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Identification of epilepsy concomitant candidate genes recognized in Saudi epileptic patients

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Abstract. – Saudi Genome program is a revolutionary nationwide transformation initiative of Saudi Vision 2030. The program goals are to recognize and reduce the incidence of genetic diseases in the Kingdom of Saudi Arabia (KSA). Accordingly, the program will establish the foundation for personalized and genomic medicine in the KSA. Epilepsy has a high prevalence in KSA reaching around 6.54 of 1000 individuals with a subsequent massive financial burden. One of the main risk factors for this high prevalence and associated with increased risk of epilepsy development is consanguinity marriage, which is traditional in KSA. In this review, we executed a comprehensive state-of-art literature review regarding epilepsy genetics to offer a perception into the genes associated with epilepsy recognized in Saudi epileptic patients. Several genes' mutations were incorporated in this review including *AFG3L2, ASPM, ATN1, ATP1A2, BMP5, CCDC88A, C12orf57, DNAJA1, EML1, ERLIN2, FRRS1L, GABRG3, NRXN3, MDH1, KCNJ10, KCNMA1, KCNT1, KIAA0226, OPHN1, PCCA, PCCB, PEX, PGAP2, PI4K2A, PODXL, PRICKLE1, PNKP, RELN, SCN2A, SCN1B, SLC2A1, SLC19A3, SLC25, SIAH1, SYNJ1, SZT2, TBCK, TMX2, TSC1, TSC2, TSEN, WDR45B, WWOX, UBR, UGDH*, and *YIF1B*. For each of these genes, we tried to explain a little about the gene associated proteins and their roles in epilepsy development.

Key Words:
Epilepsy, Gene, Saudi Arabia.

Introduction

Epilepsy is a neurological condition in which the altered activity of neurons causes convulsions, periods of infrequent behavior and, sometimes, loss of consciousness. The International League Against Epilepsy (ILAE) categorizes seizures in two main categories: firstly, idiopathic generalized epileptic seizures and focal seizures[1]. Epilepsy may exist as an isolated neurological symptom or concomitant with another neurological disease[2]. More than 25 epilepsy syndromes and disorders have been delineated till now thus epilepsies are phenotypically and genetically diverse[1]. In Kingdom of Saudi Arabia (KSA), epilepsy occurs in 6.54 of 1000 individuals[3]. One of the most imperative risk factors that was found to be associated with increased risk of epilepsy is consanguinity marriage which is habitually popular in KSA[4]. It is estimated that more than half of epilepsies have a genetic basis[5] and such inheritance can be autosomal dominant or recessive or X-linked recessive or dominant[6].

The advance application of genomic technologies has and will have an incredible influence on the detection of epilepsy genetic basis, thus anticipated to play a critical part in the diagnosis as well as the treatment of epilepsy[7]. However, epilepsies are associated with genetic irregularities and exhibit huge heterogeneity. Mutations in some genes may selectively cause epilepsy or epilepsy syndromes as the fundamental sign (e.g., *SCN1A* mutations cause epilepsies with febrile seizures)[8], whereas other genes may be related to defective brain developmental and epilepsies (e.g., *TSC1* and *TSC2* genes mutations results in tuberous sclerosis)[9]. Therefore, it is puzzling to resolve which gene, or cluster of genes, ought to be illustrated in a particular patient population before scheming an efficient as well as cost-effective genetic-testing approach.

Materials and Methods

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The aim of the existing narrative review is to offer a perception into the genes associated with epilepsy recognized in Saudi epileptic patients, which is a first repot to be performed. To attain the current review goal, we accomplished a comprehensive state-of-art literature review regarding the genetics of epilepsies. A literature search was executed using online available databases like PubMed, ClinVar, Online Mendelian Inheritance in Man (OMIM), Epilepsy Genetic Association Database (epiGAD), Phenotype-Genotype Integrator (PheGenI), DisGeNET and GWAS Catalog. The literature search was accomplished to retrieve all genetic studies implemented and published on Saudi epileptic patients till September 2021. The search was done using the following strings: (epilepsy), (Saudi), (gene), (epilepsies) and (genes).

Genes Associated with Epilepsy

AFG3L2

The ATPase family gene 3-like (*AFG3L2*) is the catalytic subunit of the m-AAA protease, an ATP-dependent proteolytic complex of the mitochondrial internal membrane that removes erroneous folded proteins and adjusts ribosome gathering[10]. The *AFG3L2* was first stated as a disease gene in spinocerebellar ataxia type 28 (SCA28)[11] and in recessive spastic ataxia type 5[12]. Epilepsy is an infrequent sign of the *AFG3L2* gene mutation. Eskandrani et al[13] described five Saudi children from a consanguineous family with a severe mitochondrial phenotype in the form of deterioration of milestones, early onset seizures, amplified lactate, and basal ganglia envelopment. Such severe mitochondrial phenotype was connected with biallelic *AFG3L2* loss of function. Exome sequencing displayed homozygous mutation of the *AFG3L2* gene c.1714G>A (p.Ala572Thr) in these five individuals[13].

