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# Epilepsy Risk Prediction Model for Patients with Tuberous Sclerosis Complex

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## Abstract

**BACKGROUND:** Individuals with tuberous sclerosis complex (TSC) are at increased risk of epilepsy. Early seizure control improves developmental outcomes, making identifying at-risk patients critically important. Despite several identified risk factors, it remains difficult to predict. The purpose of the study was to confirm previously identified risk factors for epilepsy in patients with TSC and evaluate the combined risk prediction of these factors.

**METHODS:** The study group (N=333) were participants with TSC enrolled in the TSC Autism Center of Excellence Research Network and UT TSC Biobank. The outcome was defined as having an epilepsy diagnosis. Potential risk factors included sex, *TSC* genotype, and tuber presence. Logistic regression was used to calculate the odds ratio, 95% confidence interval (CI), and p-value for the association between each variable and epilepsy. A clinical risk prediction model incorporating all risk factors was built. Area under the curve (AUC) was calculated to characterize the full model's ability to discriminate individuals with TSC with and without epilepsy.

**RESULTS:** The strongest risk for epilepsy was presence of tubers (95% CI: 2.39-10.89). Individuals with pathogenic *TSC2* variants were 3-times more likely (95% CI: 1.55-6.36) to develop seizures compared to those with TSC from other causes. The combination of risk factors resulted in an AUC of 0.73.

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**CONCLUSIONS:** Simple characteristics of TSC patients can be combined to successfully predict epilepsy risk. A risk assessment model that incorporates sex, TSC genotype, protective *TSC2* missense variant, and tuber presence correctly predicts epilepsy in 73% of TSC patients.

**Keywords**

tuberous sclerosis complex (TSC); epilepsy; seizures; risk prediction model; genotype; risk factors

## Introduction

Tuberous sclerosis complex (TSC) is a genetic syndrome that affects approximately 1 in 6,000 individuals. It is caused by pathogenic variants in *TSC1* and *TSC2*, predisposing the individual to benign tumor formation as well as neurological problems including seizures, intellectual disability, autism, and behavioral problems. Notably, the highest morbidity and mortality stems from neurological issues (Northrup et al., 2018), thus predicting which patients will develop these phenotypes carries significant prognostic value.

One of the most severe neurologic issues is epilepsy, which affects 70-90% of individuals with TSC (Asato and Hardan, 2004; Wong and Khong, 2006). A significant relationship between early-age-at-seizure-onset and poor developmental outcomes has been established (Capal et al., 2017; Jeste et al., 2016; Jansen et al., 2008; Gomez et al., 1982). Furthermore, several studies demonstrated that early control of epilepsy improves developmental outcomes (Cusmai et al., 2011; Jóźwiak et al. 2011, Bombardieri et al., 2010). Therefore, establishing early risk-prediction models for seizures is paramount in TSC clinical care (Davis et al, 2019; Wu, et al., 2016; Muzykewicz, et al., 2009), as tailoring treatment to surveil and intervene would optimize outcomes for patients with TSC.

Features implicated in seizure development among patients with TSC include: central nervous system lesions and white matter abnormalities (Curatolo, 2015; Im et al., 2015; Peters et al., 2012; Jansen et al., 2008), male sex (Au et al., 2007; Sancak et al., 2005), and *TSC* genotype. *TSC2* pathogenic variants, in general, are associated with increased risk of infantile spasms and more severe general phenotype (Sancak et al., 2005; Dabora et al., 2002); however, individuals with certain *TSC2* missense variants are less likely to develop epilepsy compared to patients with TSC from other causes (Fox et al., 2017; Farach et al., 2016; Ekong et al., 2016; van Eeghen et al., 2013; Wentink et al., 2012; Jansen et al., 2006; Mayer et al., 2004; O'Connor et al., 2003; Khare et al., 2001). Interictal epileptiform discharges found on electroencephalography (EEG) are useful in predicting impending epilepsy but are not early risk predictors (Wu et al., 2019; Wu et al., 2016).

In spite of these findings, providing patients with accurate and specific prognostic information remains a challenge. As the previously identified risk factors are not strong enough to accurately predict epilepsy themselves, a potential solution would be to combine the efforts of previous studies by incorporating identified individual risk factors into a risk prediction model to determine if the combination produces a more accurate risk prediction. Risk prediction models have been utilized in other single gene disorders (O'Mahony et al., 2013; Armstrong et al., 2009; Cassidy et al., 2008; Eagle et al., 2004) and provide an important approach to assessing outcome by identifying at-risk individuals, facilitating

the design and planning of clinical trials, informing surveillance strategies, fostering the development of benefit-risk indices, and enabling estimates of the prevalence and cost of disease. The purpose of this study was to create a weighted risk prediction model for epilepsy in patients with TSC by testing cumulative clinical risk in a well-phenotyped and genotyped cohort of patients.

