Disclosure Slide

Financial Disclosure for:
Tiffany Pang
Senior Associate, Scientific Affairs
BioMarin Pharmaceutical Inc.

BioMarin Pharmaceutical Inc.
Employee and stockholder

Update on a Sponsored No-cost Epilepsy Gene Panel for Seizure Onset Between 2–4 Years of Age: Results from 682 Tests

T. Pang[1], F. Leal-Pardinas[1], M. Bailey[1], S. Koh[2], J. J. Millichap[3], R. Truty[4], E. Wirrell[5], S. Aradhya[4]

[1]BioMarin Pharmaceutical Inc., Novato, CA, USA; [2]Emory University School of Medicine, Atlanta, GA, USA; [3]Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA; [4]Invitae, San Francisco, CA, USA; [5]Mayo Clinic, Rochester, MN, USA

ASHG VIRTUAL MEETING 2020 OCTOBER 27-30

Introduction

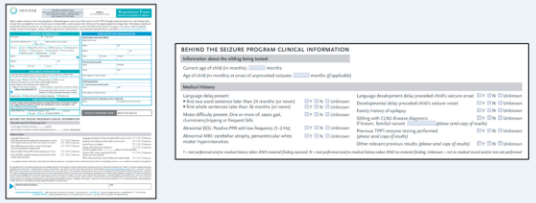
Epilepsy is a Common Childhood Neurological Disorder[1]

- >50% of pediatric-onset seizures have a genetic basis. Many epilepsies are still diagnosed based on seizure semiology (+/- EEG) and not with molecular genetic testing[2]
- Epilepsy gene panels may uncover the etiology of pediatric seizures and expedite the time to treatment[2]
- CLN2 disease, one form of neuronal ceroid lipofuscinosis (NCL), commonly presents non-specifically with seizures and a history of language development delay at 2–4 years of age[3]
- Genetic testing may impact clinical management (e.g., choice of anti-epileptic drugs, targeted therapy), shorten diagnostic journey, avoid unnecessary testing, lead to clinical trial enrollment opportunity, and facilitate genetic counseling/family planning
- Behind the Seizure (BTS, www.invitae.com/en/behindtheseizure/) is a sponsored no-cost gene panel program for children aged 2 to 4 years, who experienced their first unprovoked seizure after the age of 2
- The BTS program provides a 187-gene panel with an average turnaround time of 14 days (Invitae Epilepsy Panel) with the option to add on preliminary-evidence genes
- CLN2 disease diagnoses occur on average at 5 years old: a full 2 years after average seizure onset and after significant neurodegeneration[3,4]
- Our objective is to determine whether this testing approach (BTS) can decrease the age of diagnosis in CLN2 disease

Methods

- Data from BTS program tests reported between December 4, 2016 and February 25, 2019 **(Figure 1)**

Figure 1. Behind the Seizure® *(BTS)* Requisition Form



- Variants classified according to ACMG standards[5]:
  - Pathogenic (PATH), Likely Pathogenic (LPATH), Variant of Uncertain Significance (VUS), Benign (BEN), Likely Benign (LBEN)
- Molecular diagnosis (MDx) defined as:
  - 1 variant in a gene (PATH or LPATH) with autosomal dominant inheritance, X-linked dominant, X-linked recessive (male) OR,
  - 2 variants (PATH or LPATH) in a gene with autosomal recessive inheritance
- Outcome groups: Data divided into 3 groups by outcome:

Outcome Group	Description
No MDx	No molecular diagnosis identified
All MDx	Any molecular diagnosis in a gene included in the Invitae Epilepsy Panel
CLN2 Disease MDx	Molecular diagnosis of CLN2 disease (biallelic TPP1 variants, PATH or LPATH)

BTS Data Collected

▪ Patient Age ▪ Physician Suspicion of Genetic Basis ▪ Medical History

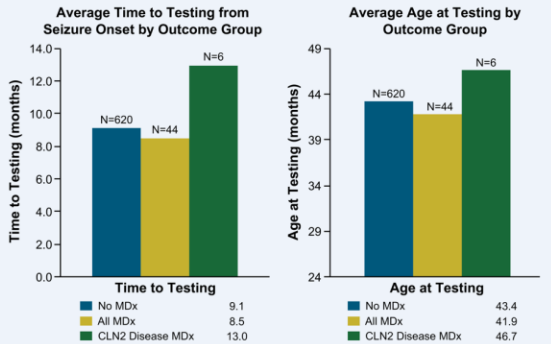
- Suspicion of genetic basis of epilepsy and medical history were optional on the requisition form — a blank item was not taken to be a negative
  - All proportions calculated based on this data used the total number of orders where "y" or "n" was selected

Results

Summary

- From December 4, 2016 to February 25, 2019, 682 tests have been conducted in eligible patients through the BTS program with 46 molecular diagnoses **(Table 1)**
- Average age at testing, age at first seizure, and time to testing from seizure onset were similar between all outcome groups **(Figure 2)**

