临床与基础桥接研究
Clinical and Basic Bridging Research

难治性癫痫患者癫痫耐药与全外显子组基因多态性相关性的临床研究

Clinical trial on the association between epilepsy drug resistance and whole exome genetic polymorphisms in refractory epilepsy patients

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摘要：目的 研究癫痫耐药与全外显子组基因单核苷酸多态性的相关性。**方法** 将就诊于本院的癫痫患者按照队列法分为癫痫耐药组和单药有效组。收集患者的病史以及实验室检查结果，观察患者充分治疗超过12个月后的发作情况。通过对12例极端病例(6例3药耐药患者 *vs.* 6例单药有效且处于减药阶段的患者)进行全外显子测序，筛选候选基因，进一步在癫痫耐药组和单药有效组中进行候选基因多态性检测验证，探究基因多态性与癫痫耐药的相关性。**结果** 560例患者中，癫痫耐药组153例、单药有效组407例。癫痫单药有效组和耐药组的年龄中位数分别为19和25岁，体重中位数分别为50和55 kg；上述指标在2组间比较在统计学上差异均有统计学意义(均 $P<0.05$)。在癫痫耐药组和单药有效组中，结构性病因占比分别为55.56%和45.46%；传染性病因分别为3.92%和2.21%；免疫性病因分别为3.27%和1.23%；代谢和遗传性病因分别为5.88%和11.30%；存在2种病因的分别为1.96%和1.23%。在癫痫耐药组和单药有效组中，存在意识障碍的患者占比分别为56.21%和39.07%；初始用药方案为二代抗癫痫药物患者的占比分别为50.98%和65.46%；存在局灶性皮层发育不良患者的占比分别为10.46%和2.95%；存在海马硬化的患者占比分别为15.03%和9.58%；存在缺血缺氧性脑病的患者占比分别为3.92%和1.47%；存在脑部血管畸形的患者占比分别为4.58%和3.93%；存在颅脑外伤的患者占比分别为1.31%和3.44%；存在脑部肿瘤的患者占比分别为3.92%和2.21%；存在多种病理学改变的患者占比分别为1.96%和0.98%；存在非癫痫相关改变的患者占比分别为23.53%和29.48%。基线信息显示，患者的年龄、体重、病因、发作时意识障碍与否、初始用药方案以及影像学结果与癫痫耐药相关($P<0.05$，$P<0.001$)。纳入102个候选单核苷酸多态性(SNPs)，在560例癫痫患者中展开基因分型检测与关联分析，共发现5个SNP与癫痫耐药相关。同时纳入临床因素与遗传因素，多因素logistic回归分析显示，海马硬化、局灶性皮层发育不良、缺血缺氧性脑病、发作时伴有意识障碍、*SCN2A* rs17183814 GG以及*SPATA31* rs1919128 GA基因型是癫痫耐药的风险因素(*SCN2A* rs17183814：$P=0.027$；*SPATA31* rs1919128：$P=0.014$)。**结论** *SCN2A*及*SPATA31*基因多态性与癫痫耐药相关，*SCN2A* rs17183814 GG以及*SPATA31* rs1919128 GA基因型患者更容易出现癫痫耐药。

关键词：癫痫；耐药；单核苷酸多态性；全外显子组测序；临床研究
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Abstract：**Objective** To investigate the association between drug resistant epilepsy (DRE) and single nucleotide polymorphisms (SNPs) in whole-exome sequencing (WES). **Methods** Patients with

