

Implication Of SCN2A In The Prognosis Of Epilepsy: A Review Paper.

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Abstract: Epilepsy is a chronic neurological disorder result in firing of the neurons due to channel defect or neuro-transmitters disturbance. Its clinical presentation is guided by the site of the abnormal neurons, and distribution pattern of the neuronal discharge. Treatment is mainly by antiepileptic drugs which have a good prognosis. However the remission and relapse is determined by some clinical and genetic factors. Many genes participate in the response to antiepileptic by affecting the metabolism, transporter, or the drug target. Sodium channel type alpha 2 gene (SCN2A) which is located in chromosome 2 encodes many antiepileptic drug receptors and incriminated in some refractory epilepsies. Science intractable epilepsy is disturbing life and consuming time early prediction of outcome will help in treating patient. More than that, using sodium channel blockers, or other modality of treatment such as ketogenic diet, deep vagus nerve stimulation, or surgery will improve outcome.

Keywords: SCN2A, Epilepsy, Prognosis, Outcome, Intractable epilepsy, Refractory epilepsy.

1. Introduction

Epilepsy

Recurrent attack of seizure is neurological disorder affects about 50 million of the population [1]. It may be due to neuron hyper- excitability, or imbalance in its neurotransmitters by gain in the excitatory ones or loss in the inhibitory [2]. According to its etiology(genetic, trauma, tumor ,infection, and electrolyte imbalance), epilepsy is categorized in to : idiopathic(genetic), symptomatic (structural-metabolic), cryptogenic, and unknown ;It has a variety of manifestations (tonic clonic, atonic, myoclonic, and spasm) [3-5]. Classified as: generalize, focal, focal to bilateral with or without impairment. [6] Diagnosis of epilepsy is mainly clinical however electroencephalogram (EEG), (magnetic resonant (MRI), genetic testing, and biological marker are helpful in some cases. The cornerstone of management is drug which has most often good outcome. [7]. As it was reported by Michel Baulac from many clinical trial about 60-70 % of patient respond well to monotherapy, while the rest modality of treatment like ketogenic diet, vagus nerve stimulation and surgery [1,8]

Genetic Background of Epilepsy

Idiopathic epilepsy may happen due to defect in some chromosomes or mutations in some genes , transmitted to next generation of the family by monogenic, oligogenic, or polygenic inheritance [9] Regarding chromosomes' defect : forming ring chromosome like chromosome 20 and chromosome 14, microdeletion which was observed in chromosome 6 , or disarrangement in chromosome 15q and chromosome 16p [10], [11].On another hand, mutations within the genes that encode the ion-channel and

neurotransmitters receptor may play a major role in epilepsy [9]- [16].

SCN2A Gene

Sodium channel voltage gated type 2 alpha subunit constitutes of two alpha subunits and one beta subunit. Its encoding gene is located in Chromosome 2: 165,194,993-165,392,310 forward strand[17].It represents sodium channel in the generation of the action potential which is distributed mainly in the axons and unmyelinated fibers [18]-[20]. Some SCN2A mutations may be involved in the pathogenesis of four phenotype groups following this manner: benign neonatal or infantile epilepsies , autism and intellectual disability, Infantile Spasms, and early onset epileptic encephalopathies including Ohtahara Syndrome and severe neonatal epilepsies [21]. These mutations may benign as some missense variants of SCN2A that respond well to high dose of phenobarbital, or may result in resistance and sudden death[22]- [24].

SCN2A-Mediated Disorders

Benign Infantile Epilepsy (BFNIS): group of partial or secondary generalize seizure occurs within the first 6 months of life and resolve. Has autosomal dominant inheritance mainly for potassium channel, voltage gated KQT-like subfamily Q, member 2gene (KCNQ2), and to some extent SCN2A [25]. SCN2A mutation in benign infantile epilepsy was identified in 1983 by Kaplan and Lacey, these mutations were found to be associated with good outcome [26]. Then Ito and his colleague reported complex partial seizure preceded by febrile seizure due to 3 missense mutations of SCN2A (R19K, R188W, and R524Q), the main mutation (R188W) was detected in a sample from 8 years old child [27]. Other variants were detected in eight families with the

