Ambry Genetics®
A Konica Minolta Company

Genetic Testing for Epilepsy in Adults

Zöe Powis, MS, CGC , KIrsten Blanco, BS, Kelly D.F. Hagman , MS, CGC , Elaine Weltmer, MS, CGC , Amanda Bergner, MS, CGC , Jing Wang , MD, FACMG, CGMBS, Sha Tang, Ph.D., DABMG

Ambry Genetics, Aliso Viejo, California, USA

BACKGROUND

- The field of epilepsy genetic testing is expanding, particularly in relation to childhood onset disease.
- Studies of epilepsy genetic testing demonstrate a high diagnostic yield and impact on treatment and counseling.(1)
- Previous studies have shown that adult healthcare providers are significantly less likely to order genetic testing. (2)
- Little is known about genetic testing in adult patients with epilepsy.
- Herein, we report the characteristics and detection rates of a cohort of adult patients with epilepsy.

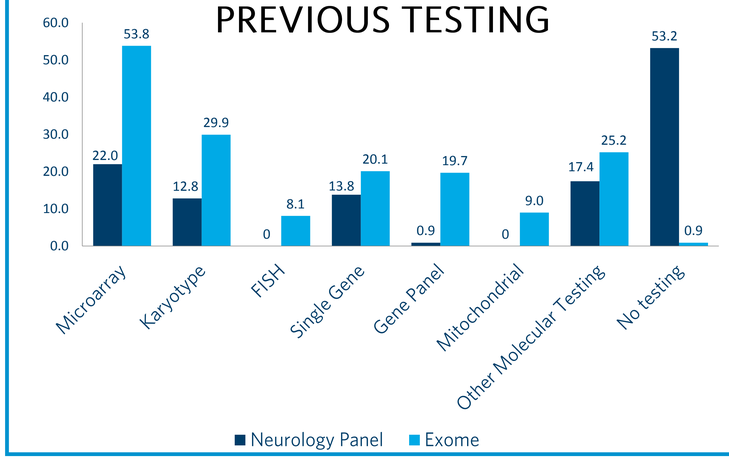
METHODS

- We reviewed an unselected cohort of 334 adults referred for epilepsy genetic testing at one commercial laboratory who underwent epilepsy multigene panel testing (MGPT) ranging from 16 to 96 genes, and/or diagnostic exome sequencing (DES). All probands with DES underwent characterized gene analysis, and if negative, novel candidate gene analysis (if an informative family trio was provided and novel genetic analysis was requested). The overall results categories were determined according to predefined diagnostic variant assessment criteria. Statistical analysis was performed using Fisher's exact test.

RESULTS

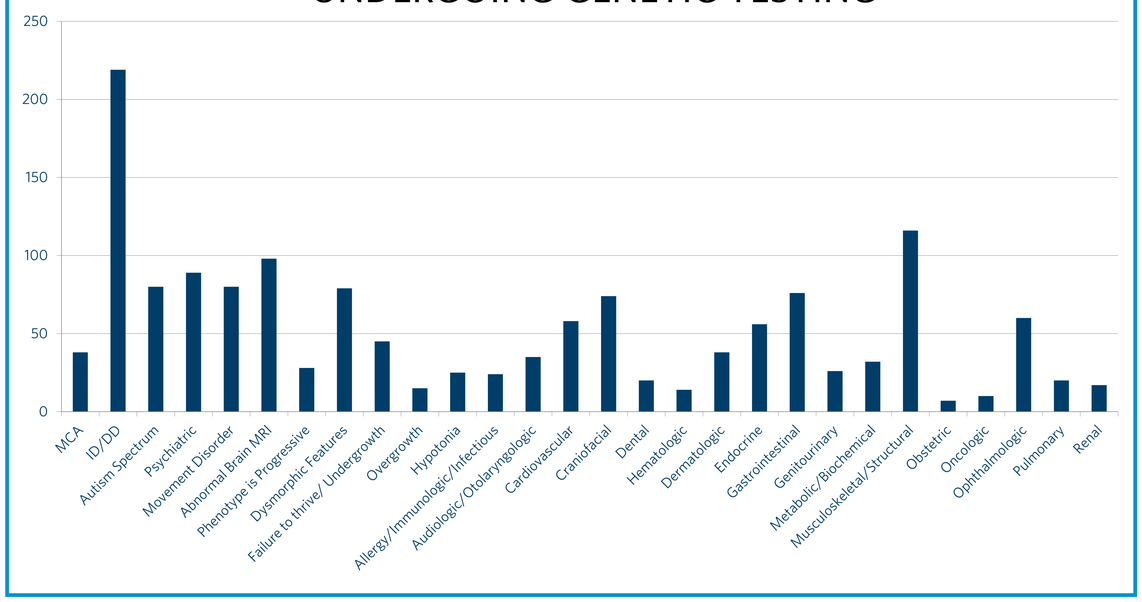
- From 334 probands, 109 MGPT tests and 234 DES tests were performed. 8 probands reflexed from MGPT to DES; 2 cases VUS, 1 carrier and the remainder negative. One patient underwent two MGPT tests. All patients undergoing DES had syndromic epilepsy, 16 patients undergoing MGPT had isolated epilepsy.