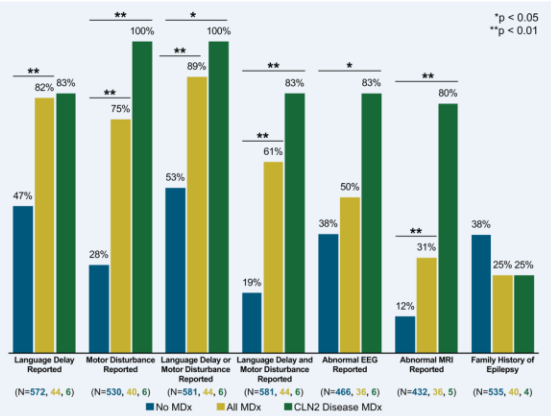
Figure 2. Age and Time to Testing



The difference between the sample means are not statistically significant. Data cut: 02/25/2019, 682 *BTS* tests reported.

- Diagnosis of CLN2 disease was 1–2 years earlier than reported average (13 months from seizure onset to diagnosis vs. 2–3 years)[3]

Figure 3. Clinical Presentation by Outcome Group



Total number of clinicians indicating presence or lack of presence of clinical feature for each outcome group. Non-responders not included in total. Data cut: 02/25/2019, 682 *BTS* tests reported.

- Large differences in clinical features were seen between No MDx and All MDx outcome groups: presence of language delay (47% vs. 82%, respectively) and motor disturbance (28% vs. 75% respectively) **(Figure 3)**

Table 1. Molecular Diagnoses

Gene	Inheritance	Conditions	Possible Management Implication	Number of Diagnoses (n=46)
MECP2	XLD	Rett syndrome	Interventional clinical trials open for enrollment, females only[6]	8
SYNGAP1	AD	Mental retardation, autosomal dominant, 5	Observational clinical trial open for enrollment[6]; Children may benefit from interventions used in treatment of autism spectrum disorder[7]	7
TPP1	AR	CLN2 disease (Ceroid lipofuscinosis, neuronal [NCL, CLN2]), 2	Cerliponase alfa (Brineura) approved for treatment in the US and other countries[8]; Clinical trials open for enrollment[6]	6
CHD2	AD	Epileptic encephalopathy, childhood-onset	Interventional clinical trial open for enrollment[6]	2
GRIN2A	AD	Epilepsy, focal, with speech disorder and with or without mental retardation	Individuals with epileptic encephalopathy with continuous spike-and-wave during sleep (ECSWS) should avoid phenytoin, barbiturates and carbamazepine[7]; Observational clinical trial open for enrollment[6]	2
KANSL1	AD	Koolen-De Vries syndrome	No disease-altering treament available[7]	2
PPT1	AR	Ceroid lipofuscinosis neuronal, 1	Observational clinical trial open for enrollment[6]	2
SCN1A	AD	Epilepsy, generalized with febrile seizures plus, type 2 Epileptic encephalopathy, early infantile, 6 (Dravet syndrome) Febrile seizures familial, 3A Migraine familial hemiplegic, 3	Stiripentol (Diacomit) approved for Dravet Syndrome treatment in the US and other countries[9]; Cannabidiol (Epidiolex) approved for Dravet Syndrome treatment in the US[10]; Fenfluramine (Fintepla) approved for Dravet Syndrome treatment in the US[11]; Clinical trials open for enrollment for Dravet Syndrome[6]	2
TSC1	AD	Focal cortical dysplasia, type II, somatic Lymphangioleiomyomatosis Tuberous sclerosis-1	Interventional clinical trials open for enrollment[6]; Everolimus (Afinitor) approved for tuberous sclerosis treatment in the US and other countries[12]	2
CACNA1A	AD	Epileptic encephalopathy, early infantile, 42 Episodic ataxia, type 2 Migraine, familial hemiplegic, 1 Migraine, familial hemiplegic 1 with progressive cerebellar ataxia Spinocerebellar ataxia, 6	Interventional clinical trial open for enrollment for Episodic Ataxia type 2[6]	1
EHMT1	AD	Kleefstra syndrome, 1	No disease-altering treament available[7]	1
FOXG1	AD	Rett syndrome, congenital variant	Observational clinical trials open for enrollment[6]	1
FRRS1L	AR	Epileptic encephalopathy, early infantile, 37	Observational clinical trial open for enrollment[6]	1
IQSEC2	XLD	Mental retardation, X-linked, 1/78	No disease-altering treament available[13]	1
KIAA2022	XLD	Mental retardation, X-linked, 98	No disease-altering treament available[14]	1
PACS1	AD	Schuurs-Hoeijmakers syndrome	No disease-altering treament available[15]	1
PCDH19	XL	Epileptic encephalopathy, early infantile, 9	Interventional clinical trial open for enrollment, females only[6]	1
PURA	AD	Mental retardation, autosomal dominant, 31	Observational clinical trial open for enrollment[6]	1
SCN2A	AD	Epileptic encephalopathy, early infantile, 11 Seizures benign familial infantile, 3	Observational clinical trial open for enrollment[6]	1
SLC6A1	AD	Myoclonic-atonic epilepsy	Observational clinical trial open for enrollment[6]	1
STX1B	AD	Generalized epilepsy with febrile seizures plus, type 9	No disease-altering treament available[16]	1
ZEB2	AD	Mowat-Wilson syndrome	No disease-altering treament available[7]	1