benign infantile epilepsy (BFNIS) phenotype [28]. R187W mutation may be incriminated in the prolongation of the action potential while some mutations may reduce the number of Na⁺ channel via the cell-surface [29], [30]. During maturation their function will be replaced by SCN6A causing seizure abrupt. [31]. Most of the benign infantile seizure mutations increase the channel function and respond to Na⁺-channel blocker like phenytoin whereas the loss of function mutations attribute in autism [32]. Autism and Intellectual Disability: autism has been defined as a spectrum of disorders that affect the social cognitive in 5.8 per thousand of children, 30% of them may develop epilepsy [33]. SCN2A gene mutations that reduce function associate with autism whilst complete function loss cause intellectual disability [32]. Infantile Spasm (West Syndrome): is a severe form of epilepsies due to some SCN2A mutations lead to drug resistance but Atkins Diet may solve this problem [34]. Epilepsy Encephalopathies: epilepsy encephalopathies develop when the neonatal seizures resist treatment and result in neurological disability. Ohtahara syndrome has higher SCN2A mutation rate than other childhood epilepsies [35]. It may be associated with intractable seizures, severe intellectual disability, optic atrophy, muscular hypotonia, and brain abnormalities [36].

SCN2A and Epilepsy Prognosis

SCN2A mutations, prognostic effect on epilepsy is controversial. Kwan and his mates found that there is association between SCN2A de-novo mutations and drug resistance. While inherited variants have more benign prognosis [37]. Rising the need for genetic testing for childhood epilepsy as basic investigation [38]. Regarding response to treatment Kamiya and his colleagues in 2004 found that a nonsense mutation R102XSCN2A reduces the Na channel activity leading to pharmacoresistance epilepsy [39]. Indian-researcher in 2010 found that SCN2A polymorphisms may decrease sensitivity to carbamazepine and phenytoin [40]. Another result was published in 2014 at China with difference in the mutation location and dominant nucleotide [28]. In fact, ethnicity variation and its relation with drug resistance was explored in more details in a Mexican study [41]. Recently in 2017, Mishra and his group suggested that deletion in SCN2A may protect from sudden death in KCNA associated epilepsies [42]. Schwarz, steam demonstrated a gain function mutation which causes neonatal epilepsy and doesn't respond to phenobarbital nor valproate but Oxcarbazepine (OXC), Levetiracetam (LEV), and phenytoin; The seizure attacks disappear within months then intractable episodic ataxia develops [38]. Other studies approved that Na channel blockers are the best treatment choice for SCN2A mutation [43,44]. In 2017, Na⁺ channel blocker found to be effective in early onset of epilepsy rather than the later one. That may be because the SCN2A mutation in the letter is a truncated mutation which inhibits the channel strongly [44]. Children with neonatal epileptic encephalopathy may respond to lidocaine, after that it can be replaced by oral mexiletine, Ethosuximide for late-onset seizures and acetazolamide for episodic ataxia [44]- [47]. Ca-channel blocker as CACNA1G may reduce seizure due to SCN2A defect while inhibition of SCN2A gene transcription by FOXD3 will help in refractory epilepsy [48]-[49].

Conclusion

SCN2A has variety of mutation found in different epilepsies, some of them carry good outcome while other result in refractory epilepsy. Since there are some manipulations for treatment such as ketogenic diet, vagus nerve stimulation, surgery, and the use of sodium channel blocker early detection and determination of these mutations may develop good prognosis.

