

Dear Editor,

Thank you for your help with our paper (Manuscript No.: 64675).

We have carefully studied all of the comments from the reviewers. The comments were very helpful for revising our paper. All comments from the reviewers have been replied to point-by-point. In addition, our manuscript has been revised according to the 'Guidelines and Requirements for Manuscript Revision'. We sincerely hope that the revised manuscript is acceptable for publication.

The responses to each reviewer, the revised manuscript, the Non-Native Speakers of English Editing Certificate, the Copyright License Agreement, and the Conflict-of-Interest Disclosure Form have been submitted to the system.

If you have any questions, please do not hesitate to let us know. We would be very pleased to make any further changes. I look forward to hearing from you.

Best wishes.

Sincerely yours,

Yan-Chun Deng

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Responses to Reviewer #1

We are very grateful for your comments on the manuscript. According to your advice, we have revised the manuscript. Our responses to your comments appear below.

Comment 1. The abstract summarizes the work described in the manuscript. I urge the authors to add a concise sentence explaining the main aim of their narrative review at the end of the abstract.

Response 1. Thank you very much for your valuable advice. We have added the following sentences to the end of the Abstract: "In this article, we describe the research progress on eleven different types of FTLE. The precise molecular typing of FTLE would facilitate the diagnosis and treatment of FTLE and genetic counseling for this disorder."

Comment 2. I suggest adding a table summarizing the genes and the various clinical presentations to give an added completion to the manuscript.

Response 2. Thank you for your thought-provoking suggestion. A table (table 1) has been added to our manuscript that summarizes the characteristics of each type of familial temporal lobe epilepsy and is reproduced below:

Table 1 Eleven different types of familial temporal lobe epilepsy

Phenotype	OMIM ID	Gene/Locus	Inheritance	Age at seizure onset (years)	Seizure types	EEG	MRI	Epilepsy types	prognosis	reference
ETL1	600512	LGI1	AD	4-50	Aud, Aph, FBTCS	T	No	LTL E	Responsive to ASM	[20,24,25]
ETL2	608096	Chr12q22-q23.3	AD	0.75-35	FS, FBTCS, Cog, Aut	No	r, H	MTL E	Responsive to ASM or SR	[27,28]
ETL3	6116	Chr4q13.2	AD	5-18	Cog,	No	No	MTL	Responsive	[32]

	30	-q21.3				FBCTS , FIAS	r, T ea	r	E	ve to ASM or SR	
						focal Mot,				Responsi ve to	
ETL4	6116 31	Chr9q21-q 22	AD	0.58 -63		Cog, Sen, Aut, FIAS, FBCTS	No r	No r	OTL E	ASM or SR; migraine 5/Mo – 2/y	[33]
						FS, FBECT S, FIAS	T ea	T atr , H S	TLE	Responsi ve to ASM or SR	[36]
ETL5	6144 17	CPA6	AR	0.75 -5							
			AD	1.25 -23		FS	-	T atr	TLE	drug-refra ctory	[36]
						FS, FIAS, Cog, Sen, Aut, FBTCS	No r, T ea, sa	No r	MTL E	responsiv e to ASMs	[37]
ETL6	6156 97	Chr3q25-q 26	AD	3-46							
						Vis, Aud, FBECT S, FIAS FIAS, Cog, Sen, Aut, FBTCS	T ea	No r	LTL E	Responsi ve to ASM or SR	[38,40]
ETL7	6164 36	RELN	AD	8-40							
						Cog, Sen, Aut, FBTCS	T ea	No r	TLE	Responsi ve to ASM	[43]
ETL8	6164 61	GAL	AD	13							
						FS, Cog, Sen, focal Mot, FBECT S	T ea	No r	TLE	Responsi ve to ASM	[44,46 ,47]
ETL9	-	DEPDC5	AD	8-13							
						Aud, Aph, FBECT S	T or FT ea	No r	LTL E	Responsi ve to ASM	[48]
ETL1 0	-	MICAL-1	AD	6-30							

ETL11	-	SCN1A	AD	10-13	FS, FIAS, Aut, focal Mot, FBECT S	T ea	H S	TLE	Responsi ve to ASM	[50]
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Comment 3. The key words reflect the focus of the manuscript- the keyword “inherit” can be removed or replaced with another specific keyword.

Response 3. Thank you for your valuable suggestion. The keyword “inherit” has been removed.

Comment 4. Does the manuscript cite appropriately the latest, important, and authoritative references in the introduction and discussion sections? Does the author self-cite, omit, incorrectly cite and/or over-cite references?

Response 4. Thank you for your valuable suggestion. We carefully checked the references and have appropriately cited the latest and most important and authoritative papers. For example, we have cited the following paper: Bisulli F, Rinaldi C, Pippucci T, et al. Epilepsy with auditory features: Contribution of known genes in 112 patients. *Seizure* 2021;85:115-118. [PMID: 33453592 doi: 10.1016/j.seizure.2020.12.015.].