ASPM

Autosomal recessive primary microcephaly (MCPH) is a neurodevelopmental syndrome, illustrated by microcephaly at birth and non-progressive mental delay[14]. Mutations in *MCPH1* (microcephalin) on chromosome 8p23 and in *ASPM* (abnormal spindle-like, microcephaly-associated) on chromosome 1q31.3 have been identified to cause MCPH1 and MCPH5, respectively, with *ASPM* mutations being the furthermost common source[15]. Shen et al[16] reported the recognition of the first *ASPM* nonsense mutations in three Saudi patients with microcephaly and seizures. They defined homozygous 6189TRG transversion in exon 18 in all three affected individuals. This mutation modifies the tyrosine-2063 (TAT) to a premature amber stop codon (TAG). Additionally, they recognized other four non-synonymous (7480T to C, 7684A to G, 7939C to A, and 9395T to G) and six synonymous (849C to T, 3579T to A, 4449A to G, 5961A to G, 7566A to G, and 7674C to T) SNPs.

ATN1

ATN1 maps at chromosomal region 12p13.31 and includes of 10 exons and encodes atrophin-1 (ATN1). ATN1 is a nuclear transcriptional regulator in brain and other organs development[17]. A human disorder ultimately connected to *ATN1* is entitled dentatorubral-pallidoluysian atrophy (DRPLA) triggered by a polyglutamine expansion in exon 5[18]. DRPLA is interpreted by progressive neurological features of choreoathetosis, myoclonus, epilepsy, ataxia, and dementia. Palmer et al[19] documented heterozygous alterations in *ATN1* gene causing substitutions within the highly conserved 16-amino acid histidine-rich 'HX repeat' motif near the C terminus (c.3178C>T, p.His1060Tyr) in one DRPLA Saudi patient[18].

ATP1A2

ATP1A2 gene located on chromosome 1q23 and encodes for the α-2 subunit of the plasma membrane Na/K pump. Na/K pump is a heteromeric protein, which utilizes ATP for actively, carry Na^+ out and K^+ into the cell. Al-Bulushi et al[20] recognized c.1766T>C. (Ile589Thr) heterozygous mutation in the *ATP1A2* gene in Saudi kindred with hemiplegic attacks and seizures.

BMP5

Bone morphogenetic protein-5 (*BMP5*) is a member of BMP family that is associated in the central as well as peripheral nervous systems development[21]. BMP-5 is displayed at high levels in the developing and adult nervous system; thus, it was suggested the possibility that BMP-5 regulates dendritic morphology[22]. Naseer, et al[23] carried out a study on a cohort of Saudi epileptic patients searching for copy number variations (CNVs) associated with epilepsy. Microduplication in the gene *BMP5* at location 6p12.1 ranged from 51.6 to 95.6 kb was identified in five Saudi

epileptic patients containing two from the same family[23].

CCDC88A

Progressive encephalopathy, edema, hypsarrhythmia, and optic atrophy (PEHO) syndrome is associated with intense intellectual disability, optic nerve/cerebellar atrophy, epileptic seizures, and early death[24]. Abdulkareem et al[25] stated a consanguineous Saudi family with a homozygous nonsense mutation of the *CCDC88A* gene causing PEHO-like syndrome. Whole exome sequencing data analysis identified a homozygous nonsense mutation c. 1292G > A, which was caused by p.Trp431* stop gain within the CCDC88A protein at codon 431, exon 12 resulted in a whole loss of protein function and PEHO phenotype[25].

C12orf57

Temtamy syndrome is a syndromic form of intellectual disability presented by ocular contribution, epilepsy and corpus callosum dysgenesis. Although autosomal recessive inheritance was obviously alleged, it was only in 2013 when Zahrani et al[26] recognized pathogenic biallelic variants in *C12orf57* gene as the cause of Temtamy syndrome[26]. Four homozygous alleles: c.-3_2delinsG (just upstream of the start codon), c.53-2A>G (anticipated to eliminate a canonical splice acceptor), 43C>T, p.(Gln15*) (nonsense), and c.229+2T>C (expected to abolish a canonical splice donor) were established. These four variants were described for the first time at that time, which bring the total number of pathogenic alleles in Temtamy syndrome to seven[26]. The other three were 1A>G, p.(Met1) (Founder mutation), c.184C>T, p.(Gln62*), p.(Gln15*), c.152T>A, p.(Leu51Gln)[26].

DNAJA1

DNAJ family is the largest heat shock proteins (HSP) family in humans and characterized by its highly conserved J-domain[27]. DNAJ proteins are responsible for numerous vital cellular processes comprising folding polypeptide chains, modulate protein assembly, conformational progress and maintenance, and targeting of proteins for degradation[28]. Alsahli et al[29] reported three Saudi siblings with homozygous alteration in *DNAJA1* gene that map at c.511 C>T p. (Glycine171*). This SNP triggered the creation of premature stop codon resulting in omitting of 227 of the 397 protein residues. These patients were all intellectually disabled with generalized tonic clonic epilepsy[29].