## Materials and Methods

### Study population:

The study was performed using participant data from two sources: the TSC Autism Center of Excellence Research Network (TACERN) study (NCT 01780441) (N=119) and UT TSC biobank (N=214). Participants were included if they had a clinical diagnosis of definite TSC, had undergone genetic testing for *TSC1* and *TSC2*, and had reliable demographic and phenotypic information including sex, seizure history, and presence or absence of tubers. We also limited our study subjects to unrelated individuals.

### TSC Genotyping:

Genotyping for the patients was performed prior to the study, either clinically or as part of the research protocol. Participants who had genotyping as part of the TACERN trial or UT Biobank study had Sanger sequencing of *TSC1* and *TSC2* with reflex to multiplex ligation-dependent probe amplification (MLPA), if Sanger sequencing was negative. All variants were classified using American College of Medical Genetics standards and guidelines (Richards et al., 2015) and the *TSC1* or *TSC2* Leiden Open Variation Databases (https://databases.lovd.nl/shared/genes/TSC1; http://chromium.lovd.nl/LOVD2/TSC/home.php?select_db=TSC2). Those who had benign, likely benign, variants of uncertain significance, or no variants were labeled “no mutation identified (NMI).” Those with pathogenic or likely pathogenic variants who met clinical criteria for TSC were considered positive for *TSC1* or *TSC2* disease-causing mutation. Known pathogenic variants considered protective against seizures included *TSC2* missense variants in exons 23-33 (van Eeghen et al., 2013) along with the following *TSC2* missense variants: p.Arg622Trp; p.Arg905Gln; p.Ser1036Pro; p.Arg1200Trp; p.Gln1503Pro; p.Gly1579Ser; p.Arg1713His (Khare et al 2001, O’Connor et al 2003, Mayer et al 2004, Jansen et al 2006, Wentink et al 2012, Farach et al 2017, Fox et al 2017).

### Phenotypic Data:

Presence of seizures for the TACERN participants was determined by study clinicians based on history, EEG, and a daily seizure diary. Presence of tubers in TACERN participants was determined based on radiologist report of brain MRIs obtained at or after 24 months. Presence of seizures and/or tubers in UT TSC Biobank participants was based on both self-reported and clinical information. Participants with two or more unprovoked seizures were designated as having epilepsy. Participants were determined not to have epilepsy if they were at least twelve months old with no history of seizure. This timepoint was chosen based on a study demonstrating that the onset of epilepsy occurs by twelve months in the majority of patients with TSC (Curatolo et al., 2012).

### Statistical Analysis:

A clinical risk prediction model was developed based on factors previously identified as associated with risk of seizure among individuals with TSC. Risk factors included sex (male, female), TSC pathogenic variant (*TSC1*, *TSC2*, NMI), protective missense variant in *TSC2* (present, absent), and tuber formation (present, absent). Logistic regression was used to determine the association between each risk factor and seizure. Specifically, an unadjusted odds ratio (OR), 95% confidence interval (CI), and p-value was determined for each clinical factor. Next, a clinical risk prediction model was built that incorporated all risk factors to estimate the adjusted OR, 95% CI, and p-value for each risk factor. Finally, the area under the curve (AUC) was calculated to characterize the full model's ability to discriminate individuals with TSC with and without seizure. A successful epilepsy risk prediction model was defined *a priori* to have AUC ≥ 0.70 (Hosmer and Lemeshow, 2000). All statistical analyses were conducted in R version 5.3.2.

## Results

Three hundred thirty-three TSC participants had the necessary clinical and demographic information to be included in the full epilepsy risk prediction model, 261 of whom had epilepsy, while 72 did not have epilepsy (Table 1). Individuals with epilepsy were a median age of 36 months at last assessment and ranging up to 43 years of age. Individuals without epilepsy were a median age of 48 months at last assessment and ranging up to 57 years of age. Per exclusion criteria, none were younger than 12 months old. Nine participants had epilepsy despite having a variant that is associated with a lower likelihood of seizure (missense variants within exons 23-33: n=6; Arg905Gln: n=2; Arg1200Trp: n=1). The protective variants in the participants without epilepsy included: Arg622Trp (n=1); Arg1200Trp (n=3); and missense variants within exons 23-33 (n=3).