epilepsy, who visited in our hospital, were enrolled in this study and divided into a drug – resistant group and a monotherapy – effective group based on treatment outcomes. Baseline demographic characteristics, medical history and laboratory test results were collected. Seizure outcomes were observed after more than 12 months under adequate treatment. WES was performed on 12 extreme cases (6 patients with resistant to three antiepileptic drugs *vs.* 6 patients effectively treated with monotherapy and undergoing dose reduction) to identify candidate SNPs. These candidate SNPs were then validated in the larger cohort to explore the association with DRE. **Results** A tota of 560 patients were enrolled, 153 were DRE group and 407 were monotherapy – effective group. The median age in the monotherapy – effective group and the drug – resistant group was 19 years old and 25 years old, respectively; the median weight were 50 kg and 55 kg, respectively. All these differences between the two groups were statistically significant (all $P<0.05$); the proportion of structural etiology was 55.56% in the drug – resistant group and 45.46% in the monotherapy – effective group; the proportion of infectious etiology were 3.92% and 2.21%; the proportion of immune etiology were 3.27% and 1.23%; the proportion of metabolic and genetic etiology were 5.88% and 11.30%; the proportion of dual etiologies were 1.96% and 1.23%; the proportion of patients with impaired consciousness were 56.21% and 39.07%; the proportion of second – generation antiseizure medication as initial medication regimen were 50.98% and 65.46%; the proportion of malformation of cortical development were 10.46% and 2.95%; the proportion of hippocampal sclerosis were 15.03% and 9.58%; the proportion of hypoxic – ischemic encephalopathy were 3.92% and 1.47%; the proportion of vascular malformation were 4.58% and 3.93%; the proportion of traumatic brain injury were 1.31% and 3.44%; the proportion with brain tumor were 3.92% and 2.21%; the proportion with dual pathologies were 1.96% and 0.98%; the proportion of abnormal nonepileptogenic were 23.53% and 29.48%. Baseline information showed statistically significant differences in age, weight, etiology, presence of impaired awareness, initial medication regimen and neuroimaging results ($P<0.05$, $P<0.001$). 102 candidate SNPs were selected for genotyping and association analysis in larger cohort including 560 patients. 5 SNPs were identified to be significantly associated with DRE. Multivariate logistic regression incorporating both clinical and genetic factors revealed that hippocampal sclerosis, malformation of cortical development, hypoxic – ischemic, presence of impaired awareness, as well as the *SCN2A* rs17183814 GG and *SPATA31* rs1919128 GA genotypes were risk factors for drug resistance (*SCN2A* rs17183814 GG: $P=0.027$; *SPATA31* rs1919128 GA: $P=0.014$). **Conclusion** *SCN2A* rs17183814 and *SPATA31* rs1919128 were found to be associated with drug resistance. Carriers of the GG genotypes of *SCN2A* rs17183814 and GA genotype of *SPATA31* rs1919128 are more likely to develop DRE.

Key words: epilepsy; drug resistance; single – nucleotide polymorphisms; whole – exome sequencing; clinical study

难治性癫痫,即癫痫耐药(drug – resistant epilepsy, DRE)是指患者正确选择且耐受2种抗癫痫药物(单用或者联合用药)后仍不能控制癫痫发作[1]。DRE患者预后差、治疗成本高,显著影响其生活质量。因此,在患者疾病早期对患者出现耐药的风险进行评估,从而选择非药物治疗的干预(如手术、迷走神经治疗等)具有重要的临床意义。目前,有关基因多态性与DRE关系的研究主要涉及转运体、代谢酶、药物作用靶点等,而各项研究由于其纳入的样本类型不同、候选位点有限,导致结果之间存在差异[2-3]。因此,本研究通过极端样本的全外显子组关联测序(whole exome sequencing, WES)筛选相关基因多态性,并在大样本中进行验证,旨在寻找与癫痫耐药相关的单核苷酸多态性(single nucleotide polymorphisms, SNPs),为难治性癫痫患者的早期风险预警和临床干预提供参考。

材料、对象与方法

1 病例选择

2017年7月至2023年7月以我院神经科门诊收治确诊为癫痫且疗效判定信息准确完整的患者纳入为研究对象。本研究经中山大学药学院医学伦理委员会批准(伦理批号:20170312)。所有患者均已签署知情同意书。

诊断和入选标准 根据2014年国际抗癫痫联盟(International League of Epilepsy, ILAE)发布的癫痫临床诊断标准《ILAE official report: A practical clinical definition of epilepsy》[4],结合患者癫痫临床发作表现(存在明确的感知、运动、自主神经、知觉、情感、认知

等障碍)以及长程视频脑电图显示存在癫痫样放电(棘波、尖波、棘慢符合波等阵发性异常),最终被临床医生确诊为癫痫的患者。

排除标准 ① 用药依从性差,未按照医嘱规律用药者;② 重要脏器损伤及其他重大疾病者;③ 妊娠期或哺乳期妇女;④ 临床信息(一般资料及发作情况)不全的患者。

2 试剂与仪器

试剂 多重聚合酶链式反应(polymerase chain reaction, PCR)引物,北京擎科生物科技股份有限公司生产;PCR 试剂(10 × PCR buffer, PCR 酶, dNTP Mix,氯化镁),美国 Agena Bioscience 公司生产;虾碱性磷酸酶(shrimp alkaline phosphatase,SAP)和单碱基延伸反应酶体系和 384 分型芯片,均由美国 Agena Bioscience公司生产;2 × plus Taq HiFi PCR mix,深圳迈科斯生物科技有限公司生产。