EML1

EML1 encodes a microtubule-binding protein that affects planar polarity, and its deficit results in irregular migration outline with resulting band heterotopia in mice[30]. Neuronal migration disorders such as lissencephaly and subcortical band heterotopia are associated with epilepsy and intellectual disability[30]. Shaheen et al[31] preformed a genetic examination for 27 consanguineous Saudi families with hereditary hydrocephalus. A 2-year-old girl with congenital hydrocephalus, and intractable epilepsy displayed a homozygous truncating variant in *EML1* gene. Exome sequencing and homozygosity mapping identified a nonsense mutation in *EML1* (c.1567C>T, p.[Arg523*]), leading to a premature stop codon which was predicted to cause loss of the largest part of C-terminal ß-propeller.

ERLIN2

Spastic paraplegia-18 (SPG18) is a serious autosomal recessive neurologic condition described by beginning in early childhood of progressive spastic paraplegia causing motor disability. SPG18 is caused by homozygous mutation in the *ERLIN2* gene on chromosome 8p11[32]. Alazami et al[33] stated a consanguineous Saudi family with a complex form of Hereditary Spastic Paraplegia (HSP). By autozygosity, they reported a linkage to an 18.2-Mb interval on chromosome 8p12-q11.22, which overlapped with the SPG18 locus delineated earlier[32]. The same research group identified a homozygous 20-kb deletion on chromosome 8, with the distal breakpoint near physical position 37,694,857 and the proximal breakpoint near 37,714,575 immediately upstream of exon 2 of the *ERLIN2* gene[33]. This 20-kb interval spans 2 protein-coding genes, *ERLIN2* and *FLJ34378*. RT-PCR analysis of patient lymphoblasts showed loss of *ERLIN2* transcription, consistent with a null allele. They hypothesized that loss of ERLIN2 may result in persistent activation of IP3 signaling and neuronal channel activity thus concluded that *ERLIN2* depletion caused HSP, though they could not dismiss a role for *FLJ34378*[33].

FRRS1L

AMPA receptors (AMPARs) signify the utmost common receptor subtype in the brain and facilitate most fast excitatory post-synaptic potentials. FRRS1L (ferric chelate reductase 1-like)

is a chief constituent of the outer core of AMPAR accessory proteins, signifying that loss of *FRRS1L* would disturb AMPAR constituency and purpose[34]. Madeo et al[35] defined 8 children from 4 families with an epileptic-dyskinetic encephalopathy. In one consanguineous Saudi family, five affected sibs had usual initial development until the age of 18 and 24 months when hemiclonic and tonic-clonic seizures started. Afterward, the patients presented developmental deterioration with loss of walking and speech. Three additional unrelated children with a similar disorder were also identified[35]. A homozygous c.961C>T (p.Gln321*) variant in *FRRS1L* within a prominent block of homozygosity (chr 9) was identified. This mutation was predicted to lead to loss of a C-terminal hydrophobic motif that might contribute to FRRS1L's membrane localization. Furthermore, the same research group identified three additional variants in unrelated individuals with similar phenotypes and biallelic *FRRS1L* variants. Whole-exome sequencing identified a homozygous c.845G>A (p.Trp282*), in-frame deletion (c.737_739del [p.Gly246del]) and (c.436dup [p.Ile146Asnfs*10]) in *FRRS1L*.

GABRG3

GABRG3 is a member of the GABA-A receptor gene family of heteromeric pentameric ligand-gated ion channels through which GABA, the main inhibitory neurotransmitter, acts. A microdeletion in *GABRG3* gene with a size of 15,134bps (24948149-24963282) deleted region was detected in one Saudi patient suffered from idiopathic generalized epileptic[36].

NRXN3

Neurexins are cell adhesion molecule, largely expressed in presynaptic terminals and inhibitory γ-aminobutyric acid (GABA)-ergic neurons[12-14]. A study[36] was conducted on eight idiopathic generalized epileptic Saudi patients who were sporadic and 2 of them were sisters. Microdeletion in *NRXN3* gene that located at 14q31.1 with 7,177 base pairs (79176037-79183213) as a deleted region was detected in 4 patients where 2 of them were sisters. Other Microduplication of groups of genes was observed in 3 patients. In the fifth patient, the size of duplicated region is 6,93,095bps (61543275-62236369) which resulted in duplicated genes including *KCNQ2*, *EEF1A2*, and *PPDPF*. In the sixth patient, the size of duplicated region is 7,67,317bps (61446244-62213560) where the size of duplicated region of the last patient is 7,95,803bps (61446244-62242046). In the last two patients, the mutation is leading to group of duplicated genes, which were *CHRNA4*, *KCNQ2*, and *EEF1A2*[36].

