **CMP** | | | *IgG, CSF SO* | 3.5 | *Influenza B Ab, CSF* | <1:1 |
| *Sodium* | 139 | 137 | **Film Array Meningitis/Enceph Panel** | | | |
| *Potassium* | 3.8 | 3.5 (L) | *Escherichia coli K1, FA* | Negative | *Enterovirus, FA* | Negative |
| *Chloride* | 107 | 101 | *Haemophilus influenzae, FA* | Negative | *Herpes simplex virus 1, FA* | Negative |
| *CO2 total* | 22 | 24 | *Listeria monocytogenes, FA* | Negative | *Herpes Simplex virus 2, FA* | Negative |
| *Anion Gap* | 10 | 13 | *Neisseria meningitidis, FA* | Negative | ***Human herpes virus 6, FA*** | **DETECTED** |
| *BUN* | 10 | 10 | *Streptococcus agalactiae, FA* | Negative | *Human parechovirus, FA* | Negative |
| *Creatinine* | 0.41 (L) | 0.41 (L) | *Streptococcus pneumoniae, FA* | Negative | *Varicella zoster virus, DA* | Negative |
| *Glucose* | 86 | 126 (H) | *Cytomegalovirus, FA* | Negative | *Cryptococcus neoformans, FA* | Negative |
| *Mag* | | 2 | **Respiratory Viral Panel** | | | |
| *Calcium* | 9.0 | 9.1 | *HHV 6 PCR* | Not detected | *Parainfluenza 1, 2, 3, 4* | Not detected |
| *Phos* | | 4.1 (H) | *Adenovirus* | Not detected | *Respiratory Syncytial Virus* | Not detected |
| *Protein, T* | 7.5 | 8.4 (H) | *Coronavirus* | Not detected | *Chlamydia Pneumoniae* | Not detected |
| *Albumin* | 4.2 | 4.6 | *Metapneumovirus* | Not detected | *Mycoplasma Pneumoniae* | Not detected |
| *Bilirubin* | 0.43 | 0.82 | *Rhinovirus/enterovirus* | Not detected | *Bordetella pertussis* | Not detected |
| *CRP* | <0.5 | 2.1 (H) | ***Influenza A*** | **DETECTED** | *Bordetella parapertussis* | Not detected |
| *AST* | 26 | 41 | *Influenza B* | Not detected | | |
| *ALT* | 18 | 30 | | | | |
| *Alk Phos* | 194 | 194 | | | | |
| *Lipase* | | 169 | | | | |
| *CK* | 56 | 56 | | | | |

**Table 1.** Diagnostic results from first (left two columns) and second (right five columns) admission, notable for CSF with leukocytosis and oligoclonal bands, positive FAME panel for HVV6, RSV panel positive for Influenza A (bolded)

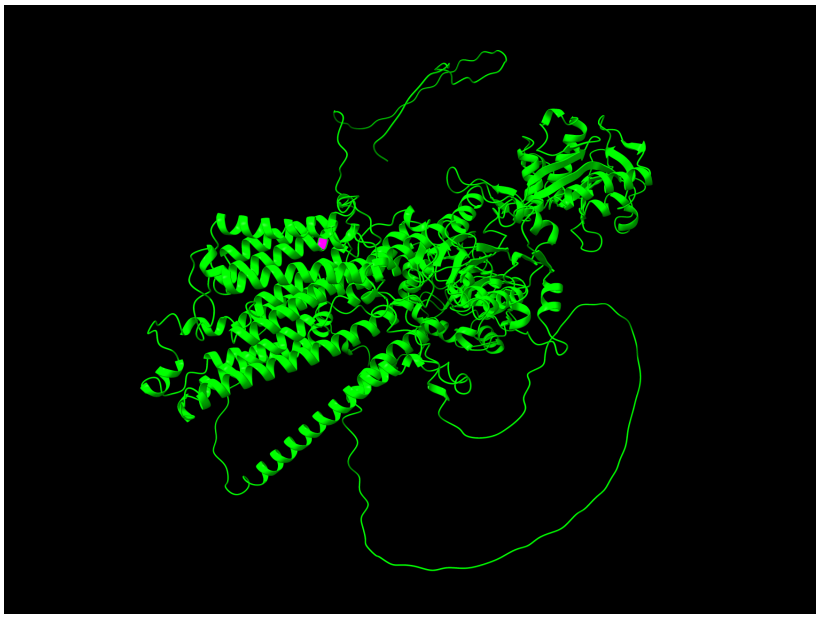

**Figure 1.** Three-dimensional structural modeling of the ATP2B2 gene (c.3028G>A, p.(Glu1010Lys)) variant; noting abnormal residue is in an alpha helix13–16. Although the amino acid substitution is not in a defined protein domain, based on the combination of missense substitution (a negatively charged Glutamic Acid to positively charged Lysine) and in-silico analysis, this variant is most likely pathogenic.

References:


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