References

- [1] WHO regional office for the eastern mediterranean, Epilepsy in The WHO Eastern Mediterranean Region, Cairo, (2010).
- [2] H. K. Et, Mukhopadhyay.al, "Epilepsy and Its Management: A Review", Journal of Pharmascitech, 1(2), pp. 20–26, (2012).
- [3] T. L. Et .Mac. al, "Epidemiology, Aetiology, and Clinical Management of Epilepsy in Asia: A Systematic Review", lancet Neurology, 6(6), pp. 533–543, (2007). Doi: 10.1016/s1474-4422(07)70127-8.
- [4] P. Camfield, And C. Camfield, "Incidence, Prevalence and Aetiology of Seizures and Epilepsy in Children", Epileptic Discord, 17(2), pp. 117–123, (2015).
- [5] B.Lee, "Classification of Epileptic Seizures and Epilepsy Syndromes", Neurology Asia, 18(supplement 1), pp. 1–4, (2013).
- [6] S.Robert Fisher, "The 2017 Ilae Classification of Seizures", 2017. Doi:10.1111/epi.13671.s
- [7] P.A. Dekker, Epilepsy: A Manual for Medical and Clinical Officers in Africa. Revised ed. Geneva: who. (2002)
- [8] M. Baulac, "Rational Conversion from Antiepileptic Polytherapy to Monotherapy", Epileptic Disorders, 5(3), pp. 125–132, (2003).
- [9] Y. G. Weber, And H. lerche, "Genetic Mechanisms in Idiopathic Epilepsies", Developmental Medicine and Child Neurology, 50(9), pp. 648–654, (2008). Doi: 10.1111/j.1469-8749.2008.03058.x.
- [10] O. K. Steinlein, "Genetic Mechanisms that Underlie Epilepsy", Nature Reviews, 5(may), pp. 400–408, (2004). Doi: 10.1038/nrn1388.
- [11] C. G. F. De et al Kovel, "Recurrent Microdeletions at 15q11.2 and 16p13.11 Predispose to Idiopathic Generalized Epilepsies", Brain, 133, pp. 23–32, (2010). Doi: 10.1093/brain/awp262.
- [12] Giulianoavanzini, massimo mantegazza, benedetta terragni, laura canafoglia, paolo scalmani, silvana franceschetti, "The Impact Of Genetic and Experimental Studies on Classification and Therapy of The Epilepsies, Neuroscience Letters <http://dx.doi.org/10.1017> (no date). Elsevier Ireland Ltd. Doi: 10.1016/j.neulet.2017.05.026
- [13] C. Marini, Et al. "Genetic Architecture of Idiopathic Generalized Epilepsy: Clinical Genetic Analysis of 55 Multiplex Families", Epilepsia, 45(5), pp. 467–478, (2004). Doi: 10.1111/j.0013-9580.2004.46803.x.
- [14] A. Pitkänen, "Therapeutic Approaches to Epileptogenesis-Hope on The Horizon", Epilepsia, 51(s3), pp. 2–17, (2010). Doi: 10.1111/j.1528-1167.2010.02602.x.