The strongest risk for epilepsy was identified among participants with tubers, who had more than 5-times the adjusted odds of epilepsy than individuals with no tubers (adjusted OR: 5.1, 95% CI: 2.4-10.9; Table 2). Individuals with pathogenic *TSC2* variants had 3.1-times the adjusted odds of epilepsy compared to individuals without known mutations (95% CI: 1.6-6.4), whereas individuals with pathogenic *TSC1* variants had similar adjusted odds of epilepsy (adjusted OR: 0.7, 95% CI: 0.3-1.6). The epilepsy-protective association of specific missense variants in *TSC2* were confirmed (adjusted OR: 0.3, 95% CI: 0.1-0.8). Male sex was not identified as a risk factor for seizure in our study population (adjusted OR: 0.9, 95% CI: 0.5-1.6). The model incorporating all previously reported risk factors for seizure in TSC patients resulted in an area under the curve of 0.73 (Figure 1).

## Discussion

In one of the first assessment to generate and evaluate a clinical risk prediction model for epilepsy among those with TSC, we found the combined risk prediction of sex, TSC genotype, protective *TSC2* missense variants, and tuber presence offers improved epilepsy risk prediction beyond each risk factor individually. Notably, the epilepsy risk prediction model is based on factors that can easily be assessed upon specialist referral at or around the time of TSC diagnosis, so incorporation into the model would not necessitate extra testing.

The individual risk factors, while helpful, do not accurately predict epilepsy alone. However, by including the known risk factors together in one model, clinicians are armed with more reliable and accurate information regarding risk of epilepsy in their patient. It is interesting that even with all of the factors incorporated, the risk prediction model can only predict with 73% reliability, demonstrating there is much to be learned about the pathogenesis of epilepsy in TSC. Still, the information is valuable as it may be used to both inform prognosis and guide treatment. For instance, due to the high risk of epilepsy in patients with TSC, current management recommendations include getting a baseline EEG (Kruger et al., 2012) to evaluate for unrecognized or sub-clinical seizures. EEGs are also useful as interictal epileptiform discharges serve as a biomarker for impending seizures, with seizure onset occurring an average of four months later (Wu et al., 2016; Wu et al., 2019). However, if seizure onset has not yet occurred and is not impending, the EEG is likely to be normal. For patients predicted to be at high risk for epilepsy, clinicians may choose to do closer surveillance with additional follow up EEGs as early identification and control of seizures is crucial to improving developmental outcomes (Cusmai et al., 2011; Jóźwiak et al. 2011, Bombardieri et al., 2010).

We specifically focused on risk factors that were previously reported and/or confirmed to be associated with epilepsy (Fox et al., 2017; Farach et al., 2016; Ekong et al., 2016; Curatolo, 2015; Im et al., 2015; van Eeghen et al., 2013; Peters et al., 2012; Wentink et al., 2012; Jansen et al., 2008; Au et al., 2007; Jansen et al., 2006; Sancak et al., 2005; Mayer et al., 2004; O'Connor et al., 2003; Dabora et al., 2002; Khare et al., 2001). As evidence regarding correlation between tuber count and/or location, and epilepsy, specifically, is weak and overall studies are conflicting (Doherty et al., 2005; Wong and Khong, 2006; Kassiri et al., 2011), the specifics of tubers, such as count and location were not included. Instead, the dichotomaous approach of presence or absence of tubers, which has better evidence (Curatolo, 2015; Im et al., 2015; Peters et al., 2012; Jansen et al., 2008) was used. Because the risk factors incorporated were proven risk factors, we did not divide our population into training and validation sets. In fact, our cohort reflected these previously described associations. For instance, presence of tubers and a *TSC2* genotype that was not one of the protective missense variants reliably predicted seizures in our cohort. Interestingly, the strongest risk appeared to be presence of tubers. Tubers are present in about 90% of individuals with TSC (Krueger et al., 2012), so while the information is useful, it is not very specific. Males are previously reported to have more severe TSC phenotype (Au et al., 2007; Sancak et al., 2005); however, in our cohort, males did not appear to have increased risk for seizure, specifically. Notably, nine patients with a protective variant still had epilepsy and more patients with protective variants had epilepsy than did not. While those variants demonstrate statistical significance for protecting against epilepsy in our cohort, it is apparent they are not fully protective.

