Oregon Health & Science University
School of Medicine

Scholarly Projects Final Report

Title *(Must match poster title; include key words in the title to improve electronic search capabilities.)*

> Prognostication of Pediatric Genetic Epilepsy

Student Investigator's Name

> John Bartlett

Date of Submission *(mm/dd/yyyy)*

> 03/16/2024

Graduation Year

> 2024

Project Course *(Indicate whether the project was conducted in the Scholarly Projects Curriculum; Physician Scientist Experience; Combined Degree Program [MD/MPH, MD/PhD]; or other course.)*

> Scholarly Project

Co-Investigators *(Names, departments; institution if not OHSU)*

> Jason Coryell, MD

Mentor's Name

> Jason Coryell, MD

Mentor's Department

> Pediatric Neurology

Scholarly Project Final Report

Concentration Lead's Name

> Lisa Silbert

Project/Research Question

> What is the difference in severity between Pediatric Epilepsy and Pediatric Epilepsy associated with a genetic diagnosis?

Type of Project *(Best description of your project; e.g., research study, quality improvement project, engineering project, etc.)*

> Research Study

Key words *(4-10 words describing key aspects of your project)*

> Pediatric Epilepsy, Genetic, Severity, Prognostication

Meeting Presentations
If your project was presented at a meeting besides the OHSU Capstone, please provide the meeting(s) name, location, date, and presentation format below (poster vs. podium presentation or other).

Publications *(Abstract, article, other)*
If your project was published, please provide reference(s) below in JAMA style.

Submission to Archive
Final reports will be archived in a central library to benefit other students and colleagues. Describe any restrictions below (e.g., hold until publication of article on a specific date).

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Next Steps
What are possible next steps that would build upon the results of this project? Could any data or tools resulting from the project have the potential to be used to answer new research questions by future medical students?

> The next steps for this project would be to try to get more participants and look at specific gene severity to determine where there would be more immediate benefit from devoting resources. It might also be providential to add some fields in the database so that the current number of prescribed medications could be examined as well as looking at the number of times particular patients had an episode of status epilepticus in the past year rather than if they only had one or more episodes.

Please follow the link below and complete the archival process for your Project in addition to submitting your final report.

https://ohsu.ca1.qualtrics.com/jfe/form/SV_3ls2z8V0goKiHZP

Student's Signature/Date *(Electronic signatures on this form are acceptable.)*
This report describes work that I conducted in the Scholarly Projects Curriculum or alternative academic program at the OHSU School of Medicine. By typing my signature below, I attest to its authenticity and originality and agree to submit it to the Archive.

St

Mentor's Approval *(Signature/date)*

March 20, 2024

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Report*: Information in the report should be consistent with the poster, but could include additional material. Insert text in the following sections targeting 1500-3000 words overall; include key figures and tables. Use Calibri 11-point font, single spaced and 1-inch margin; follow JAMA style conventions as detailed in the full instructions.*

Introduction *(≥250 words)*

While epilepsy has been described throughout human history, there has been a significant increase in the knowledge and understanding that we have gained throughout the twentieth century[7,10]. While pioneers like William Lennox and Henri Gastaut began to expand our knowledge significantly, it wasn't until decades later when we began to develop more of an understanding of genetic epilepsy. We knew about a heritable disposition to epilepsy but could not comprehend the gravitas of the situation without the proper diagnostic tools. It wasn't until around the turn of the twenty first century that we were able to get a better understanding of genetic epilepsy and be able to test for specific genes[16].

There have however been significant advancements in testing methods and targets of testing in the past 25 years[1]. Current molecular diagnostic tests routinely look for genetic mutations as well as checking for chromosomal abnormalities as well as gene number variants and even mutations in introns and splice sites through whole exome sequencing which are not incorporated into the finished gene product[6,15,18,]. While these tests have advanced our knowledge of genetic epilepsies, they are not able to assist clinicians with prognostication after diagnosis. Currently the gene panels, which test for genetic mutations in over 300 different genes, give the report of mutation classified as pathogenic, likely pathogenic, or a variant of unknown significance.

