

Table 1 PK and PD altered genes in refractory epilepsy

Gene	Alterations	Product	References	Possible mechanisms of drug refractoriness
<i>ABCB1</i> (MIM171050)	C3435T	ATP-binding cassette (ABC) transporter	[32-37]	Overexpression or increased activity of efflux transporter in the blood-brain barrier enhanced drug extrusion from target site
	T1236C		[36, 38, 39]	
	G2677T		[36-38]	
	G2677A		[36, 38]	
<i>ABCC2</i> (MIM601107)	ABCC2 - 24T		[47]	
<i>CYP3A4</i> (MIM124010)	CYP3A4*1B	Cytochrome P450 3A4 enzyme	[49, 52-54]	Alterations in metabolic activity
<i>CYP2C9</i> (MIM601130)	CYP2C9*3 CYP2C9*3/*3	Cytochrome P450 2C9 enzyme	[48, 49, 54]	
<i>SCN1A</i> (MIM182389)	SCN1A IVS5-91 G>A	Voltage-gate Na ⁺ channel α 1 subunit	[72]	Structure alteration and reduction of sensitivity to the drug
	rs6730344A/C		[74]	
	rs6732655A/T		[74]	
	rs10167228A/T		[74]	
<i>SCN2A</i> (MIM182390)	c.56 G→A	Voltage-gate Na ⁺ channel α 2 subunit	[71]	
	c.R19K		[70]	
	IVS7-32A>G		[69]	
<i>GABRA1</i> (MIM137160)	IVS11 + 15 A> G	GABA _A receptor α 1 subunit	[84]	Aberrant formation of the drugs-binding pocket
	rs6883877		[85]	
<i>GABRA2</i> (MIM137140)	rs511310	GABA _A receptor α 2 subunit	[85]	
<i>GABRA3</i> (MIM305660)	rs4828696	GABA _A receptor α 3 subunit	[85]	
<i>GRIN2A</i> (MIM138253)	L812M	NMDA receptor GluN2A subunit	[92]	
	M817V		[91]	