Our study should be considered in the light of certain strengths and limitations. First, we had a relatively large sample size and a subpopulation with very detailed phenotypic information. However, risks of specific aspects of epilepsy such as onset, type, and severity could not be ascertained as the information was not available for the majority of individuals in the study. Specifics of tubers, such as number and location, were not included in analysis as overall the correlation with epilepsy is unproven (Doherty et al., 2005; Wong and Khong,

2006; Kassiri et al., 2011). Information was self-reported for some of the participants and thus could be inaccurate. Finally, while we did not divide our sample into training validation sets, we: 1) selected factors that have been demonstrated to be associated with epilepsy among those with TSC; and 2) observed associations that were consistent with previous reports. Therefore, we believe our model accurately reflects the ability of epilepsy risk factors to simultaneously predict risk of epilepsy in patients with TSC.

This is the first model to predict manifestations of TSC and sets the groundwork for creation of more models in future studies to predict epilepsy onset, type, and severity; as well as other neurological features of TSC. While the current model has acceptable discrimination, it also demonstrates that there is much more to be learned about risks and pathogenesis of epilepsy in TSC. A future goal is to strengthen the model by incorporating genetic modifiers.

## Conclusion

A successful epilepsy risk prediction model for patients with TSC can be made by incorporating known risks including sex, TSC genotype, protective variants, and presence of tubers. The model increases the utility of previously identified risk factors and may be strengthened if other risk factors are discovered, such as modifier genes.

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## Appendix

## Appendix

**Members of the Tuberous Sclerosis Autism Center of Excellence Research Network (TACERN):** Principal Investigators: Sahin, M[1]; Krueger, D[2]; Bebin, M[3]; Wu, JY[4]; Northrup, H[5]; Co-Investigators: Warfield, S[1]; Peters, J[1]; Scherrer, B[1]; Goyal, M[3]; Project managers: Filip-Dhima, R[1]; Dies, K[1]; Bruns, S[2]; Neuropsychological assessment team: Hanson, E[1]; Bing, N[2]; Kent, B[2]; O'Kelley, S[3]; Williams, M E[9]; Pearson, D[5]; Data Coordinating Center at UAB: Cutter, G[6]; TS Alliance: Roberds, S[7]; Autism Speaks: Murray DS[8]; Affiliations for TACERN: [1]Boston Children's Hospital, Boston, MA, [2]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [3]University of Alabama at Birmingham, Birmingham, AL, [4]University of California, Los Angeles, Los Angeles, CA, [5]McGovern Medical School, University of Texas Health Science Center at

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## HIGHLIGHTS

- Predicting which patients with TSC will develop epilepsy is crucial to early identification and intervention but remains difficult despite known clinical risk and protective factors
- A risk assessment model that incorporates known risk factors for epilepsy including sex, TSC genotype, protective *TSC2* missense variant, and tuber presence, correctly predicts risk of epilepsy in individuals with TSC better than individual factors alone
- The strongest risk factors for epilepsy in those with TSC in the studied cohort was the presence of tubers and *TSC2* pathogenic variant
- This model accurately predicts epilepsy in 73% of individuals with TSC and may be strengthened with the discovery and incorporation of additional risk factors, such as modifier genes