While this is beneficial for knowing if a certain gene has been shown to be a cause of epilepsy, it still does not necessarily give prognostic data for the various genetic abnormalities. Dravet syndrome, which is caused by a genetic mutation in the SCN1A gene, has been studied more than most of the other genetic variants, and has subsequently given us more information about this specific form of genetic epilepsy than other less common causes[2,3]. If we are able to further analyze these genes to provide trends with certain genes to allow for better prognostication for both families of patients to further understand the disease, but also to allow for better clinical decision making.

It is likely that certain gene variants will cause an epilepsy that is more severe and has more impacts in the life of the patient, so if we are able to analyze these genetic variants, then as research is poised on the brink of precision epilepsy therapy[9] this information could be used as a launching point for creating precision therapies for specific epilepsies as well as allowing for earlier intervention to try to help the deficiencies that can accompany these diagnoses. Thus, the goal is to look at concrete variables between different genetic mutations and determine a modicum of prognostication between the different genes to allow for a better treatment of genetic epilepsy.

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Methods *(≥250 words)*

This was a cross sectional study looking at pediatric patients from four institutions of pediatric patients that were diagnosed with genetic epilepsy via genetic testing. The records were pulled from a database that consists of patients that participating clinicians have on their census at Oregon Health and Science University, University of Michigan Health, Medical University of South Carolina, and Children's National Hospital. Patients were identified and consented to be part of this database for future studies to be completed. The deidentified data of 197 participants was pulled from the database which included information from both an annual family survey as well as initial characteristics at the time of study which was pulled from the most recent clinical visit documentation. Participants were excluded for adult onset of epilepsy as well as no quantification of multiple markers examined. Markers for epilepsy severity, including age of onset, number of medications trialed, incidence of status epilepticus within the past year whether rescue medication was given or not, prevalence of drug resistance defined as trail or three or more anti-seizure drugs either individual or concurrently without significant improvement in seizure quantity, prevalence of Autism as a comorbidity, and prevalence of ADD/ADHD as a comorbidity were chosen to correlate with symptoms that would most directly affect both clinical care and parental care of the patient as well as factoring in what parents would most likely want to know in terms of comorbidities. The incidence and prevalence of these were then compared to the average for general pediatric epilepsy, and for the comorbidities to the general population to compare prevalence. Statistical analysis between groups was performed using two-sample t tests.

Results *(≥500 words)*

178 participants were included in the study for final data analysis. Each marker may have less than 178 due to omission of data from the research center.

Each participant on genetic testing had a mutation that was listed as Pathogenic, Likely Pathogenic, or Variant of Unknown Significance. With 58 genes classified as pathogenic or likely pathogenic, 41 of which only appeared a single time, 10 genes appearing twice, 3 genes appearing twice, 1 gene appearing four times, and 1 gene appearing 8 times. The gene that is most prevalent is SNC1A which is associated with Dravet syndrome. The other genes that appeared multiple times, in order of prevalence include KCNQ2, PCDH19, TPP1, ARX, CDKL5, FRRS1L, GLDC, MECP2, NPRL3, PRRT2, SCN8A, SGSH, TSC2.

The overall age of onset for genetic epilepsy in the pediatric population is quite low. While the data is skewed by a small minority of patients that developed seizures and were diagnosed with epilepsy as a teenager, 76% of patients had an onset of seizures before 5 years of age with the overall average age of onset being 3.33 years and the median age being 2 years of age.

The number of antiseizure medications trialed was on a scale from 0 to 5+ which does not allow for accurate statistics to be compiled, but 71/178 patients had trialed 5+ medications/therapies for their seizures, with the vast majority of patients currently on two or more anti-seizure drugs for seizure control and only two participants not having trialed any medications and have had no recurrent seizures.