仪器 Multiskan FC 酶标仪, 美国 Thermo Fisher 公司产品; GeneAmp PCR system 2700,美国 ABI 公司产品;Sequenom MassArray iplex 基因分型质谱检测仪和 MassArray 4.0 飞行时间质谱仪,均为美国 Agena® 公司产品; NovaSeq 测序仪,美国 Illumina 公司产品。

3 患者分组、疗效判定与治疗方法

患者分组 收集患者基线时期的人口学特征、病史(病因、发作类型、初始用药方案、家族史、精神共患病、颅脑创伤、热性惊厥病史、脑炎病史)、实验室检查结果、影像学结果以及脑电图检查结果。随访患者充分治疗 12 个月的发作情况,根据疗效将癫痫患者分为耐药组和单药有效组。

疗效判定 根据 2010 年 ILAE 发布的癫痫临床诊断标准《Definition of drug resistant epilepsy: Consensus proposal by the ad hoc task force of the ILAE commission on therapeutic strategies》[1],经 2 种正确选择且达到最大耐受剂量的抗癫痫药物(无论单药或联合治疗)进行充分治疗后,仍未达到至少 12 个月以上持续无发作的患者判定为耐药组;仅使用 1 种正确选择且可耐受的抗癫痫药物进行充分治疗达到 12 个月以上持续无发作的患者判定为单药有效组。

治疗方法 所有患者均遵照神经科医师建议的剂量和用药方案每日口服抗癫痫药物进行治疗。

4 观察指标

本研究采用“发现 - 验证”研究设计,先选取 12 例极端病例(6 例 3 药耐药患者 *vs.* 6 例单药有效且处于减药阶段的患者)进行全外显子组测序,初步筛选与癫痫耐药相关的候选 SNPs,随后在耐药组和单药有小组中对筛选出得候选 SNPs 与耐药的相关性进行验证分析。

全外显子测序 将 6 对极端病例交由杭州联川生物科技有限公司进行全外显子组关联测序,后续通过卡方检验筛选候选 SNPs。

SNPs 筛选 对原始序列进行处理后,依据美国医学遗传学与基因组学学会(American College of Medical Genetics and Genomics, ACMG)指南的建议以及其他文献的报道进行筛选[5-6]。

DNA 提取与基因分型 取耐药组和单药有效组癫痫患者血液样本,用乙二胺四乙酸(ethylene diamine tetraacetic acid, EDTA)抗凝,取全血离心后的血细胞 100 μL,用改良的碘化钠 - 氯仿法[7]提取基因组脱氧核糖核酸(deoxyribonucleic acid, DNA),并使用酶标仪对 DNA 样本进行质控,浓度不小于 20 $\mu g \cdot mL^{-1}$ 且在 260 nm 和 280 nm 的光密度(optical density, OD)比值 OD_{260}/OD_{280} 介于 1.6 ~ 1.9 之间的样本方可用于后续基因分型试验。用 Assay Design Suite 在线软件设计多重 PCR 反应的正、反引物及延伸引物,由北京擎科生物科技股份有限公司股份有限公司进行合成。用飞行时间质谱系统在耐药组和单药有效组中进行 SNP 基因分型检测。

5 统计学处理

用 SPSS 25.0 软件进行统计分析。符合正态分布的连续变量用 $\bar{x} \pm s$ 表示,组间比较用独立样本 t 检验,非正态分布连续变量用中位数及四分位数间距表示,组间比较用 Manny - Whitney U 检验;分类变量的比较用卡方检验。用 SNP Stats 在线网站(https://www.snpstats.net/start.htm)进行 Hardy - Weinberg 平衡检验。一般资料和 SNP 先进行单因素 logistic 回归,取单因素 logistic 回归中 $P < 0.05$ 的因素纳入二元多因素 logistic 回归分析,衡量纳入因素对癫痫耐药的影响,以优势比(odds ratio, OR)和置信区间(confidence interval, CI)表示。

