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### Hydrological response of an afforested catchment in a Mediterranean humid mountain area: a comparative study with a natural forest

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# THE LANCET **Neurology**

## **Supplementary webappendix**

This webappendix formed part of the original submission and has been peer reviewed.  
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Supplement to: Pitkänen A, Löscher W, Vezzani A, et al. Advances in the development of biomarkers for epilepsy. *Lancet Neurol* 2016; **15**: 843–56.

**Supplementary Table 1.** Comprehensive list of genes with allelic variants related to the increased susceptibility to develop epilepsy after acquired brain insults. The gene list was generated based on PubMed search in November 2015. **Abbreviations:** VNTR: variable number tandem repeats, DNP: Dinucleotide polymorphism, TBI: traumatic brain injury, PTS: Posttraumatic seizures, TLE: Temporal lobe epilepsy. MTLE-FS+: Mesial temporal lobe epilepsy with febrile seizures plus.

Gene	SNP or polymorphism	Function & Relevance
<b>Post-traumatic epilepsy</b>		
<i>ADORA1</i> , adenosine A1 receptor	rs3766553 rs10920573	Inhibitory neuromodulation, antiseizure properties; rs3766553 associated with latency to PTS, rs10920573 associated with late PTS occurrence. <sup>1</sup>
<i>APOE</i> , apolipoprotein E	ε4 status	Binding, internalization, and catabolism of lipoprotein particles; ε4 allele increases risk of posttraumatic seizures following TBI. <sup>2</sup>
<i>GAD1</i> , glutamic acid decarboxylase	rs3828275 rs769391 rs3791878	Inhibitory neurotransmission, enzyme catalyzing of GABA production from L-glutamic acid; rs3828275 associated with risk of early (< 1 wk) PTS after TBI; rs769391 and rs3791878 associated with risk of PTS > 1 wk – 6 mo post TBI. <sup>3</sup>
<i>IL-1β</i> , interleukin 1β	rs1143634	Proinflammatory cytokine; CT genotype associated with decreased serum <i>IL-1β</i> levels, higher <i>IL-1β</i> CSF/serum ratios, and increased risk of PTE after TBI. <sup>4</sup>
<i>MTHFR</i> , methylene-tetrahydrofolate reductase	rs1801133	TT genotype is linked to increased plasma/serum levels of pro-convulsive homocysteine; predisposes for epilepsy following TBI in military personnel <sup>5</sup> .
<b>Post-stroke epilepsy</b>		
<i>CD40</i> , CD40 molecule, TNF receptor superfamily 5	rs1883832	Proinflammatory action; T allele associated with increased sCD40L plasma levels, CD40 mRNA expression in peripheral blood mononuclear cells and with increased PSE susceptibility <sup>6</sup> .
<i>ALDH2</i> , mitochondrial aldehyde dehydrogenase 2	rs671	Alcohol metabolism, protects against oxidative stress; A allele associated with higher plasma levels of oxidative stress marker 4-hydroxy-2-nonenal (4-HNE), and more frequent in PSE patients <sup>7</sup> .
<b>Other (etiology non-specified)</b>		
<i>AQP4</i> , aquaporin 4	ss119336753 ss119336753 rs1058424	Glial water channel; Combination of three SNPs in <i>AQP4</i> together with two SNPs in the <i>KCNJ10</i> gene associated with TLE <sup>8</sup> .
<i>ALDH5A1</i> , aldehyde dehydrogenase 5 family, member A1	rs1883415	Metabolism of GABA; C allele influencing Egr-3 binding to <i>ALDH5A1</i> promoter and resulting in higher <i>ALDH5A1</i> mRNA expression is more frequent in TLE patients. <sup>9</sup>
<i>ASIC1a</i> , acid-sensing ion channel 1a	rs844347	Ligand-gated cation channel activated by extracellular H <sup>+</sup> enhancing neuronal excitability; A allele more frequent in TLE patients. <sup>10</sup>
<i>BDNF</i> , brain-derived neurotrophic factor	Rs6265	Neurotrophin; Met66 allele frequency lower in TLE. <sup>11</sup>

