Title: *STXBP1* Encephalopathy with Epilepsy *GeneReview* – Phenotypes Associated with Recurrent Pathogenic Variants in *STXBP1*

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Phenotypes Associated with Recurrent Pathogenic Variants in *STXBP1*

Some *STXBP1* pathogenic missense variants occurring in more than one affected individual were listed below, comparing phenotypes:

- **c.1217G>A** was found in eight unrelated individuals. All had severe to profound global developmental delay or intellectual disability (ID). Seizures required two or more anti-epileptic drugs (AEDs) or were drug resistant [Saitsu et al 2010, Mignot et al 2011, Allen et al 2013, Di Meglio et al 2015, Romaniello et al 2015, Stamberger et al 2016].
- **c.875G>A** was found in five unrelated individuals [Michaud et al 2014, Helbig et al 2016, Stamberger et al 2016, Trump et al 2016]. Age at seizure onset varied from 6 months to 8 years. Seizure types included infantile spasms and partial seizures. ID ranged from mild to severe. Two individuals had a good response to AEDs becoming seizure free [Stamberger et al 2016].
- **c.703C>T** was found in three unrelated individuals. All had severe to profound global developmental delay or ID. Two became seizure free [Saitsu et al 2010, Allen et al 2013, Boutry-Kryza et al 2015].
- **c.364C>T** was found in four unrelated individuals [Lemke et al 2012, Mercimek-Mahmutoglu et al 2015, Stamberger et al 2016]. Age of seizure onset varied between the neonatal period and age one year. One individual had no seizure history.
- **c.1439C>T** was found in three unrelated individuals. All had severe developmental delay. Two became seizure free and one was refractory to anti-seizure treatment [Milh et al 2011, Tso et al 2014, Di Meglio et al 2015].
- **c.703C>T** was found in three unrelated individuals. All had severe to profound global developmental delay or ID. Two became seizure free [Saitsu et al 2010, Allen et al 2013, Boutry-Kryza et al 2015].
- **c.568C>T**, **c.416C>T**, **c.1162C>T**, **c.1651C>T**, and **c.902+1G>A** were each found in two or three unrelated individuals for whom no detailed phenotypic information was available [Hamdan et al 2009, Milh et al 2011, Kodera et al 2013, Allen et al 2013, Weckhuysen et al 2013, Barcia et al 2014, Michaud et al 2014, Di Meglio et al 2015, Keogh et al 2015, Helbig et al 2016, Li et al 2016].

References

Allen AS, Berkovic SF, Cossette P, Delanty N, Dlugos D, Eichler EE, Epstein MP, Glauser T, Goldstein DB, Han Y, Heinzen EL, Hitomi Y, Howell KB, Johnson MR, Kuzniecky R, Lowenstein DH, Lu YF, Madou MR, Marson AG, Mefford HC, Esmaeeli Nieh S, O'Brien TJ, Ottman R, Petrovski S, Poduri A, Ruzzo EK, Scheffer IE, Sherr EH, Yuskaitis CJ, Abou-Khalil B, Alldredge BK, Bautista JF, Berkovic SF, Boro A, Cascino GD, Consalvo D, Crumrine P, Devinsky O, Dlugos D, Epstein MP, Fiol M, Fountain NB, French J, Friedman D, Geller EB, Glauser T, Glynn S, Haut SR, Hayward J, Helmers SL, Joshi S, Kanner A, Kirsch HE, Knowlton RC, Kossoff EH, Kuperman R, Kuzniecky R, Lowenstein DH, McGuire SM, Motika PV, Novotny EJ, Ottman R, Paolicchi JM, Parent JM, Park K, Poduri A, Scheffer IE, Shellhaas RA, Sherr EH, Shih JJ, Singh R, Sirven J, Smith MC, Sullivan J, Lin Thio L, Venkat A, Vining EP, Von Allmen GK, Weisenberg JL, Widdess-Walsh P, Winawer MR, Epi4K Consortium, Epilepsy Phenome/Genome Project. De novo mutations in epileptic encephalopathies. Nature. 2013;501:217-21.