Status epilepticus was looked at for incidence in the past year to look at severity of epilepsy. There was a significantly higher rate of status epilepticus within the past year for pediatric genetic epilepsy compared to the overall pediatric epilepsy rates of status epilepticus. Overall 7% (12/171, 7 participants not included due to response for status epilepticus marked as uncertain) of patients with pediatric genetic epilepsy had one

or more episodes of status epilepticus within the past year.
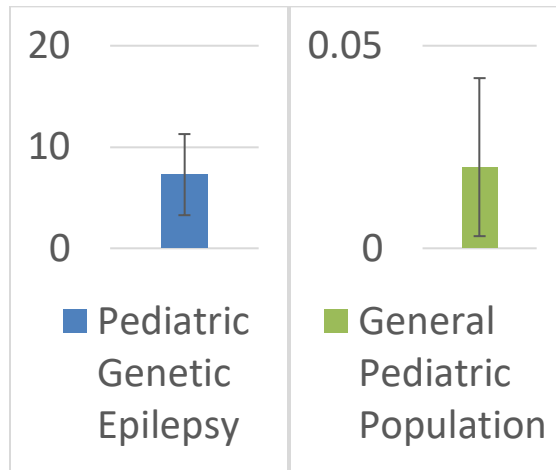
Figure 1. Incidence of Status Epilepticus within the past year
y axis shows prevalence per 100 patients. p<0.001

The incidence of drug resistance is defined as a trial of 3 or more medications or therapies either sequentially or concurrently. 50.6% (82/162) of participants had drug resistance epilepsy as of their most recent clinical encounter (Figure 2). The remainder of participants did not have any data indicating the presence or lack of drug resistant epilepsy.
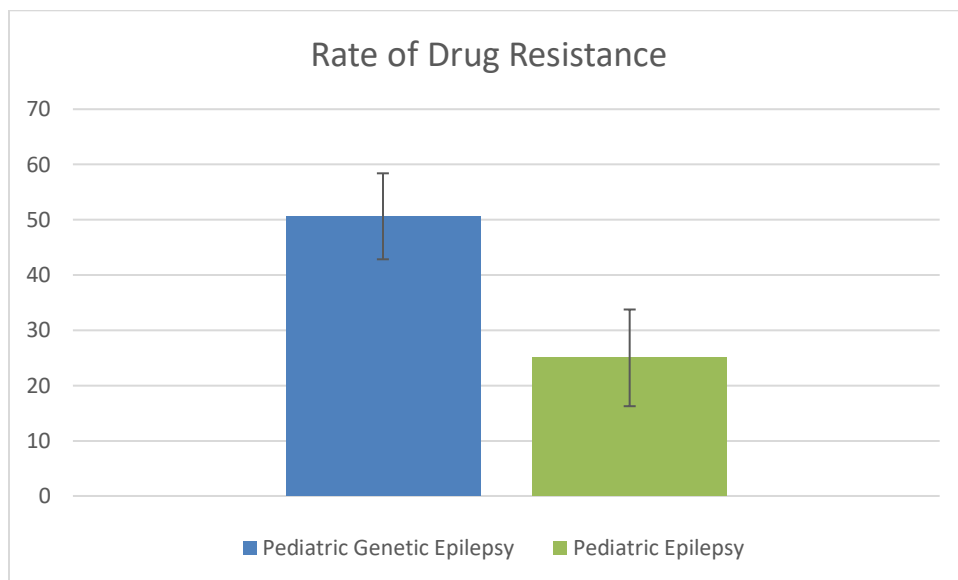
**Figure 2. Rate of drug resistance per 100 patients**
P<0.01