<i>CALHM1, Ca<sup>2+</sup> homeostasis modulator 1</i>	rs11191692	Ca <sup>2+</sup> channel involved in Ca <sup>2+</sup> homeostasis and processing of APP; A allele frequency increased in TLE patients. <sup>12</sup>
<i>CAMSAP1L1, calmodulin regulated spectrin-associated protein family 2</i>	rs6660197	Cytoskeletal protein regulating organization of cellular organelles; associated with susceptibility to epilepsy in Chinese population. <sup>13</sup>
<i>C3, complement complement C3</i>	DNP: GF100472	Complement activation, participates in synapse elimination during development and adult neurogenesis, increased expression in TLE; associated with susceptibility to MTLE-FS+. <sup>14</sup>
<i>GABRB1, GABA<sub>A</sub>receptor, Beta 1</i>	G1465A	GABA <sub>A</sub> receptor subunit; associated with TLE, A-allele increases risk of mTLE. <sup>15-17</sup>
<i>GABRB2, GABA<sub>A</sub>receptor, Beta 2</i>	rs967932	GABA <sub>A</sub> receptor subunit; A allele increases risk of mTLE. <sup>18</sup>
<i>GABRB3, GABA<sub>A</sub>receptor, Beta 3</i>	rs4906902	GABA <sub>A</sub> receptor subunit; G allele influencing MEF-2 binding to GABRB3 promoter overrepresented in mTLE patients with depression. <sup>9</sup>
<i>GABRG2, GABA<sub>A</sub> receptor, Gamma 2</i>	rs211037 rs210987	GABA <sub>A</sub> receptor subunit; rs211037 associated with occurrence of symptomatic epilepsy and partial seizures and rs210987 associated with symptomatic epilepsy in Chinese population. <sup>19,20</sup>
<i>SLC6A4, serotonin transporter</i>	VNTR in 2nd intron	Serotonin transporter; association of frequency of the 10 repeat in TLE patients (conflicting results). <sup>21,22</sup>
<i>HTR1B, serotonin receptor 1B</i>	rs6296	Serotonin receptor; G allele overrepresented in TLE patients. <sup>23</sup>
<i>SESN3, sestrin 3</i>	rs10501829	Stress responsive protein; rs10501829 in the vicinity of SESN3. SESN3 expression correlates with transcription module relevant for TLE. <sup>24</sup>
<i>IL1A (IL-1α), interleukin 1α</i>	rs1800587	Proinflammatory cytokine; associated with hippocampal sclerosis in TLE patients. <sup>25</sup>
<i>IL1B (IL-1β), interleukin 1β</i>	rs16944	Proinflammatory cytokine; associated with hippocampal sclerosis in TLE patients. <sup>26,27</sup>
<i>IL-1RA, IL-1 receptor agonist</i>	VNTR in exon 2	Differences between controls and TLE-HS- patients. <sup>25</sup>
<i>KCNJ10 (Kir4.1), inwardly rectifying K<sup>+</sup> channel</i>	rs1130183	ATP-sensitive inward rectifier K <sup>+</sup> channel 10; missense variation in KCNJ10 or a variation in close vicinity is related to general seizure susceptibility. <sup>28</sup>
<i>NRG1, neuregulin 1</i>	rs35753505	Membrane glycoprotein mediating cell-cell signaling; associated with TLE in males. <sup>29</sup>
<i>NFE2L2, Nuclear Factor, Erythroid 2-Like 2 (Nrf2)</i>	rs7557529– rs35652124– rs6706649– rs6721961– rs2886161– rs1806649– rs2001350–	Transcription factor regulating the expression of many genes in antioxidant pathway; the haplotype AAGC AGAGG was associated with an increased risk of TLE. <sup>30</sup>

	rs10183914– rs2706110	
<i>PRNP, prion protein</i>	rs1799990	Cu <sup>2+</sup> -binding membrane sialoglycoprotein involved in protection against oxidative stress, cell adhesion, differentiation, and survival in the CNS; V allele overrepresented in women with moderate TLE. <sup>31</sup>
<i>PDYN, prodynorphin</i>	VNTR in the promoter	Anticonvulsant peptide; low expression allele associated with increased risk of TLE in patients with family history of seizures. <sup>32</sup>
<i>SCN1A, Na<sub>v</sub>1.1 Na<sup>+</sup> channel alpha subunit</i>	rs6732655	Voltage-gated Na <sup>+</sup> channel; mutations reported in a range of paroxysmal neurological disorders including familial hemiplegic migraine and rarely in focal epilepsies; locus relates to an all-epilepsy group. <sup>33</sup>
<i>PCDH7, protocadherin 7</i>	rs28498976	Integral membrane protein with putative function in cell-cell recognition and adhesion; mutations in other protocadherins, i.e. PCDH19, cause epilepsy and mental retardation; locus relates to an all-epilepsy group. <sup>33</sup>
<i>RORA, RAR-related orphan receptor A</i>	rs12912233	Nuclear hormone receptor; rs12912233 alone associated with epilepsy in Malaysians and having synergistic effect with RORA rs880626 and SCN1A rs3812718. <sup>34</sup>
<i>TIMP4, tissue inhibitor of metalloproteinase 4</i>	rs3755724	Inflammation-induced factor; associated with susceptibility to focal epilepsy in Malaysian population. <sup>35</sup>

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