MDH1

MDH plays crucial roles in the malate–aspartate transport and the tricarboxylic acid cycle[37]. Developmental and epileptic encephalopathy-88 (DEE88) is caused by homozygous mutation in the *MDH1* gene on chromosome 2p15. DEE88 is an autosomal recessive severe neurologic disorder characterized by global developmental delay, early-onset epilepsy, and progressive microcephaly. Broeks et al[38] reported two affected first cousins, a boy and a girl, from a consanguineous Saudi family with early-onset epileptic encephalopathy. The boy was recognized with DEE88, whereas his 4-year-old cousin had severe developmental delay, epilepsy, microcephaly, and similar facial dysmorphisms. The homozygous missense variant in the NAD^+ binding domain of MDH1 led to severely reduced MDH protein expression. One homozygous variant was distinguished in both patients in MDH1: c.413C>T. The subsequent missense variant p.Ala138Val replaces the conserved alanine in the NAD^+ binding domain producing diminished MDH protein expression.

KCNJ10

EAST (Epilepsy, ataxia, sensorineural deafness and tubulopathy) syndrome is a varied disease caused by loss of function mutation in the *KCNJ10*[39]. *KCNJ10* gene located on chromosome 1q23.2, encodes potassium inward-rectifying channel subfamily J, member 10[40]. Mir et al[41] reported the first case series of five Saudi patients spotted with EAST syndrome. All five patients have the same homozygous c.170C>T (p.Thr57Ile) missense mutation in *KCNJ10* gene in exon number 57, which caused in the transformation of threonine into isoleucine[41].

KCNMA1

The large-conductance voltage- and Ca^{2+} activated K^+ channel, also called the BK channel, are activated by both intracellular Ca^{2+} ions and membrane depolarization. The BK channel consists of four α subunits and 4 optional auxiliary β subunits. The pore-forming α subunit is programmed by the potassium channel, calcium-activated, large conductance, subfamily m, α member 1 (*KCNMA1*) gene[42]. In 2 sisters, born of consanguineous Saudi parents, with cerebellar at-

rophy, developmental delay, and seizures, Tabarki et al[43] identified a homozygous 1-bp duplication (c.2026dupT) in the *KCNMA1* gene.

KCNT1

The *KCNT1* responsible for encoding a ligand gated potassium channel. Borlot et al[44] has implemented one of the largest international cohorts examining pediatric patients diagnosed with *KCNT1* related epilepsy. In that cohort, twenty-seven children were included, five from Saudi Arabia. Four Saudi patients cases diagnosed with epilepsy of infancy with migrating focal seizures (EIMFS) has revealed the *KCNT* variant as c.1885A>G,p-Lys629Glu, c.1421G>A,p.Arg474His, c.862G>A,pGly288Ser and c.2800G>A,pAla934Thr respectively[44]. Whereas last patient suffered from unclassified early onset epileptic encephalopathy (EOEE) in which the *KCNT* variant was c.1130G>c, pCys377Ser[44].

KIAA0226

The *KIAA0226* gene encodes rubicon, a protein implicated in vesicular trafficking and late endosome development. In three sisters, born of consanguineous Saudi Arabian parents, presented with autosomal recessive spinocerebellar ataxia-15 (SCAR15), Assoum et al[45] recognized a homozygous mutation in the *KIAA0226* gene (c.2624delC). Such mutation caused the loss of the highly conserved DAG binding-like motif. Furthermore, transfecting the mutant *KIAA0226* in COS-1 and HeLa cells resulted in mislocalization of the mutant protein from the late endosome and lysosomes to diffuse cytosolic distribution. Protein mislocalization signifying that this mutation resulted in the loss of proper protein function[45].

OPHN1

X-linked mental retardation (XLMR), a heterogeneous disorder, triggered by a mutation in the oligophrenin-1 (*OPHN1*) gene on chromosome Xq12. The OPHN1 is a protein with a Rho-GTPase-activating domain necessary in the G-protein cycle regulation[46]. Al-Owain et al[47] reported a large Saudi family of four boys and one girl affected with XLMR. A deletion of at least exons 7-15 was identified by PCR analysis and multiple ligation probe amplification of the *OPHN1* gene. The array comparative genomic hybridization further delineated around 68 kb deletion of the 7–15 exons in the *OPHN1* gene and almost half of intron 15.

PCCA and PCCB

Propionic acidemia is an inborn error of metabolism that is inherited in an autosomal recessive manner. It is displayed by propionyl-CoA carboxylase (PCC) deficiency due to mutations in either of its β or α subunits[48]. The conventional clinical demonstration involves poor feeding, vomiting, metabolic acidosis, hyperammonemia, lethargy, neurological problems including epilepsy. AlGhamdi et al[49] studied 14 propionic acidemia patients in Saudi Arabia retrospectively, out of which 10 patients displayed a homozygous missense mutation (c.425G>A; p. Gly142Asp) in *PCCA* gene. Two patients had a homozygous duplication in the gene *PCCB* (c.1050dupT p. E351X) at the exon 11. The two remaining patients had homozygous mutation in the gene *PCCA* G117D:350G>A, and (c.1288C>T p.(Arg430*).

