# Diagnostic yield and clinical utility of genetic testing in children with seizure onset after two years of age: Update over a 3-year program in Europe and the Middle East

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# Background and Methods

## Background

- Seizure disorders are among the most common neurological conditions presenting in childhood
- Molecular diagnosis and confirmation provides the potential for etiologically-based treatment and management
- Existing research on the diagnostic yield and clinical utility of genetic testing for these patients has focused on early-onset (<2 years of age) epilepsies, while data regarding later-onset epilepsies is limited

## Objectives

- To evaluate the diagnostic yield of a comprehensive next-generation sequencing (NGS)-based epilepsy panel in patients with seizure onset after 2 years of age and assess the impact on age of diagnosis of neurodegenerative diseases such as late-infantile neuronal ceroid lipofuscinosis type 2 (CLN2 disease)

## Methods

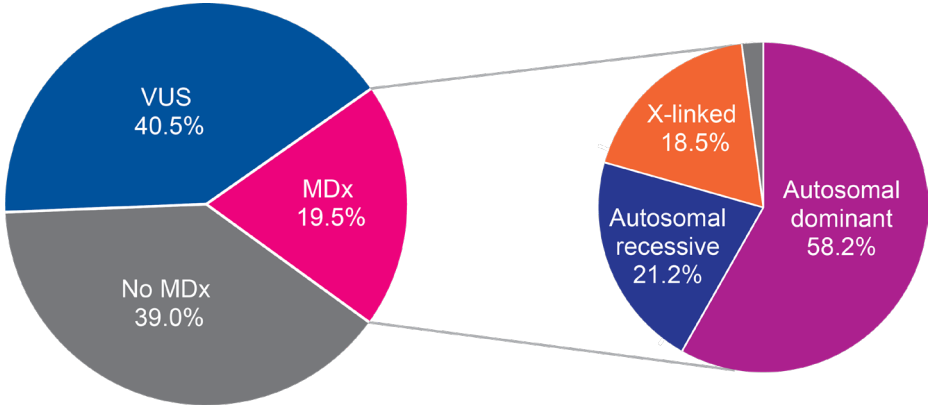
- Inclusion criteria:
  - Aged 24 to 48 months at the time of testing
  - First seizure at or after 24 months of age
  - At least 1 additional finding, i.e. EEG or MRI abnormalities, speech delay, or motor symptoms
- Comprehensive NGS-based epilepsy panel, including high-resolution copy number variant (CNV) and custom target of intronic variants cataloged as pathogenic/likely pathogenic by HGMD and ClinVar
- Variant interpretation was performed according to ACMG-AMP guidelines

Beyond Paediatric Epilepsy Panel – for Europe and Middle East. https://blueprintgenetics.com/tests/panels/neurology/beyond-paediatric-epilepsy-panel/
Richards S et al. *Genet Med* 2015;17:405–23.

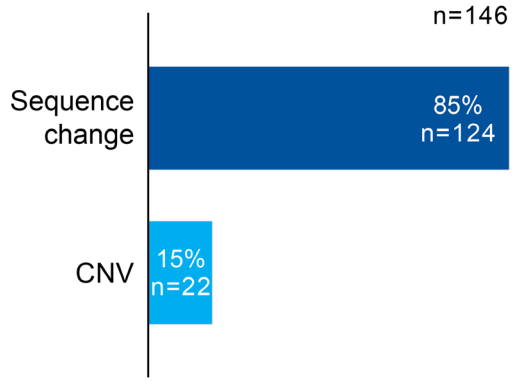
# Results

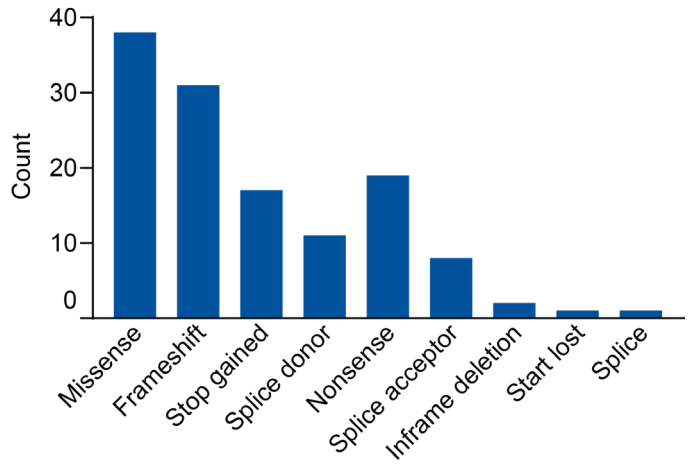
- Results are reported from 748 patients in Europe and the Middle East tested between November 2017 and December 2020
  - Median age at testing was 38 months
  - Median age at first seizure onset was 27 months
  - Average time from first seizure to genetic testing was 9 months
- A genetic diagnosis was established for 146 patients: a molecular diagnostic yield (MDx) of 19.5%

- The most common pattern of inheritance was autosomal dominant, followed by autosomal recessive, and X-linked