The prevalence of Autism in participants was observed to be 20.7% (35/161) as a formal diagnosis taken form the chart rather than the family survey (Figure 3). This includes a diagnosis at any age for the participant.
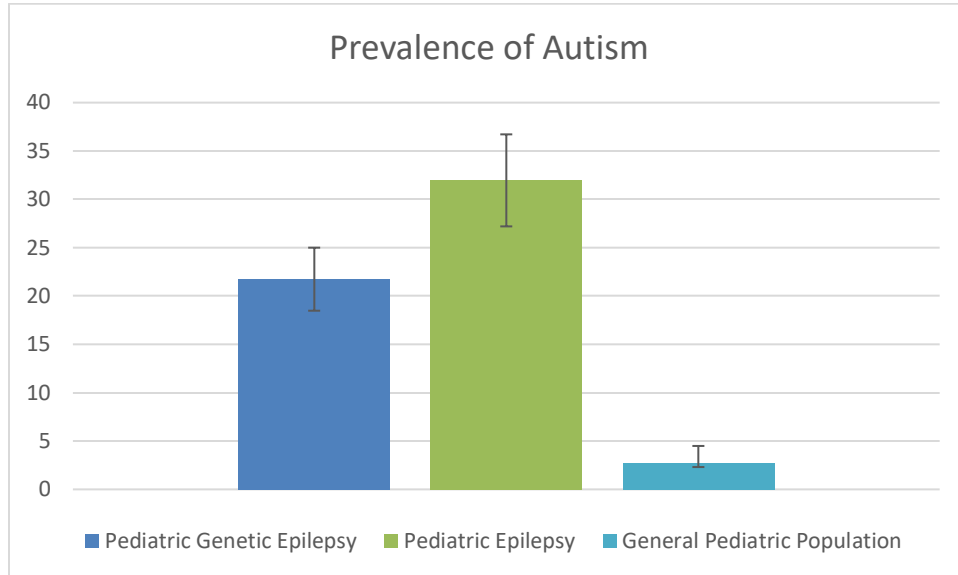
Figure 3. Prevalence of Autism per 100 patients
Between all groups p<0.05

The prevalence of ADD/ADHD diagnoses in pa rticipants was 21.1% (31/161) listed in their chart. It is compared to both the prevalence of autism in the pediatric epilepsy population as well as the general pediatric population.
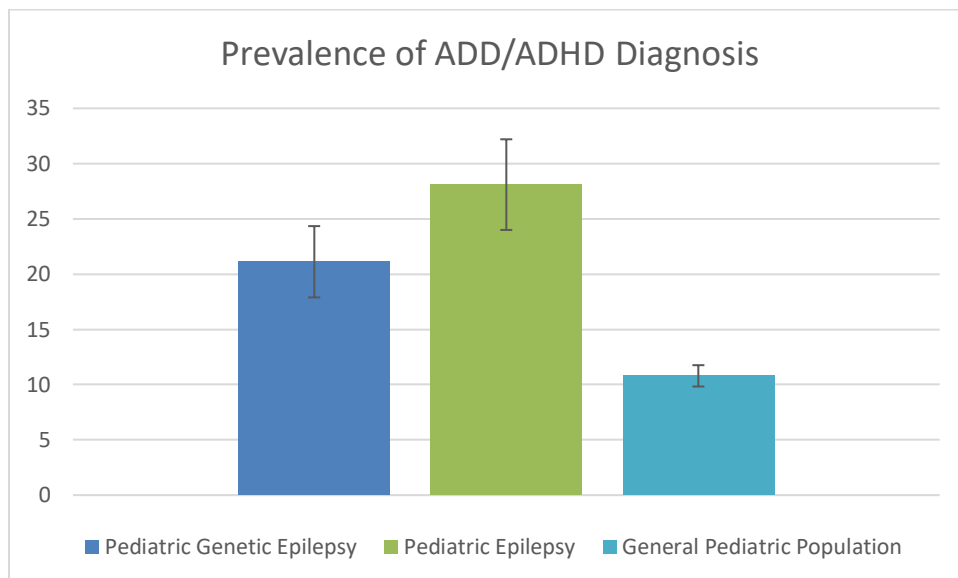
Figure 4. Prevalence of ADD/ADHD per 100 patients
Between epilepsy population p>0.05, both epilepsy groups compared to general pediatric population
p<0.01

Discussion *(≥500 words)*

The difference between epilepsy in the general pediatric population and genetic epilepsy is one that has not been explored as much as it should have been. As such it is appropriate that we create this prognostication for genetic epilepsy so that clinicians not only have a general idea of what to expect when they are treating a patient with genetic epilepsy, but also are able to give a realistic description of what the future will entail for parents that have a child with genetic epilepsy.

The age of onset for patients with pediatric epilepsy, while it can be used as a marker for severity, is often not a useful prognostication tool. Unless it is known that the child will have genetic epilepsy prior to birth or through genetic screening or counseling, it is often only after children start having seizures that testing for genetic epilepsy begins. With the age being so skewed, it is difficult to have a positive correlation with an early onset for increasing severity, but it is reasonable to think that patients with later onset will have a less severe form of since they had no significant impacts on their life from the genetic mutation causing the epilepsy.