- [15] E. Rossignol. Et al, “Wonoep Appraisal : New Genetic Approaches to Study Epilepsy”, *Epilepsia*, 55(8), pp. 1170–1186,(2015). Doi: 10.1111/epi.12692.wonoep.
- [16] S. Hwang, And S. Hirose, “Genetics of Temporal Lobe Epilepsy”, *Brain and Development*, 34(8), pp. 609–616,(2012). Doi: 10.1016/j.braindev.2011.10.008.
- [17] N. Kasai. Et. al, “Genomic Structures of Scn2a and Scn3a - Candidate Genes for Deafness at The Dfna16 Locus”, *Gene*, 264, pp. 113–122, (2001).
- [18] M. Mastrangelo, “Pediatric Neurology Novel Genes of Early-Onset Epileptic Encephalopathies : From Genotype to Phenotypes”, *Pediatric Neurology*, xxx, pp. 1–11,(2015). Doi: 10.1016/j.pediatrneurol.2015.04.001.
- [19] S. K. G. Et al. Maier, “Distinct Subcellular Localization of Different Sodium Channel Alfa and Beta Subunits in Single Ventricular Myocytes from Mouse Heart”, *Circulation*, 109(11), pp. 1421–1427,(2004). Doi: 10.1161/01.cir.0000121421.61896.24.
- [20] E. Westenbroek, A. catterall, And K. merrick, “Differential Subcellular Localization Of The Ri And R ., Na + Channel Subtypes in Central Neurons Results”, *Neuron*, 3(december), pp. 695–704,(1989).
- [21] Ingo helbig - <http://epilepsygenetics.net/2015/08/11/scn2a-this-is-what-you-need-to-know-in-2015/>
- [22] S. R. Karia, “High Dose Phenobarbital Is Safe and Effective Treatment for Scn2a Related Epilepsy”, *Clinical Neurophysiology*, 129(2018), p. E8,(2017). Doi: 10.1016/j.clinph.2018.04.019.
- [23] R. ET AL. Lakhan, “Differential Role of Sodium Gene Polymorphisms with Epilepsy and Multiple Drug Resistance in The North Indian Population”, *British Journal of Clinical Pharmacology*, 68(2), pp. 214–220, (2009). Doi: 10.1111/j.1365-2125.2009.03437.x.
- [24] L. Nashef, N. hindocha, And A. makoff, “Risk Factors in Sudden Death in Epilepsy (SUDEP) : The Quest for Mechanisms”, *Epilepsia*, 48(5), pp. 859–871,(2007). Doi: 10.1111/j.1528-1167.2007.01082.x.
- [25] B. E. ET AL. Grinton, “Familial Neonatal Seizures in 36 Families : Clinical and Genetic Features Correlate with Outcome”, *Epilepsia*, 56(7), pp. 1071–1080, (2015). Doi: 10.1111/epi.13020.
- [26] M. I. Shevell, D. B. sinclair, And K. metrakos, “Benign Familial Neonatal Seizures: Clinical and Electroencephalographic Characteristics”, *Pediatric Neurology*, 2(5), pp. 272–275, (1986). Doi: 10.1016/0887-8994(86)90018-4
- [27] M. ito, “Seizure Phenotypes Of A Family With Missense Mutations In SCN2A”, *Pediatric Neurology*, 31(2), pp. 5–7, (2004). Doi: 10.1016/j.pediatrneurol.2004.02.013.
- [28] D. ET AL. Matalon, “Confirming an Expanded Spectrum of Scn2a Mutations: A Case Series”, *Epileptic Disord*, 16(1), pp. 13–18,(2014).
- [29] T. ET AL. Sugawara, “A Missense Mutation of The Na + Channel Alfa Ii Subunit Gene Na V 1 . 2 in A Patient with Febrile and Afebrile”, *Pnas*, 22(may), (2001).
- [30] S. N. Misra, K. M. kahlig, And A. L. george, “Impaired Na V 1 . 2 Function and Reduced Cell Surface Expression in Benign Familial Neonatal-Infantile Seizures”, *Epilepsia*, 49(9), pp. 1535–1545,(2008). Doi: 10.1111/j.1528-1167.2008.01619.x.
- [31] Y. ET AL. Liao, “Molecular Correlates of Age-Dependent Seizures in an Inherited Neonatal-Infantile Epilepsy”, *Brain*, 133, pp. 1403–1414,(2010). Doi: 10.1093/brain/awq057.
- [32] H. G. ET AL. Brunner, “Diagnostic Exome Sequencing in Persons with Severe Intellectual Disability”, *The New England Journal of Medicine*, 367(20), pp. 1921–1929, (2012). Doi: 10.1056/nejmoa1206524.
- [33] Rapin, i., tuchman, r. And moshe, s. L. (2009) ‘convulsing toward the pathophysiology of autism’, *brain and development*, 31, pp. 95–103. Doi: 10.1016/j.braindev.2008.09.009.
- [34] D. Turkdogan, G. thomas, And B. demirel, “Ketogenic Diet as A Successful Early Treatment Modality for Scn2a Mutation”. *Brain and Development*, 41(4), 389–391,(2019).
- [35] K. Nakamura. al, “Clinical Spectrum of SCN2A Mutations Expanding to Ohtahara Syndrome”. *Neurology*, 81(11), 992–998,(2013). Doi: 10.1212/wnl.0b013e3182a43e57.
- [36] Anna-lena baasch. al. “Exome Sequencing Identifies A De Novo Scn2a Mutation in A Patient with Intractable Seizures , Severe Intellectual Disability , Optic Atrophy , Muscular Hypotonia , and Brain Abnormalities”, *Epilepsia*, 55(4), pp. 25–29,(2014). Doi: 10.1111/epi.12554.
- [37] P. ET AL. Kwan, “Multidrug Resistance in Epilepsy and Polymorphisms in The Voltage-Gated Sodium Channel Genes Scn1a, Scn2a, And Scn3a: Correlation among Phenotype, Genotype, and mRNA Expression”, *Pharmacogenetics And Genomics*, 18(11), pp. 989–998,(2008). Doi: 10.1097/fpc.0b013e3283117d67.
- [38] A. T. Berg. al, “ Early-Life Epilepsies and The Emerging Role of Genetic Testing”. *Jama Pediatrics*, 171(9), 863,(2017).
- [39] K. ET AL. Kamiya, “A Nonsense Mutation of The Sodium Channel Gene Scn2a in A Patient with Intractable Epilepsy And Mental Decline”, *The Journal of Neuroscience*, 24(11), pp. 2690–2698, (2004). Doi: 10.1523/jneurosci.3089-03.2004.
- [40] S. ET AL. Grover, “Genetic Profile of Patients with Epilepsy on First-Line Antiepileptic Drugs and Potential Directions for Personalized Treatment”, *Pharmacogenomics*, 11(7), pp. 927–941,(2010).
- [41] I. ET .al. Fricke-galindo l, “Allele and Genotype Frequencies of Genes Relevant to Anti-Epileptic Drug Therapy in Mexican-Mestizo Healthy Volunteers”, *Pharmacogenomics*, 10.2217/pg, (2016).
- [42] Mishra, v. Et al, “Scn2a Deletion Improves Survival and Brain – Heart Dynamics in The Kcna1 -Null Mouse Model of Sudden Unexpected Death in Epilepsy (SUDEP)”, *Human Molecular Genetics*,