结 果

1 一般资料

全外显子关联测序部分纳入 12 例成人患者,6 名为 3 药耐药患者,6 名为单药有效且处于减药阶段的患者。这些患者的年龄、性别、病因、发作类型等一般资料在统计学上差异均无统计学意义(均 $P > 0.05$),组间具有可比性。

大样本验证部分纳入癫痫患者 560 例,其中单药有效组 407 例,耐药组 153 例。2 组患者的年龄、体

重、病因、发作时是否存在意识障碍、初始用药方案以及影像学结果，在统计学上差异均有统计学意义（均 $P<0.05$），见表 1。

2 候选 SNPs 的基本信息与 Hardy－Weinberg 平衡结果

共纳入 102 个 SNP 位点，所有 SNP 在东亚人群中的最小等位基因频率（minor allele frequency，MAF）值均大于 0.05，Hardy－Weinberg 平衡检验结果显示38 个 SNP 不满足 Hardy－Weinberg 平衡（均 $P<0.05$），其余 SNP 符合 Hardy－Weinberg 平衡（均 $P>0.05$）。

3 基因多态性与癫痫耐药的相关性

电压门控钠离子通道Ⅱα（sodium channel voltage－gated type Ⅱ alpha，*SCN2A*）rs17183814 位点与癫痫耐药显著相关，GG 基因型患者比 GA＋AA 基因型患者更容易出现癫痫耐药（OR＝1.70，95% CI＝1.09～2.64，$P<0.05$）；层粘连蛋白亚基 3（laminin subunit beta 3，*LAMB3*）rs2076349 位点与癫痫耐药显著相关，TT 基因型患者比 CT＋CC 基因型患者更容易出现癫痫耐药（OR＝1.52，95% CI＝1.03～2.25，$P<0.05$）；亮氨酰和胱氨酸氨肽酶（leucyl and cystinyl

表 1 2 组患者一般资料的比较（$n=560$）

Table 1 Comparison of general information between two groups ($n=560$)

Variables	Response ($n=407$)	DRE ($n=153$)	Variables	Response ($n=407$)	DRE ($n=153$)
Gender (n,%)			History of febrile convulsions (n,%)		
Female	193(47.42)	73(47.71)	No	349(85.75)	135(88.24)
Male	214(52.58)	80(52.29)	Yes	58(14.25)	18(11.76)
Age, median (IQR)	19.00 (11.00, 27.00)	25.00 (16.00, 33.00)*	History of SE (n,%)		
Weight, median (IQR)	50.00 (37.00, 61.50)	55.00 (46.75, 67.12)*	No	394(96.81)	146(95.42)
Etiology (n,%)			Yes	13(3.19)	7(4.58)
Unknown	157(38.57)	45(29.41)*	Family history (n,%)		
Structural	185(45.46)	85(55.56)*	No	391(96.07)	145(94.77)
Infectious	9(2.21)	6(3.92)*	Yes	16(3.93)	8(5.23)
Immune	5(1.23)	5(3.27)*	Presence of psychiatric disorders (n,%)		
Others#	46(11.30)	9(5.88)*	No	394(96.81)	145(94.77)
Dual	5(1.23)	3(1.96)*	Yes	13(3.19)	8(5.23)
Seizure type (n,%)			History of significant head trauma (n,%)		
Generalized	85(20.88)	23(15.03)	No	389(95.58)	149(97.39)
Focal	322(79.12)	130(84.97)	Yes	18(4.42)	4(2.61)
Presence of impaired awareness (n,%)			History of encephalitis (n,%)		
No	248(60.93)	67(43.79)*	No	385(94.59)	141(92.16)
Yes	159(39.07)	86(56.21)*	Yes	22(5.40)	12(7.84)
Presence of tonic－clonic seizure (n,%)			Neuroimaging (n,%)		
No	93(22.85)	42(27.45)	Normal	187(45.95)	54(35.29)*
Yes	314(77.15)	111(72.55)	Malformation of cortical development	12(2.95)	16(10.46)*
Initial medication regimen (n,%)			Hippocampal sclerosis	39(9.58)	23(15.03)*
First－generation antiepileptic medications△	141(34.64)	75(49.02)*	Hypoxic－ischemic	6(1.47)	6(3.92)*
Second－generation antiepileptic medications▲	266(65.46)	78(50.98)*	Vascular malformation	16(3.93)	7(4.58)*
Age at onset (n,%)			Traumatic brain injury	14(3.44)	2(1.31)*
Adult	127(31.20)	47(30.72)	Tumor	9(2.21)	6(3.92)*
Infant	54(13.27)	29(18.95)	Dual pathologies	4(0.98)	3(1.96)*
Childhood	126(30.96)	45(29.41)	Abnormal nonepileptogenic&	120(29.48)	36(23.53)*
Adolescent	95(23.34)	31(20.26)			
Elder	5(1.23)	1(0.66)			