PEX

Enzymes enclosed peroxisomes are required for numerous critical metabolic functions, such as β-oxidation of very long chain fatty acids (VLCFA) and synthesis of bile acids, among others[50]. Peroxisomal biogenesis disorders (PBDs) are broadly classified into two subgroups: Zellweger spectrum disorders (ZSDs) caused by mutations in *PEX1*, *2*, *3*, *5*, *6*, *10*, *11B*, *12*, *13*, *14*, *16*, *19*, *26* genes, and Rhizomelic chondrodysplasia punctata type1 (RCDP1), caused by *PEX7* mutation [51,52]. Alshenaifi et al[53] collected a relatively large PBDs cohort including 80 patients. They recognized 43 variants from which 20 were novel at the time. The most commonly mutated gene was *PEX1* with seven different variants: a founder missense (c.3037C > T: p.Arg1013Cys) recognized in five families and a nonsense variant (c.2176C > T: p.Gln726*) documented in two families. Additionally, 11 variants in other *PEX* genes were found. All RCDP patients had the same splice-site *GNPAT* variant (c.569-3 T > G) except one with a missense variant in the same gene (c.487C > G: p.Arg163Gly). Furthermore, Mohamed et al[54] studied a Saudi female infant diagnosed with ZSDs and revealed homozygosity for a c.320delA frame shift mutation in *PEX19* gene.

PGAP2

PGAP2 (Post-GPI Attachment to Proteins 2) plays a role in maturation of the glycosyl phosphatidyl inositol (GPI) anchor on GPI-anchored proteins[55]. Recessive mutations in *PGAP2* induce hyperphosphatasia with mental retardation syndrome-3 (HPMRS3)[56]. HPMRS3 patients develop repeated seizures in early childhood[57].

PGAP2 gene, localized at chromosomal11p15.4, is involved in the synthesis of Golgi/ER-resident membrane protein. Absence of this protein leads to transport to surface of the cell of lyso-GPI-APs and resultantly are more prone to cleavage by phospholipase D [58]. Naseer et al[59] acknowledged a large consanguineous Saudi family with HP-MRS3, exhibited mutation c.191CNT in *PGAP2* gene resulting in alanine to valine substitution (Ala64Val) at position 64 in exon[59].

PI4K2A

PI4K2A encodes phosphatidylinositol 4-kinase type 2 α, one of a number of phosphoinositide (PI) kinases responsible for phosphorylating phosphatidylinositol[60]. Alkhater et al[61] defined Saudi family with two children presented with developmental deferral, dystonia, epilepsy and heat intolerance. *Via* genome sequencing, they identified a nonsense variant in the first exon of *PI4K2A* that was homozygous in both affected individuals and was absent from, or heterozygous, in seven unaffected siblings. This variant produced *PI4K2A* total loss, as a premature stop codon introduced only 22 amino acids, signifying that *PI4K2A* loss of functional outcome is neurodevelopmental phenotype with mild epilepsy.

PODXL

Podocalyxin (PODXL) is type-1 membrane mucin protein belongs to CD34 family expressed in kidney epithelial cells (podocytes) plentifully[62]. PODXL plays pivotal roles in several processes during early brain development[63]. A microdeletion was observed in three Saudi patients at the location 7q32.3 of *PODXL* gene in which the deletion ranges from 56.6 to 63.9 kb[23].

PRICKLE1

Progressive myoclonus epilepsy (PME) involves a group of heterogeneous syndromes defined by a mixture of action myoclonus, epileptic seizures, and progressive neurologic deterioration[64]. *PRICKLE1* gene was associated to autosomal recessive and autosomal dominant PME[65]. *PRICKLE1* is mapped on chromosome 12q12 and encodes the nuclear receptor prickle planar cell polarity protein 1. Algahtani et al[66] described a Saudi family with an exceptional form of autosomal dominant PME. Two patients had heterozygous missense mutation in *PRICKLE1* gene in exon number 84 at c.251 G > A, resulting in the transformation arginine into glutamine[66].

PNKP

The Polynucleotide kinase 3-prime phosphatase (*PNKP*) gene encodes a polynucleotide kinase 3-prime phosphatase, which catalyzes the 5-prime phosphorylation of nucleic acids [67]. In affected members of 2 unrelated families with microcephaly, seizures, and developmental delay, Shen et al[68] acknowledged a homozygous 17-bp duplication (c.1250_1266dup) in exon 14 of the *PNKP* gene, producing a frame shift and premature termination.