- 26(11), pp. 2091–2103,(2017). Doi: 10.1093/hmg/ddx104.
- [43] R.E.T. AL. dilena , “Efficacy of Sodium Channel Blockers in Scn2a Early Infantile Epileptic Encephalopathy”. *Brain Dev* (2016), <http://dx.doi.org/10.1016/j.braindev.2016.10.015> (no date). The japanese society of child neurology. Doi: 10.1016/j.braindev.2016.10.015.
- [44] M. ET AL. Wolff, “Genetic and Phenotypic Heterogeneity Suggest Therapeutic Implications in Scn2a -Related Disorders”, *Brain*, 140(5), pp. 1316–1336, (2017). Doi: 10.1093/brain/awx054.
- [45] I. A. Et al. Foster, “Infantile Epileptic Encephalopathy Associated with Scn2a Mutation Responsive to Oral Mexiletine”, *Pediatric Neurology*,(2016). Elsevier ltd. Doi: 10.1016/j.pediatrneurol.2016.10.008.
- [46] S. J. sanders.al, “ Progress in understanding and treating scn2a -mediated disorders”. *Trends in neurosciences*, 41(7), 442–456,(2018). Doi: 10.1016/j.tins.2018.0
- [47] I. Ogiwara.al, “De Novo Mutations of Voltage-Gated Sodium Channel Alfa Ii Gene Scn2a in Intractable Epilepsies”, *Neurology*, 73, pp. 1046–1053, (2009).
- [48] J. D. ET AL. Calhoun, “Cacna1g Is A Genetic Modifier of Epilepsy in A Mouse Model of Dravet Syndrome”, *Epilepsia*, 58(8), pp. 111–115,(2017). Doi: 10.1111/epi.13811.
- [49] Jun xianga, fang wenb, Y. Z. lingyun zhang, “Foxd3 Inhibits SCN2A Gene Transcription in Intractable Epilepsy Cell Models”, *Experimental Neurology*. Elsevier, 302(may 2017), pp. 14–21,(2018). Doi: 10.1016/j.expneurol.2017.12.012.