- Language delay or motor disturbance was reported in 89% of patients in the All MDx group, vs. 53% in the No MDx group. These features may be subtle
- Abnormal EEG and MRI higher in All MDx outcome groups – Use of EEG and MRI, as defined by clinician reporting, was similar between the two groups (73–78% vs. 68–78%)
- Family history of epilepsy was not a good predictor of molecular genetic testing outcome (25% of All MDx, 38% of No MDx) – Most conditions here are autosomal dominant **(Table 1)**
- Suspicion of a genetic etiology of epilepsy was not different between the No MDx and All MDx group (95% of ordering clinicians vs. 94%, respectively)
- Where a molecular diagnosis of CLN2 disease was found, only 1 of 6 (17%) ordering physicians noted suspicion of CLN2 disease

Acknowledgements

The authors would like to thank Nicole Miller (BioMarin) for her contributions to the study and analysis, and Gillian Clague (BioMarin) for poster graphic editing and design.

References

1. Camfield P, Camfield C. Incidence, prevalence and aetiology of seizures and epilepsy in children. *Epileptic Disord.* 2015;17(2):117-23. **2.** Wang J et al. Epilepsy-associated genes. *Seizure* 2017;44:11-20. **3.** Nickel M, Simonati A, Jacoby D, et al. Disease characteristics and progression in patients with late-infantile neuronal ceroid lipofuscinosis type 2 (CLN2) disease: an observational cohort study. *Lancet Child Adolesc Health.* 2018; 2(8):582-590. **4.** Schulz A et al. Neuronal ceroid lipofuscinosis-2 (CLN2) natural history and path to diagnosis: international experts' current experience and recommendations on CLN2 disease, a type of Batten disease, resulting from TPP1 enzyme deficiency. *Eur J Paediatr Neurol.* 2015;19:S119. **5.** Richards S et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med.* 2015;17(5):405. **6.** ClinicalTrials.gov, accession 09/18/2019. **7.** Adam MP et al. *GeneReviews®.* University of Washington, Seattle; 1993-2019. **8.** Markham A. Cerliponase alfa: first global approval. *Drugs* 2017;77(11):1247–9. **9.** Eschbach K, Knupp KG. Stiripentol for the treatment of seizures in Dravet syndrome. *Expert Rev Clin Pharmacol.* 2019;12(5):379–88. **10.** Sekar K, Pack A. Epidiolex as adjunct therapy for treatment of refractory epilepsy: a comprehensive review with a focus on adverse effects. *F1000Res.* 2019;8:234. **11.** Lagae L et al. ZX008 (Fenfluramine) in Dravet syndrome: results of a phase 3, randomized, double-blind, placebo-controlled trial. Poster presented at: 71st Annual Meeting of the American Epilepsy Society; December 2017; Washington, DC. **12.** Everolimus. National Center for Biotechnology Information. PubChem Compound Database. U.S. National Library of Medicine. **13.** Zipper R et al. Developmental progression of intellectual disability, autism, and epilepsy in a child with an IQSEC2 gene mutation. *Clin Case Rep.* 2017;5(10):1639–43. **14.** Maldergem LV et al. Loss of function of KIAA2022 causes mild to severe intellectual disability with an autism spectrum disorder and impairs neurite outgrowth. *Hum Mol Genet.* 2013;22(16):3306–14. **15.** Schuurs-Hoeijmakers JHM et al. Clinical delineation of the PACS1-related syndrome - Report on 19 patients. *Am J Med Genet A.* 2016;170(3)670-5. **16.** Wolking S et al. Clinical spectrum of STX1B-related epileptic disorders. *Neurology* 2019.

Conclusions

- Increased rates of MDx in patients with language delay or motor disturbance supports early testing in these patients presenting with seizures
- Decreased time from seizure onset to diagnosis through BTS points to sponsored no-cost gene panel testing as an effective means to decrease time to diagnosis in CLN2 disease
- Suspicion of a genetic etiology and family history of epilepsy are not good predictors of genetic testing outcome in this dataset; language delay and motor disturbance are the best indicators of genetic testing outcome
- Time from seizure onset to testing does not appear to influence outcome of molecular genetic testing (MDx vs. No MDx). However, MDx can decrease the time to the identification of the etiology of seizures such as in diagnosis of CLN2 disease

ASHG American Society of Human Genetics