RELN

RELN encodes a large, secreted protein reelin which direct layer formation by eliciting responses in target neurons and leads to the formation of cell layers and the growth of neuronal processes[69]. Hong et al[70] studied an autosomal recessive form of lissencephaly associated with severe abnormalities of the cerebellum, hippocampus, and brainstem in a Saudi family. This autosomal recessive form of lissencephaly was associated with two independent mutations in *RELN*, which mapped to chromosome 7q22. These mutations disrupted *RELN* cDNA splicing, subsequently producing little or undetectable reelin protein.

SCN2A

The sodium channel neuronal type 2 α subunit (*SCN2A*) gene encodes the voltage-gated sodium channel Nav α1.2, which is chiefly responsible for action potentials generation in excitable cells[71]. A phenotype associated with *SCN2A* mutation is the early infantile epileptic encephalopathy type 11 (EIEE11)[72]. AlSaif et al[73] testified a Saudi patient with a biallelic missense mutation in the *SCN2A* gene with an autosomal recessive inheritance. Genetic testing with an EIEE gene panel identified a homozygous missense mutation (c.5242A>G; p.Asn1748Asp) in *SCN2A* situated on chromosome 2q24.3.

SCN1B

SCN1B, positioned on chromosome 19q13.11, encodes the voltage-gated sodium channel β1 subunit, and is known to have various isoforms. Mutations in *SCN1B* result in generalized epilepsy with febrile seizures and, very rarely, Dravet syndrome[74]. Ramadan et al[75] reported the existence of recessive *SCN1B* mutations in 3 Saudi families with developmental epileptic encephalopathy. In family 1 and 3, the same splicing variant was identified (c.449-2A>G). In family two, a missense ho-

mozygous *SCN1B* variant (c.355T>G:p.Y119D) was recognized[75].

SLC2A1

Cerebral metabolism is mainly relied on glucose for which a facilitated diffusion *via* glucose transporter protein 1 (GLUT1) across the blood-brain barrier is fundamental. The *SLC2A1* gene encodes GLUT1; thus, mutations in *SLC2A1* will lead to GLUT1 deficiency syndrome[76]. Algahtani et al[77] described a heterozygous intronic variant c.1278+12delC in the *SLC2A1* gene in a Saudi patient with myoclonic epilepsy, inherited in an autosomal dominant manner.

SLC13A5

Nashabat et al[78] preformed genetic descriptive retrospective study of 72 molecularly characterized EIEE Saudi patients. They recognized 26 diverse kinds of EIEE and identified 50 variants from which 26 were novel at the time. The most prevalent type of EIEE in that cohort was EIEE type 25 caused by *SLC13A5* mutation, which was established in 11 patients, followed by type 11 and type 37, each of which was confirmed in seven patients. Additionally, Alhakeem et al[79] testified three Saudi siblings with *SLC13A5* transporter deficiency with intractable seizures[79].

SLC19A3

Biotin-responsive basal ganglia disease (BBGD) patients present with a progressive condition characterized by dystonia, seizure disorders, and psychomotor delay. Early administration of biotin and thiamine results in partial or complete improvement within days. BBGD is autosomal recessive, connected to *SLC19A3* gene mutations[80]. The *SLC19A3* gene is one of the SLC19 gene family, which is accountable for the uptake of water-soluble vitamins into cells[80,81]. The *SLC19A3* gene encodes human thiamine transporter 2 (hTHTR2), a second thiamine transporter. Homozygous mutations in *SLC19A3* are the cause of BBGD[80]. Tabarki et al[82] retrospectively studied 10 Saudi BBGD patients (5 females and 5 males). Sequencing of *SLC19A3* disclosed a pathogenic homozygous mutation c.1264A.G (p.Thr422Ala) in all 10 patients[82]. Furthermore, Eichler et al[83] reported a 20-year-old Saudi woman with BBGD who was homozygous for the T422A mutation in the *SLC19A3* gene.

SLC25

The *SLC25* gene family encodes mitochondrial carriers, which carry various metabolites through the inner mitochondrial membrane. The SLC25A22 protein[84] catalyzes either the cotransport of L-glutamate with H^+ or its exchange with OH^-. Poduri et al[85] objective was to identify the genetic cause for migrating partial seizures in infancy (MPSI). Two regions of linkage, chromosome 4p16.1-p16.3 and chromosome 11p15.4-pter in a consanguineous pedigree with 2 entities with MPSI were identified[85]. Using whole exome sequencing, eight homozygous variants were established in these regions. From which, only one variant, *SLC25A22* c.G328C, resulted in a change of the amino acid (p.G110R), that specific G110R mutation, located in a transmembrane domain of the protein thus disrupting mitochondrial glutamate passage.

SIAH1

Buratti-Harel syndrome (BURHAS) is a neurodevelopmental disorder described by infantile hypotonia, global developmental delay, mild motor and speech delay, and mild to moderately diminished intellectual development. BURHAS is triggered by heterozygous mutation in the *SIAH1* gene on chromosome 16q12 [86]. Monies et al[87] informed of a Saudi boy with BURHAS who was found to carry a homozygous in-frame deletion in exon 1 of the *SIAH1* gene (c.91_91del, Glu31fs) by exome sequencing.