Barcia G, Chemaly N, Gobin S, Milh M, Van Bogaert P, Barnerias C, Kaminska A, Dulac O, Desguerre I, Cormier V, Boddaert N, Nabbout R. Early epileptic encephalopathies associated with STXBP1 mutations: Could we better delineate the phenotype? Eur J Med Genet. 2014;57:15-20.

Boutry-Kryza N, Labalme A, Ville D, de Bellescize J, Touraine R, Prieur F, Dimassi S, Poulat AL, Till M, Rossi M, Bourel-Ponchel E, Delignieres A, Le Moing AG, Rivier C, des Portes V, Edery P, Calender A, Sanlaville D, Lesca G. Molecular characterization of a cohort of 73 patients with infantile spasms syndrome. Eur J Med Genet. 2015;58:51-8.

Di Meglio C, Lesca G, Villeneuve N, Lacoste C, Abidi A, Cacciagli P, Altuzarra C, Roubertie A, Afenjar A, Renaldo-Robin F, Isidor B, Gautier A, Husson M, Cances C, Metreau J, Laroche C, Chouchane M, Ville D, Marignier S, Rougeot C, Lebrun M, de Saint Martin A, Perez A, Riquet A, Badens C, Missirian C, Philip N, Chabrol B, Villard L, Milh M. Epileptic patients with de novo STXBP1 mutations: Key clinical features based on 24 cases. Epilepsia. 2015;56:1931-40.

Hamdan FF, Piton A, Gauthier J, Lortie A, Dubeau F, Dobrzeniecka S, Spiegelman D, Noreau A, Pellerin S, Cote M, Henrion E, Fombonne E, Mottron L, Marineau C, Drapeau P, Lafreniere RG, Lacaille JC, Rouleau GA, Michaud JL. De novo STXBP1 mutations in mental retardation and nonsyndromic epilepsy. Ann Neurol. 2009;65:748-53

Helbig KL, Farwell Hagman KD, Shinde DN, Mroske C, Powis Z, Li S, Tang S, Helbig I. Diagnostic exome sequencing provides a molecular diagnosis for a significant proportion of patients with epilepsy. Genet Med. 2016;18:898-905.

Keogh MJ, Daud D, Pyle A, Duff J, Griffin H, He L, Alston CL, Steele H, Taggart S, Basu AP, Taylor RW, Horvath R, Ramesh V, Chinnery PF. A novel de novo STXBP1 mutation is associated with mitochondrial complex I deficiency and late-onset juvenile-onset parkinsonism. Neurogenetics. 2015;16:65-7.

Kodera H, Kato M, Nord AS, Walsh T, Lee M, Yamanaka G, Tohyama J, Nakamura K, Nakagawa E, Ikeda T, Ben-Zeev B, Lev D, Lerman-Sagie T, Straussberg R, Tanabe S, Ueda K, Amamoto M, Ohta S, Nonoda Y, Nishiyama K, Tsurusaki Y, Nakashima M, Miyake N, Hayasaka K, King MC, Matsumoto N, Saitsu H. Targeted capture and sequencing for detection of mutations causing early onset epileptic encephalopathy. Epilepsia. 2013;54:1262-9.

Lemke JR, Riesch E, Scheurenbrand T, Schubach M, Wilhelm C, Steiner I, Hansen J, Courage C, Gallati S, Burki S, Strozzi S, Simonetti BG, Grunt S, Steinlin M, Alber M, Wolff M, Klopstock T, Prott EC, Lorenz R, Spaich C, Rona S, Lakshminarasimhan M, Kroll J, Dorn T, Kramer G, Synofzik M, Becker F, Weber YG, Lerche H, Bohm D, Biskup S. Targeted next generation sequencing as a diagnostic tool in epileptic disorders. Epilepsia. 2012;53:1387-98.