It is worth noting that there were a few things that were better in genetic epilepsy compared to the pediatric epilepsy population. The prevalence of autism in patients with genetic epilepsy was significantly less than in the general pediatric epilepsy population with near 22% (35/161) carrying an autism diagnosis along with genetic epilepsy while in overall pediatric epilepsy there a rate of 32% of patients that carry an autism diagnosis as well as an epilepsy diagnosis[4,12]. It is worth noting that both of these populations do, however, have significantly higher rates of carrying an autism diagnosis than the general pediatric population which has a rate of just under 3% of children[5]. Overall if a child is diagnosed with a genetic form of epilepsy, they have an increased risk of carrying an autism diagnosis nearly seven times greater than that of the overall population.

The overall prevalence of children having a concurrent diagnosis of ADD/ADHD with a genetic epilepsy is significantly higher than the general population. The rate of ADD/ADHD in patients with genetic epilepsy is 21% (34/161) and for the general pediatric epilepsy population it was 28%[13]. However, both were significantly higher than the general pediatric population which carries a prevalence in the population of just under 11%[11]. While patients with epilepsy have a higher rate of ADD/ADHD than the general population, it is worth mentioning that this is a quite common diagnosis. While genetic epilepsy did not have a significantly less amount of this diagnosis than the overall pediatric epilepsy patients, it was nearly twice the rate of the general population with 1 in 5 children that have genetic epilepsy also having ADD/ADHD.

We found that the rate of drug resistance was significantly elevated in patients with genetic epilepsy with nearly 51% (82/163) patients having drug resistant epilepsy. This is compared to the rate in the general pediatric epilepsy population of 25%[17]. This pairs with the fact that over half of patients in the study had trialed over 5 medications. We were unable to find a study that showed how many medications had been trialed for the general epilepsy population, but over 60% of patients with epilepsy have adequate seizure control on a single medication[14]. While there is not a comparison that can be made to the general population, it is good to mention that there is a high likelihood that a child with genetic epilepsy will take multiple attempts at medications to control their seizures if they are able to be controlled at all. Unfortunately, our study did not look at how many medications that patients were currently on, but that could be an avenue for further exploration.

Status Epilepticus is one of the most dangerous complications of epilepsy with the damage that it can cause to the brain with seizures lasting longer than 5 minutes, and often will have a significant impact on the lifestyle of the patient as well as for many families determine where they live so they can be close to a hospital that is equipped to handle these situations. Patients with pediatric genetic epilepsy had an annual incidence of status epilepticus of 7.3% (13/171). This is compared to the general pediatric epilepsy population which had an annual incidence of 0.02% for status epilepticus[8]. While each patient is different, it is important to let parents as well as patients know that they have a significantly increased risk of status epilepticus during any given year. A comparison was made between genetic epilepsy and general pediatric epilepsy because there is little research explaining the annual incidence of status epilepticus in the general population, and while the rate is still low, it is something that parents of children with genetic epilepsy need to be prepared for should it ever happen. This however only looks at if they had status epilepticus and not how often they have status epilepticus.

The biggest limitation of this study is the heterogeneity of the sample population. With a wide variety of gene mutations present, and the vast majority only being observed in one patient, it is hard to determine if the specific genes have an effect, and impossible to quantify the severity of specific genes to each other without having a much larger sample size. The other big limitation is that the data collection was in a method that was not as quantifiable and relatable as with the number of medications that patients have trialed compared to the current number of medications that they have prescribed.

Conclusions *(2-3 summary sentences)*

When giving a patient and their family a diagnosis of genetic epilepsy, being able to tell them what to expect will be imperative. With this data, we will be able to tell them that the patient will have an increased likelihood of having comorbidities of Autism and ADD/ADHD as well as a higher severity of the burden from epilepsy including the incidence of status epilepticus as well as drug resistance. While this is a good start, there are modifications to the database that can be made to allow for more precise documentation that could further quantify variables.

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