SYNJ1

SYNJ1 gene encodes a polyphosphoinositide phosphatase that plays an important role in clathrin-coated pit-mediated endocytosis[88]. Biallelic genetic disruption of *SYNJ1* account for impaired synaptic vesicle recycling dynamics and clathrin-coated vesicles buildup. Loss of *SYNJ1* dual phosphatase activity leads to early onset refractory seizures and advanced neurological deterioration[89]. Samanta and Arya[90] described a Saudi Arabian infant girl who witnessed multifocal seizures. Whole exome sequence investigation disclosed homozygous pathogenic variant (p.Q287PfsX27) in the *SYNJ1* gene. This variant causes a frame shift starting with codon glutamine 287, modified into proline, generating a premature stop codon at position 27 with a new reading frame, denoted p.Gln287ProfsX27, consequential a loss of normal protein function (113).

SZT2

Developmental EE are indicated by severe epileptic seizures and developmental delay or regression[91]. The seizure threshold 2 (*SZT2*) gene, containing 71 exons and located on chromosome 1p34.2, is expressed in the CNS and is associated with the regulation of mammalian target of rapamycin mTOR[92]. Naseer et al[93] identified two Saudi siblings' patients with homozygous missense mutation in the *SZT2* gene in the exon 67 at c.9368G>A, which led to the exchange of glycine to glutamic acid[93].

TBCK

TBC1 domain-containing kinase (TBCK) is a conserved protein kinase that associates with the mitotic apparatus and regulates cell size, cell proliferation, and mTOR signaling[94]. In 2 sibs, born of consanguineous Saudi parents, presented with characteristic facies-3 (IHPRF3), Alazami et al[95] recognized a homozygous c.1708+1G-A (c.1708+1G-A) transition in the *TBCK* gene, anticipated to cause a splicing defect. Additionally, Bhoj et al[96] provided a follow-up to these sibs and identified a homozygous c.1897+1G-A transition (c.1897+1G-A), predicted to result in a frame shift[95].

TMX2

Protein disulfide isomerase (PDI) proteins participate in the creation and relocation of disulfide bonds between cysteine residues in the endoplasmic reticulum throughout protein folding [97]. Eight children from four consanguineous families were recruited [97]. All patients presented with microlissencephaly, developmental delay, intellectual incapacity as well as epilepsy. An identical homozygous variant in *TMX2* (c.500G>A), encoding thioredoxin-related transmembrane protein 2, segregated with disease in all four families. This variant transformed the last coding base of exon 6, and impacted mRNA stability, signifying that *TMX2* c.500G>A allele connects with recessive microlissencephaly.

TSC1 and TSC2

Tuberous Sclerosis Complex (TSC) is an autosomal dominant genetic multisystem syndrome which primarily associated with the lack of functional TSC1-TSC2 complex due to mutations in *TSC1* or *TSC2* genes encoding hamartin and tuberin, respectively[9]. Almobarak et al[98] preformed the genetic analysis for 44 TSC Saudi patients, for whom 13 patients had *TSC1* mutation, 29 patients had *TSC2* gene mutation. Genetic examinations for *TSC* 1 and *TSC* 2 were negative for 2 patients despite positive gene mutation in their relative with TSC. Most of the patients develop epilepsy with multiple seizure types. *TSC2* mutation is more common than *TSC1* mutation. Three patients from the same cohort were genetically confirmed with *TSC2* and also had a mutation in *PKD1*/*PKD2* gene of autosomal dominant polycystic kidney disease which designates more rigorous form of the disease.

TSEN

The tRNA splicing endonuclease is a highly evolutionarily conserved protein complex, intricate in the cleavage of intron-containing tRNAs. In human, it consists of the catalytic subunits TSEN2 and TSEN34, as well as the non-catalytic TSEN54 and TSEN15[99]. One Saudi boy, who was born to consanguineous parents, exhibited severe epilepsy. He carried a homozygous missense mutation in *TSEN15* gene resulting in a p.Trp76Gly substitution. This p.Trp76Gly variant in *TSEN15* gene ensued lower protein levels and affected protein folding, stability, or both[99].

WDR45B

WDR45B is associated with neurodevelopmental syndrome presented by intellectual disability, spastic quadriplegia, epilepsy, and cerebral developmental flaw leading to cerebral hypoplasia[100]. Because of their exceptional construction, WD repeat proteins can act as a core to which diverse proteins can simultaneously interact[101]. Six Saudi patients from three different families were recognized with homozygous pathogenic nonsense variants in *WDR45B*: c.799C>T (p.Q267*) in one of these families and c.673C>T (p.R225*) in two families[100].