PERCENTAGE OF PATIENTS WITH PREVIOUS TESTING



Characteristic	Total Number of Probands (n = 334)	%
Gender		
Male	165	49.4%
Female	169	50.6%
Ethnicity		
Caucasian	118	35.3%
Hispanic	24	7.2%
African American	19	5.7%
Asian	9	2.7%
Middle Eastern	4	1.2%
Ashkenazi Jewish	8	2.4%
Multiple Ethnicities	21	6.3%
Unknown/Other	131	39.2%
Average Age at Seizure Onset (range 0-66)	9.9	
Childhood-Onset Seizures	157	47.0%
Epilepsy Type		
Infantile/epileptic spasms	7	2.1%
Tonic	11	3.3%
Atonic	7	2.1%
Myoclonic	35	10.5%
Typical Absence	29	8.7%
Atypical Absence	2	0.6%
Generalized tonic-clonic	93	27.8%
Focal	73	21.9%
Status epilepticus	14	4.2%
Convulsive	11	3.3%
Non-Convulsive	4	1.2%
Neonatal	0	0.0%
Febrile	18	5.4%
Unclassified	4	1.2%
Other	170	50.9%
Seizures - Refractory	90	26.9%
Seizures - Well-controlled	53	15.9%
Syndromic Epilepsy	38	11.4%

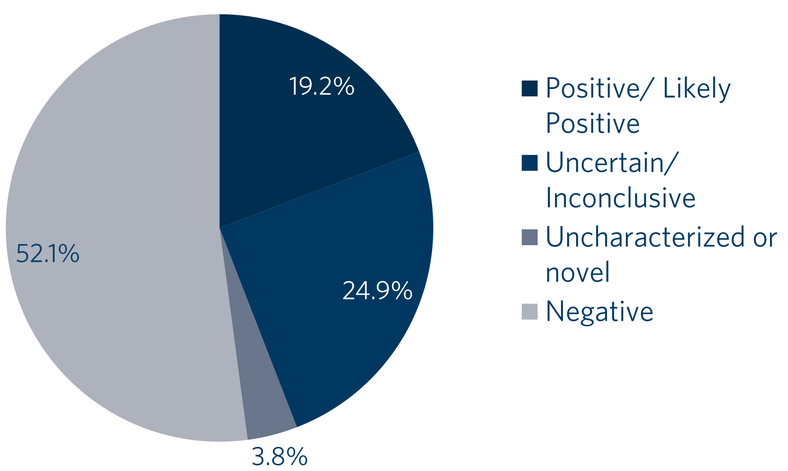
CLINICAL CHARACTERISTICS OF ADULT PROBANDS UNDERGOING GENETIC TESTING



Exome Gene Findings			
Characterized Positive/Likely Positive			
ARID1B	*FHL1*	*PAFAH1B1*	*STAT3*
B4GALNT1	*GLI2*	*PKD1* (2 cases)*	*STX1B*
CASK	*KAT6B*	*PURA*	*STXBP1*
CDKL5	*KCNQ2*	*SATB2*	*THRB*
CHD2 (2 cases)	*MAN1B1*	*SCN1A (5 cases)*	*TRPV4*
CUL4B	*MAP2K1**	*SETD5*	*TSC2*
DNM1	*MECP2* (4 cases)	*SLC2A1* (2 cases)	*WDR45* (2 cases)
DYRK1A	*MEF2C* (2 cases)	*SLC9A1*	*WDR81*
FA2H	*MT-TL1*	*SMC1A*	*XK*
*FBN1**	*NALCN* (2 cases)	*SPAST*	
Candidate/Suspected Candidate			
FBXO28	*IL21R**	*KCNN2*	*PPP3CA*

*unrelated to seizure phenotype

DETECTION RATES (n=334)



Neurology Panel Gene Findings	
ALDH7A1	*MECP2*
ATP13A2	*MEF2C*
CHD8	*POLG* (3 cases)
CNTNAP2	*PPT1*
DYNC1H1	*PRRT2*
GABRA1	*SCN1A* (2 cases)
GABRB3	*SCN1B*
GAMT	*SLC2A1*
MAN1B1	*STX1B*
MBD5	*UBE3A*

ADDITIONAL RESULTS

- Overall, testing was ordered mostly by geneticists (53.6%) and neurologists (43.1%), with geneticists more likely to order DES and neurologists more likely to order MGPT.
- ($p<0.001$).
- The detection rate for childhood onset and adult onset epilepsy were both 17.8%.
- 7 probands that underwent multigene panel testing had carrier results (6.4%)

CONCLUSIONS

- While adults with epilepsy are less likely to have genetic testing offered, our results show that patients have similar diagnostic yields to pediatric cohorts and may still benefit, not only to test at risk family members but also for personal therapeutic management.
- Testing of adults may be utilized not only for reproductive risks but also for personalized precision medicine.
- Our results also demonstrate the complexity of genetic testing for adults with epilepsy as most patients had a range of additional clinical findings, and showed a wide spectrum of seizure types.
- Genetic testing for epilepsy continues to be challenging, but testing of adults is an area in which even less is known.
- The continual discovery of new genetic etiologies for epilepsy can aid in treatment but also underscores the complexity of genetic testing.
- Additional studies are needed to expand what is known about epilepsy testing of adults and its clinical utility.

REFERENCES

1. Helbig, KL et al "Diagnostic exome sequencing provides a molecular diagnosis for a significant proportion of patients with epilepsy" Genet Med. 2016 Sep;18(9):898-905. doi: 10.1038/gim.2015.186.
2. Ferraro, L et al "Attitudes Toward Epilepsy Genetics Testing Among Adult and Pediatric Epileptologists—Results of a Q-PULSE Survey" Epilepsy Curr. 2016 Jan-Feb; 16(1): 46–47.

15 Argonaut, Aliso Viejo, CA 92656 Toll Free 866 262 7943 Fax 949 900 5501 ambrygen.com