#: Other etiologies include genetic and metabolic etiology; △: First－generation antiepileptic medications include valproic acid, carbamazepine, phenobarbital and phenytoin; ▲: Second－generation antiepileptic medications include topiramate, oxcarbazepine, levetiracetam and lamotrigine; &: Abnormal nonepileptogenic include small vessel ischemic changes, white matter hyperintensity, other cystic lesions, nonspecific T2 signal, cerebral atrophy, hippocampal structures asymmetry, developmental venous anomaly, Chiari I malformation, calcification, lipoma, cerebral aneurysm, brachycephaly, cerebellar atrophy, congenital asymmetry of ventricles, cortical thickening, thinning of frontal lobes, hydrocephalus, hypoplastic right vertebral artery and pontine myelinolysis; Compared with response group, * $P<0.05$.

aminopeptidase, *LNPEP*) rs2303138 位点与癫痫耐药显著相关,GA + GG 基因型患者比 AA 基因型患者更容易出现癫痫耐药(OR = 1.76,95% CI = 1.07 ~ 2.90, $P < 0.05$);精子发生相关蛋白 31(spermatogenesis associated protein 31,*SPATA*31)rs1919128 位点与癫痫耐药显著相关,GA 基因型患者比 GG + AA 基因型患者更容易出现癫痫耐药(OR = 1.48,95% CI = 1.01 ~ 2.15,$P < 0.05$);粘附 G 蛋白偶联受体 V1(adhesion g protein - coupled receptor V1,*ADGRV*1)rs16868972 位点与癫痫耐药显著相关,GG + TT 基因型患者比 GT 基因型患者更容易出现癫痫耐药(OR = 1.58,95% CI = 1.07 ~ 2.31,$P < 0.05$)。其他 SNPs 比较,在统计学上差异均无统计学意义(均 $P > 0.05$),见表 2。

4 多因素 logistic 回归分析

基于一般信息与 SNP 的统计分析,纳入年龄、体重、病因、发作时存在意识障碍、影像学结果、初始用药方案以及在统计学上差异有统计学意义的 5 个 SNPs 进行多因素 Logistic 回归分析。发作时体重、存在意识障碍、影像学结果、初始用药方案、SCN2A rs17183814 和 SPATA31 rs1919128 与癫痫耐药均显著相关(均 $P < 0.05$)。其中,*SCN*2*A* rs17183814 GG 基因型患者(OR = 1.78,95% CI: 1.07 ~ 2.95, $P < 0.05$)和 *SPATA*31 rs1919128 GA 基因型患者(OR = 1.77, 95% CI: 1.12 ~ 2.78, $P < 0.05$)有较高的癫痫耐药风险,见表 3。

表 2 耐药组和单药有效组中与癫痫耐药(DRE)具有相关性的单核苷酸多态性(SNPs)

Table 2 Single nucleotide (SNPs) associated with drug resistance in response and drug - resistant epilepsy (DRE) groups

Gene	SNP	Genotype	Response (n = 407)	DRE (n = 153)
*ADGRV*1	rs16868972	GT	194	58
		GG + TT	195	92
*LAMB*3	rs2076349	TT	119	63
		CT + CC	250	87
LNPEP	rs2303138	AA	99	23
		GA + GG	301	123
*SCN*2*A*	rs17183814	GG	263	117
		GA + AA	126	33
*SPATA*31	rs1919128	GA	177	83
		AA + GG	214	68

表 3 耐药组和单药有效组患者中癫痫耐药的的二元 logistic 回归分析

Table 3 Binary logistic regression analysis for drug resistance in DRE and monotherapy - effective groups