WWOX

WWOX is a cytoplasmic protein that is intricate in several cellular processes[102]. *WWOX* gene is mapped on chromosome 16q23, which contains two N-terminal WW domains, a short chain of dehydrogenase reductase domain at the C-terminal, and a nuclear localization sequence[103]. Mutations in the *WWOX* gene are associated with EIEE[104]. In a Saudi family, Ehaideb et al[105] characterized a homozygous variant in intron 4 of the *WWOX* gene, c.409+1G>T which led to include the intron sequence in the mRNA or neither elimination of the exon. Both these potentials lead to modify the protein function or to non-functioning.

UBR

The ubiquitin-proteasome system (UPS) plays universal roles in cellular homeostasis by degrading proteins in a time-regulated fashion[106]. Li et al[107] showed that variants in *UBR7* cause a neurodevelopmental syndrome with epilepsy and hypothyroidism, joining *UBR1* as the second UBR to be implicated in a human disorder. A homozygous 1-bp deletion (c.618delT) in the *UBR7* gene was identified in two Li-Campeau syndrome (LICAS) unrelated boys, each born of consanguineous parents of Saudi Arabian origin. Such mutation is anticipated to cause a frame shift and premature termination (Glu207ArgfsTer12) of the protein synthesis[107].

UGDH

UGDH codes for an enzyme that transforms UDP-glucose (UDP-Glc) to UDP-glucuronic acid (UDP-GlcA) *via* reduction of NAD^+ into NADH[108]. Hengel et al[109] recruited 25 families from all over the world including Saudi Arabia from which 23 coding variants were identified representing an allelic series of germline mutations. The biochemical conclusions indicated that these missense mutations mainly influence the enzymatic function of UGDH *via* fluctuating its quaternary structure and/or directly impairing its oxidoreductive ability. All Saudi patients had biallelic mutations in *UGDH* (in chromosome 4 c.950G>A) showed with a common core phenotype involving of marked developmental delay, epilepsy, mild dysmorphism, and motor disorder with axial hypotonia.

YIF1B

Kaya-Barakat-Masson syndrome (KABAMAS) is a severe autosomal recessive neurodevelopmental disorder presented by extremely diminished global development with inconsistent motor abnormalities. KABAMAS is triggered by homozygous or compound heterozygous mutation in the *YIF1B* gene on chromosome 19q13[110]. YIF1B belongs to the FinGER protein family and is elaborate in endoplasmic reticulum (ER)-to-Golgi trafficking. Loss of YIF1B function leads to myelination change, neuronal death, Golgi, ER, and ciliary defects with pathology related to disrupted trafficking of proteins, eventually resulting in neurodevelopmental abnormalities[111]. Diaz et al[112] studied 2 sisters, born of consanguineous Saudi Arabian parents, identified with KABAMAS. They distinguished a homozygous c.186dup mutation (c.186dup) in the *YIF1B* gene, causing a frameshift and premature termination (Ala63CysfsTer18), resulting in a loss of function.

Conclusions

One of most important risk factors that associated with the increased prevalence of epilepsy KSA is consanguinity marriage, which is habitually popular. In this review, we performed a comprehensive literature review concerning epilepsy genetics to compromise an insight into the genes associated with epilepsy recognized in Saudi Arabia patients. Several genes' mutations were included in this review including *AFG3L2*, ASPM, *ATN1*, *ATP1A2*, *BMP5*, *CCDC88A*, *C12orf57*, *DNAJA1*, *EML1*, *ERLIN2*, *FRRS1L*, *GABRG3*, *NRXN3*, *MDH1*, *KCNJ10*, *KCNMA1*, *KCNT1*, *KIAA0226*, *OPHN1*, *PCCA*, *PCCB*, *PEX*, *PGAP2*, *PI4K2A*, PODXL, *PRICKLE1*, *PNKP*, *RELN*, *SCN2A*, *SCN1B*, *SLC2A1*, *SLC19A3*, *SLC25*, *SIAH1*, *SYNJ1*, SZT2, *TBCK*, *TMX2*, *TSC1*, *TSC2*, *TSEN*, *WDR45B*, *WWOX*, *UBR, UGDH*, and *YIF1B*. For each of these genes, we tried to explain a little about the gene and it is role in nervous system and associated protein and their role in disease development and clinical phenotype on the Saudi patients and the mutation occurring in these genes.

Conflict of Interest

The authors declare that they have no conflicts of interest.

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Authors' Contribution

Conceptualization, N.S.Y, M.E.M and M.E.; methodology, A.A.A, G.Y.A, H.A.A, J.A.A, M.A.A M.A.A, Z.A.A, Z.S.A, and Z.A.A. ; data curation, A.A.A, G.Y.A, H.A.A, J.A.A.; writing—original draft preparation, A.A.A, G.Y.A, H.A.A, J.A.A, M.A.A, M.A.A, Z.A.A, Z.S.A, and Z.A.A.; writing—review and editing, N.S.Y, M.E.M.; supervision, N.S.Y, M.E.M and M.E.; project administration, N.S.Y, M.E.M and M.E.; All authors have read and agreed to the published version of the manuscript.

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