Li D, Bhoj E, McCormick E, Wang F, Snyder J, Wang T, Zhao Y, Kim C, Chiavacci R, Tian L, Falk MJ, Hakonarson H. Early infantile epileptic encephalopathy in an STXBP1 patient with lactic acidemia and normal mitochondrial respiratory chain function. Case Rep Genet. 2016;2016:4140780.

Mercimek-Mahmutoglu S, Patel J, Cordeiro D, Hewson S, Callen D, Donner EJ, Hahn CD, Kannu P, Kobayashi J, Minassian BA, Moharir M, Siriwardena K, Weiss SK, Weksberg R, Snead OC,3rd. Diagnostic yield of genetic testing in epileptic encephalopathy in childhood. Epilepsia. 2015;56:707-16.

Michaud JL, Lachance M, Hamdan FF, Carmant L, Lortie A, Diadori P, Major P, Meijer IA, Lemyre E, Cossette P, Mefford HC, Rouleau GA, Rossignol E. The genetic landscape of infantile spasms. Hum Mol Genet. 2014;23:4846-58.

Mignot C, Moutard ML, Trouillard O, Gourfinkel-An I, Jacquette A, Arveiler B, Morice-Picard F, Lacombe D, Chiron C, Ville D, Charles P, LeGuern E, Depienne C, Heron D. STXBP1-related encephalopathy presenting as infantile spasms and generalized tremor in three patients. Epilepsia. 2011;52:1820-7.

Milh M, Villeneuve N, Chouchane M, Kaminska A, Laroche C, Barthez MA, Gitiaux C, Bartoli C, Borges-Correia A, Cacciagli P, Mignon-Ravix C, Cuberos H, Chabrol B, Villard L. Epileptic and nonepileptic features in patients with early onset epileptic encephalopathy and STXBP1 mutations. Epilepsia. 2011;52:1828-34.

Romaniello R, Saettini F, Panzeri E, Arrigoni F, Bassi MT, Borgatti R. A de-novo STXBP1 gene mutation in a patient showing the Rett syndrome phenotype. Neuroreport. 2015;26:254-257.

Saitsu H, Kato M, Okada I, Orii KE, Higuchi T, Hoshino H, Kubota M, Arai H, Tagawa T, Kimura S, Sudo A, Miyama S, Takami Y, Watanabe T, Nishimura A, Nishiyama K, Miyake N, Wada T, Osaka H, Kondo N, Hayasaka K, Matsumoto N. STXBP1 mutations in early infantile epileptic encephalopathy with suppression-burst pattern. Epilepsia. 2010;51:2397-405.

Trump N, McTague A, Brittain H, Papandreou A, Meyer E, Ngoh A, Palmer R, Morrogh D, Boustred C, Hurst JA, Jenkins L, Kurian MA, Scott RH. Improving diagnosis and broadening the phenotypes in early-onset seizure and severe developmental delay disorders through gene panel analysis. J Med Genet. 2016;53:310-7.

Tso WW, Kwong AK, Fung CW, Wong VC. Folinic acid responsive epilepsy in Ohtahara syndrome caused by STXBP1 mutation. Pediatr Neurol. 2014;50:177-80.

Weckhuysen S, Holmgren P, Hendrickx R, Jansen AC, Hasaerts D, Dielman C, de Bellescize J, Boutry-Kryza N, Lesca G, Von Spiczak S, Helbig I, Gill D, Yendle S, Moller RS, Klitten L, Korff C, Godfraind C, Van Rijckevorsel K, De Jonghe P, Hjalgrim H, Scheffer IE, Suls A. Reduction of seizure frequency after epilepsy surgery in a patient with STXBP1 encephalopathy and clinical description of six novel mutation carriers. Epilepsia. 2013;54:e74-80.