**Supplementary Information**

**Germline and somatic mutations in *STXBP1* with diverse neurodevelopmental phenotypes**

Mohammed Uddin1,\*, Marc Woodbury-Smith1,3, Ada Chan4,5, Ledia Brunga4,Sylvia Lamoureux3,4, Giovanna Pellecchia3,4, Ryan KC Yuen3,4, Muhammad Faheem3,4,Dimitri J. Stavropoulos6, James Drake7, Cecil D Hahn8,9, Cynthia Hawkins9, Adam Shlien4, Christian R Marshall3, Lesley A Turner10, Berge Minassian4,7, Stephen W. Scherer3,4,5,11 , Cyrus Boelman12,\*

1) Mohammed Bin Rashid University of Medicine and Health Sciences, Dubai, UAE.

2) Department of Psychiatry and Behavioural Neurosciences, McMaster University, Hamilton, Ontario, Canada;

3) The Centre for Applied Genomics, The Hospital for Sick Children, Toronto, Ontario, Canada;
4) Program in Genetics and Genome Biology (GGB), The Hospital for Sick Children, Toronto, Ontario, Canada;

5) Department of Molecular Genetics, University of Toronto, Toronto, Ontario, Canada
6) Genome Diagnostics, Paediatric Laboratory Medicine, The Hospital for Sick Children, Toronto, Ontario, Canada;
7) Division of Neurosurgery, The Hospital for Sick Children, Toronto, Ontario, Canada;
8) Division of Neurology, The Hospital for Sick Children, Toronto, Ontario, Canada;
9) Department of Paediatrics, University of Toronto, Toronto, Ontario, Canada;

10) Discipline of Genetics, Faculty of Medicine, Memorial University of Newfoundland, St. John’s, Newfoundland, Canada;
11) McLaughlin Centre, University of Toronto, Toronto, Ontario, Canada.

12) Division of Neurology, BC Children’s Hospital, Vancouver, BC, Canada;

\*Cyrus Boelman, Division of Neurology, BC Children’s Hospital, Vancouver, BC Canada,(cyrus.boelman@cw.bc.ca); Mohammed Uddin, College of Medicine, Mohammed Bin Rashid University of Medicine and Health Sciences, Dubai, UAE (mohammed.uddin@mbru.ac.ae)

**Supplementary Table e-2.** Epilepsy encephalopathy cohort analyzed to quantify the rate of *de novo* mutations from published literatures[1-33](#_ENREF_1).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Study Cohort Size** | **PMID** | **Number of *de novo* within *STXBP1*** | **Number of *de novo* mutationwithin *STXBP1*** | **% of de novo in a cohort** |
| 45 | 23020937 | 3 | 3 | 6.7 |
| 29 | 21762454 | 3 | 3 | 10.3 |
| 106 | 20876469 | 6 | 5 | 4.7 |
| 95 | 21376300 | 2 | 2 | 2.1 |
| 50 | 21364700 | 1 | 1 | 2.0 |
| 70 | 24623842 | 3 | 3 | 4.3 |
| 284 | 26514728 | 24 | 20 | 7.0 |
| 68 | 23662938 | 3 | 3 | 4.4 |
| 44 | 24781210 | 1 | 1 | 2.3 |
| 33 | 22612257 | 1 | 0 | 0.0 |
| 52 | 21770924 | 5 | 5 | 9.6 |
| 86 | 21204804 | 2 | 2 | 2.3 |
| 73 | 25497044 | 3 | 3 | 4.1 |
| 110 | 25818041 | 2 | 2 | 1.8 |
| 28 | 22211739 | 2 | 2 | 7.1 |
| 83 | 20887364 | 9 | 9 | 10.8 |
| 160 | 23409955 | 6 | 6 | 3.8 |
| 1131 | 26795593 | 3 | 3 | 0.3 |
| 22 | 27171548 | 1 | 1 | 4.5 |

**References for Meta-analysis of Literature:**

1. Barcia G, Barnerias C, Rio M, et al. A novel mutation in STXBP1 causing epileptic encephalopathy (late onset infantile spasms) with partial respiratory chain complex IV deficiency. European journal of medical genetics 2013;56:683-685.

2. Boutry-Kryza N, Labalme A, Ville D, et al. Molecular characterization of a cohort of 73 patients with infantile spasms syndrome. European journal of medical genetics 2015;58:51-58.

3. Campbell IM, Yatsenko SA, Hixson P, et al. Novel 9q34.11 gene deletions encompassing combinations of four Mendelian disease genes: STXBP1, SPTAN1, ENG, and TOR1A. Genetics in medicine : official journal of the American College of Medical Genetics 2012;14:868-876.

4. Carvill GL, Weckhuysen S, McMahon JM, et al. GABRA1 and STXBP1: novel genetic causes of Dravet syndrome. Neurology 2014;82:1245-1253.

5. Dilena R, Striano P, Traverso M, et al. Dramatic effect of levetiracetam in early-onset epileptic encephalopathy due to STXBP1 mutation. Brain & development 2016;38:128-131.

6. Hamdan FF, Gauthier J, Araki Y, et al. Excess of de novo deleterious mutations in genes associated with glutamatergic systems in nonsyndromic intellectual disability. American journal of human genetics 2011;88:306-316.

7. Hamdan FF, Gauthier J, Dobrzeniecka S, et al. Intellectual disability without epilepsy associated with STXBP1 disruption. European journal of human genetics : EJHG 2011;19:607-609.