Variables	OR (95% CI)	P value
Weight	1.02(1.01,1.04)	0.005
Presence of impaired awareness		
No	Reference	-
Yes	1.99(1.26,3.14)	0.003
Initial medication		
First - generation AEDs	Reference	-
Second - generation AEDs	0.56(0.35,0.89)	0.014
Neuroimaging		
Normal	Reference	-
Malformation of cortical development	10.19(3.34,31.08)	<0.001
Hippocampal sclerosis	2.28(1.02,5.11)	0.044
Hypoxic - ischemic	3.81(1.01,14.34)	0.048
Vascular malformation	1.69(0.56,5.09)	0.351
Traumatic brain injury	0.72(0.13,4.15)	0.718
Tumor	2.29(0.59,8.81)	0.230
Dual pathologies	1.50(0.20,11.53)	0.696
Abnormal nonepileptogenic	1.10(0.61,1.99)	0.761
*SCN*2*A* rs17183814		
GA + AA	Reference	-
GG	1.78(1.07,2.95)	0.027
*SPATA*31 rs1919128		
AA + GG	Reference	-
GA	1.77(1.12,2.78)	0.014

AEDs: Antiepileptic drugs; OR: Odds ratio; CI: Confidence interval.

讨 论

癫痫耐药的影响因素众多,单纯的临床因素并不能解释癫痫耐药背后潜在的机制。因此,本研究通过 WES 在 12 例极端病例中筛选候选 SNPs,而后在 560 例患者中进行验证,旨在探究基因多态性与癫痫耐药的相关性。本研究表明,发作时体重、存在意识障碍、影像学结果、初始用药方案、*SCN*2*A* rs17183814 和 *SPATA*31 rs1919128 的基因多态性与癫痫耐药显著相关。

在发作时体重方面,目前,有文献显示,脂质代谢紊乱可能与癫痫耐药相关,且生酮饮食可以控制难治性癫痫患者癫痫发作[8-9]。在影像学结果方面,局灶性皮层发育不良、海马硬化以及缺血缺氧性脑病与癫痫耐药相关,这与既往的报道一致[10-11]。在意识障碍方面,文献显示,发作时反复出现意识障碍可能对脑代谢产生累积效应,导致 DRE 患者发作间期皮质 - 皮质下代谢异常[12]。在初始用药方面,文献显示,第一代抗癫痫药物已被证明同时作用于多个靶点,这表明如果患者接受第一代抗癫痫药物后未获得最佳治疗结局,那么后续使用其他类似靶点的抗癫痫药物可能也会出现治疗失败的现象[13-14]。

*SPATA*31 属于灵长类特异性扩增的基因簇,在睾丸中高表达,可能与精子发生和基因组稳定性相关[15-17]。*SPATA*31 rs1919128 位点位于人类 2 号染色

体上[16]。该基因突变频率呈现显著的种族差异,在东亚人群中突变频率为0.49,而在非洲人群的突变频率为0.08,在欧洲人群中的突变频率为0.27。本研究发现,*SPATA*31 rs1919128 GA 型基因型呈现较高的癫痫耐药风险(OR=1.77,95% CI: 1.12~2.78,P=0.014)。有研究发现,*SPATA*31 参与 DNA 损伤修复和应激反应,可能在维持基因组稳定性中发挥作用,因此该基因的突变可能通过影响神经元氧化应激反应进而影响参与癫痫的发病过程[15-17]。*SCN2A* 位于人类 2 号染色体上,是神经元动作电位起始和传导的关键蛋白。该基因的突变与多种神经系统疾病密切相关,有研究显示 *SCN2A* rs17183814 与遗传性癫痫伴热性惊厥附加症、重度抑郁症和精神分裂症疾病的易感有关[18-20]。本研究发现,*SCN2A* rs17183814 GG 基因型患者出现癫痫耐药的风险更高(OR=1.78,95% CI: 1.07~2.95,P=0.027)。

本研究提示:在 12 例极端样本的 WES 结果中筛选候选 SNPs,在 560 例患者中对候选 SNP 进行验证,结果显示,*SCN2A* 和 *SPATA*31 基因突变与癫痫耐药相关,*SCN2A* rs17183814 GG 基因型以及 *SPATA*31 rs1919128 GA 基因型患者更容易出现癫痫耐药。本研究存在一定局限性,SNP 均来自 WES,而这部分突变仅占全基因组突变的 1%~2%,对于那些非编码区但有潜在影响的 SNP 并没有纳入,且本研究最开始的 WES 筛选是在 6 对极端样本中进行,这可能遗漏有潜在作用的 SNPs,应进一步开展大样本的 WES。

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