Responses to Reviewer #2

Thank you very much for your valuable comments. Based on your comments and suggestions, we have made extensive revisions to the manuscript.

Comment 1. The following quotation demands being referenced, “Epilepsy can be classified into focal, generalized, combined generalized and focal, and unknown according to the origin of the seizures.” No reference for this statement is offered. The same applies to the following quotation also lifted from the introduction, “Epilepsy affects approximately 50 million people worldwide, among which up to 60~70% of affected individuals have focal epilepsy.”

Response 1. Thank you for your valuable advice. We have added supporting

references to the manuscript, cited as [2] and [3,4] as follows:

"Epilepsy can be classified as focal, generalized, combined generalized and focal, and unknown according to the origin of the seizures^[2]. Epilepsy affects approximately 50 million people worldwide, among whom up to 60~70% have focal epilepsy^[3, 4]."

Comment 2. The word "However", being the first word from page 2 is superfluous and should be omitted, as is the case very soon thereafter, as per the following quotation, "However, due to the lack of..." This same sentence requires referencing as it is a challenging bold statement and no reference is offered. In the following quotation the words, "In fact" should not appear as if it is not fact then it should not be in the paper and if it is fact then it need not be so stated, "In fact, due to the high rates..."

Response 2. We apologize for the improper language. The word "However" has been deleted from the sentences formerly beginning with "However, the cause of TLE was heterogeneous..." and "However, due to the lack of..." In addition, "In fact" has been deleted from the sentence formerly beginning with "In fact, due to the high rates..."

Comment 3. I could criticise every sentence in this submission along similar lines, namely poor syntax, grammatical issues, superfluous language or lack of referencing and will refrain from providing further editorial input, other than to suggest that the author(s) revisit the paper and address these short comings. Scientific papers should be in third person, past tense not first person. One should avoid the use of commas before conjunctives such as 'and' and 'but'.

Response 3. We apologize for the unprofessional writing of our manuscript. We have carefully rewritten some parts of our manuscript, including the Abstract and Introduction, please check. Furthermore, the revised manuscript has been edited by a professional English language editing company to ensure that all grammatical, syntactical, formatting and other errors have been corrected.

Comment 4. There has been a change in nomenclature such that the following quotation, namely, "prognosis was good with anti-epilepsy drugs" should be modified to read 'anti-seizure medications', rather than "anti-epilepsy drugs". The same applies to the use of "AED" which should now read 'ASM' to denote the change in

acceptance of the abbreviation/acronym.

Response 4. Thank you very much for your valuable advice. The phrase ‘anti-epilepsy drugs (AEDs)’ has been replaced with ‘anti-seizure medications (ASMs)’ in our manuscript.

Comment 5. When using acronyms, such as MRI, it should be in full the first time it is used although many of the acronyms used by these authors have been adopted as common jargon but they should be encouraged to stick to the rules.

Response 5. We are apologize for our negligence regarding the use of acronyms. Abbreviations have been defined upon their first appearance in our paper.

Comment 6. As previously stated, I will not discuss language shortcomings further but this is the major flaw of this paper. I have marked the survey below but the author(S) need to revisit the paper to address language issues although I believe the paper is informative and, with suitable corrections, should then be accepted for publication.

Response 6. Thank you very much for your affirmation of the content of our paper. We have carefully revised our manuscript and have had it edited for English language by a professional English language editing company to improve the language of our manuscript to a level suitable for publication.

Responses to the Science Editor

Comment 1. Reviewer 1 has commented that the quality of the language is poor and has suggested re-writing the manuscript to address this and other concerns. Reviewer 2 has suggested adding a concise sentence explaining the main aim of their narrative review at the end of the abstract, changes to the keywords, and adding a table summarizing the genes and the various clinical presentations.

Response 1. Thank you for your help with our manuscript. We have revised our manuscript to address all the issues raised by the reviewers and have provided point-by-point responses to their comments.

Comment 2. The authors also need to re-write their abstract (minimum 200 words), and add more references from the last 5 years particularly to support the statements made (see comments by reviewer 1). The references need to be formatted uniformly to meet the requirements of the journal.

Response 2. Thank you very much for your suggestion. We have rewritten the Abstract (minimum 200 words) to summarize the main content of the article and describe the purpose and significance of the paper. In addition, we have added more references from the last 5 years. The references have been revised according to the Format for References Guidelines to meet the requirements of the journal.

Responses to the Editor-in-Chief

Comment 1. Before final acceptance, the author(s) must provide the English Language Certificate issued by a professional English language editing company.

Response 1. Thank you for your help with our manuscript. We have carefully revised our manuscript. The revised manuscript has been edited by a professional English language editing company.