8. Helbig KL, Farwell Hagman KD, Shinde DN, et al. Diagnostic exome sequencing provides a molecular diagnosis for a significant proportion of patients with epilepsy. Genetics in medicine : official journal of the American College of Medical Genetics 2016.

9. Jay JJ, Brouwer C. Lollipops in the Clinic: Information Dense Mutation Plots for Precision Medicine. PloS one 2016;11:e0160519.

10. Keogh MJ, Daud D, Pyle A, et al. A novel de novo STXBP1 mutation is associated with mitochondrial complex I deficiency and late-onset juvenile-onset parkinsonism. Neurogenetics 2015;16:65-67.

11. Kodera H, Kato M, Nord AS, et al. Targeted capture and sequencing for detection of mutations causing early onset epileptic encephalopathy. Epilepsia 2013;54:1262-1269.

12. Lemke JR, Riesch E, Scheurenbrand T, et al. Targeted next generation sequencing as a diagnostic tool in epileptic disorders. Epilepsia 2012;53:1387-1398.

13. Lim JS, Kim WI, Kang HC, et al. Brain somatic mutations in MTOR cause focal cortical dysplasia type II leading to intractable epilepsy. Nature medicine 2015;21:395-400.

14. Liu LL, Hou XL, Zhou CL, Tang ZZ, Bao XH, Jiang Y. [STXBP1 gene mutation in newborns with refractory seizures]. Zhongguo dang dai er ke za zhi = Chinese journal of contemporary pediatrics 2014;16:701-704.

15. Mastrangelo M, Peron A, Spaccini L, et al. Neonatal suppression-burst without epileptic seizures: expanding the electroclinical phenotype of STXBP1-related, early-onset encephalopathy. Epileptic disorders : international epilepsy journal with videotape 2013;15:55-61.

16. Matsumoto H, Zaha K, Nakamura Y, Hayashi S, Inazawa J, Nonoyama S. Chromosome 9q33q34 microdeletion with early infantile epileptic encephalopathy, severe dystonia, abnormal eye movements, and nephroureteral malformations. Pediatric neurology 2014;51:170-175.

17. Michaud JL, Lachance M, Hamdan FF, et al. The genetic landscape of infantile spasms. Human molecular genetics 2014;23:4846-4858.

18. Olson HE, Tambunan D, LaCoursiere C, et al. Mutations in epilepsy and intellectual disability genes in patients with features of Rett syndrome. American journal of medical genetics Part A 2015;167A:2017-2025.

19. Rauch A, Wieczorek D, Graf E, et al. Range of genetic mutations associated with severe non-syndromic sporadic intellectual disability: an exome sequencing study. Lancet 2012;380:1674-1682.

20. Saitsu H, Hoshino H, Kato M, et al. Paternal mosaicism of an STXBP1 mutation in OS. Clinical genetics 2011;80:484-488.

21. Saitsu H, Kato M, Okada I, et al. STXBP1 mutations in early infantile epileptic encephalopathy with suppression-burst pattern. Epilepsia 2010;51:2397-2405.

22. Saitsu H, Kato M, Shimono M, et al. Association of genomic deletions in the STXBP1 gene with Ohtahara syndrome. Clinical genetics 2012;81:399-402.

23. Sajan SA, Jhangiani SN, Muzny DM, et al. Enrichment of mutations in chromatin regulators in people with Rett syndrome lacking mutations in MECP2. Genetics in medicine : official journal of the American College of Medical Genetics 2016.

24. Tso WW, Kwong AK, Fung CW, Wong VC. Folinic acid responsive epilepsy in Ohtahara syndrome caused by STXBP1 mutation. Pediatric neurology 2014;50:177-180.

25. Barcia G, Chemaly N, Gobin S, et al. Early epileptic encephalopathies associated with STXBP1 mutations: Could we better delineate the phenotype? European journal of medical genetics 2014;57:15-20.

26. Di Meglio C, Lesca G, Villeneuve N, et al. Epileptic patients with de novo STXBP1 mutations: Key clinical features based on 24 cases. Epilepsia 2015;56:1931-1940.

27. Gburek-Augustat J, Beck-Woedl S, Tzschach A, Bauer P, Schoening M, Riess A. Epilepsy is not a mandatory feature of STXBP1 associated ataxia-tremor-retardation syndrome. European journal of paediatric neurology : EJPN : official journal of the European Paediatric Neurology Society 2016;20:661-665.

28. Grone BP, Marchese M, Hamling KR, et al. Epilepsy, Behavioral Abnormalities, and Physiological Comorbidities in Syntaxin-Binding Protein 1 (STXBP1) Mutant Zebrafish. PloS one 2016;11:e0151148.

29. Mignot C, Moutard ML, Trouillard O, et al. STXBP1-related encephalopathy presenting as infantile spasms and generalized tremor in three patients. Epilepsia 2011;52:1820-1827.

30. Otsuka M, Oguni H, Liang JS, et al. STXBP1 mutations cause not only Ohtahara syndrome but also West syndrome--result of Japanese cohort study. Epilepsia 2010;51:2449-2452.

31. Patzke C, Han Y, Covy J, et al. Analysis of conditional heterozygous STXBP1 mutations in human neurons. J Clin Invest 2015;125:3560-3571.

32. Stamberger H, Nikanorova M, Willemsen MH, et al. STXBP1 encephalopathy: A neurodevelopmental disorder including epilepsy. Neurology 2016;86:954-962.

33. Yamashita S, Chiyonobu T, Yoshida M, et al. Mislocalization of syntaxin-1 and impaired neurite growth observed in a human iPSC model for STXBP1-related epileptic encephalopathy. Epilepsia 2016;57:e81-86.