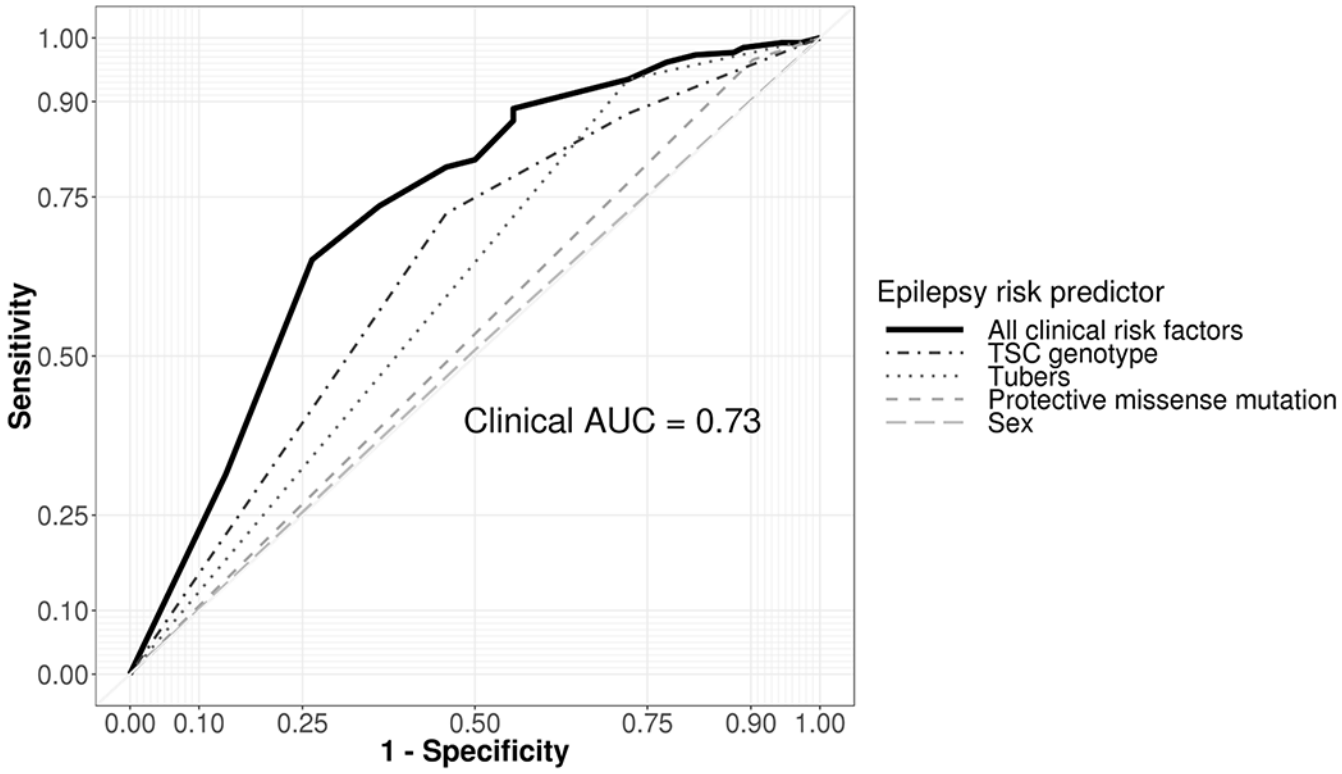


**Figure 1.**

Receiver operating curve for the ability of sex, TSC genotype, protective missense variant, and tuber formation to individually and simultaneously predict the presence of epilepsy among individuals with TSC. The area under the curve (AUC) indicates that the model will indicate greater likelihood of epilepsy among 73% of randomly selected patients with TSC and epilepsy than a randomly chosen individual with TSC without epilepsy. Combination of risk factors has increased accuracy over individual risk predictors.

**Table 1.**

Characteristics of Participants

| | With Epilepsy (n=261) | Without Epilepsy (n=72) | P-value* |
|---|---|---|---|
| **Sex, n (%)** | | | 0.99 |
| Female | 133 (51.0) | 36 (50.0) | |
| Male | 128 (49.0) | 36 (50.0) | |
| **Pathogenic variant, n (%)** | | | <0.001 |
| *TSC1* | 31 (11.9) | 20 (27.8) | |
| *TSC2*<br>NMI | 189 (72.4)<br>41 (15.7) | 33 (45.8)<br>19 (26.4) | |
| **Protective variant, n (%)** | | | 0.06 |
| No | 252 (96.6) | 65 (90.3) | |
| Yes | 9 (3.4) | 7 (9.7) | |
| **Tubers, n (%)** | | | <0.001 |
| No | 17 (6.5) | 20 (27.8) | |
| Yes | 244 (93.5) | 52 (72.2) | |

*P-values are derived from the Chi-square test with continuity correction. NMI-no mutation identified, n-number of patients, %-percent of patients within the group.

**Table 2.**

Epilepsy clinical risk prediction model for individuals with tuberous sclerosis

| ***Risk predictors*** | **Adjusted odds ratio (95% CI)** | **P-value** |
|---|---|---|
| **Sex (male)** | 0.88 (0.50, 1.55) | 0.6 |
| **TSC Genotype** | | |
| **NMI** | Ref | |
| ***TSC1*** | 0.71 (0.32, 1.62) | 0.4 |
| ***TSC2*** | 3.14 (1.55, 6.36) | 0.002 |
| **Protective variant** | 0.25 (0.08, 0.78) | 0.017 |
| **Tubers** | 5.10 (2.39, 10.89) | <0.001 |

* P-values are from the Wald test for each logistic regression coefficient. AUC- area under the receiver operating curve, CI- confidence interval, NMI-no mutation identified, Ref- reference