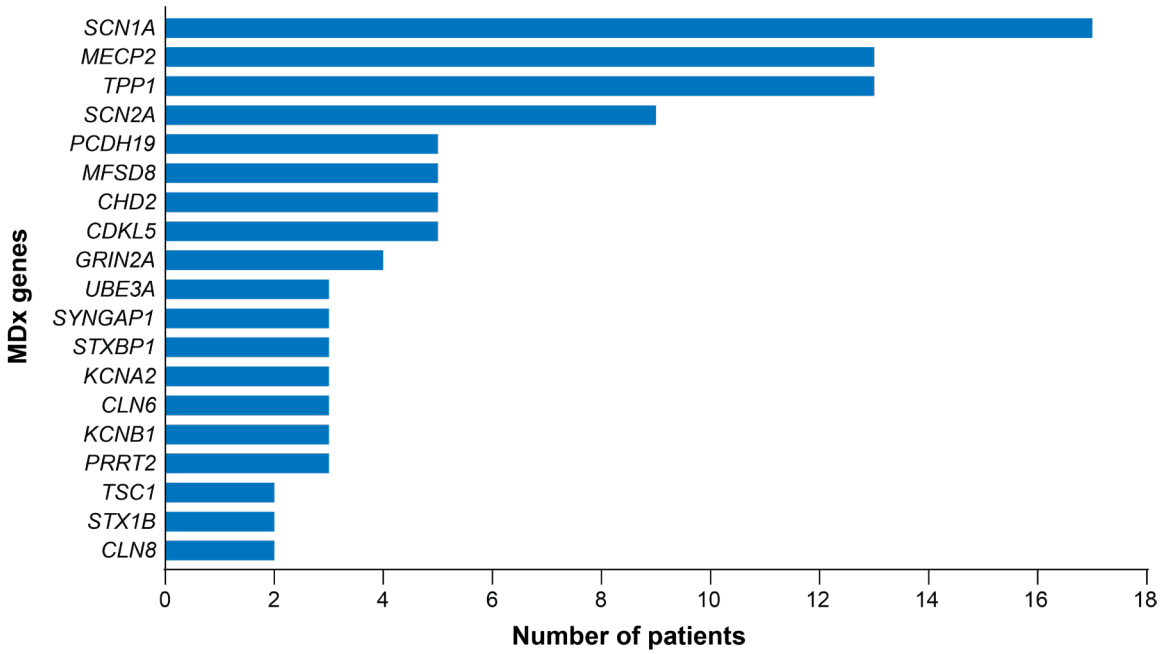

- CNVs were reported in 15% of diagnosed patients and 32% of the CNVs identified were intragenic
- Among sequence changes, missense variants were most common



# Results

- The most frequent molecular diagnoses included *SCN1A* (N=17), *MECP2* (n=13), and *TPP1* (CLN2; n=13)
  - CLN2 disease patients received a molecular diagnosis at an average age of 3 years, 11 months




- Over 60% of diagnosed patients had a disorder for which there are possible clinical management implications

| Gene | Conditions (MDx) | Possible Management Implication |
|---|---|---|
| *TPP1* | Neuronal ceroid lipofuscinosis type 2[1] | Ceriponase alfa approved ERT therapy for eligible patients in the EU, US, Ukraine, Brazil, Australia, Canada, Mexico[2,3] |
| *MECP2* | Rett syndrome[1] | Interventional clinical trials [4,5,6] |
| *CDKL5* | Angelman-like syndrome[7], Early infantile epileptic encephalopathy-2[1] | Ataluren for nonsense variants (clinical trial)[4]; Ganaloxone (clinical trial) [4] |
| *SCN2A* | Early infantile epileptic encephalopathy[1] Epileptic encephalopathy, early infantile, Seizures, benign familial infantile[8] | Specific AEDs are recommended according to the variant (depending on gain or loss of function)[5]: Observational clinical trial[4], Interventional clinical trial[5] |
| *SCN1A* | Dravet Syndrome[1] | Avoid sodium channel blockers[10]; Interventional clinical trials open for enrolment [4,5]; EPIDIOLEX (cannabidiol) approved treatment [4,5] |
| *STXBP1* | Epileptic encephalopathy early infantile[1] | Pharmacogenomic information available (AEDs to consider phenobarbital, valproic acid, and vigabatrin[7]); Observational clinical trial[2] |
| *UBE3A* | Angelman syndrome, Prader–Willi syndrome [1] | Interventional clinical trials [4,5] |
| *TSC1* | Tuberous sclerosis[1] | Interventional clinical trials [4,5]<br>Everolimus approved treatment (mTOR inhibitors)[1,4] |
| *72-kb del. 16p11.2* | 16p11.2 microdeletion syndrome[1] | Observational and interventional clinical trials[4,5]; Specific deficit target treatment[10]; Recommendation: to establish neurodevelopement[10] |
| *SLC19A3* | Thiamine metabolism dysfunction syndrome[9] | Biotin and thiamine therapy[10, 11] |
| *SLC6A8* | Creatine deficiency syndromes[1] | Creatine, L-arginine and L-glycine supplementation[10, 12] |
| *PCDH19* | Dravet-like Syndrome[1] | Most effective AED clobazam and bromide[13], Interventional clinical trials[4,5] |
| *PPT1* | Neuronal ceroid lipofuscinosis type I[7] | Biochemical testing assessing enzymatic activity[10] |
| *RNASEH2B* | Aicardi-Goutières syndrome[1] | Possible management with Ruxolitinib[14]; Interventional clinical trials[4] |
| *STX1B* | Generalized epilepsy with febrile seizures plus, type 9[1, 11] | Treatment with different AEDs are discussed by Wolking et al. 2019[15] |
| *KCNQ2* | kcnq2-related epileptic encephalopathy, Epileptic encephalopathy, early infantile, 7, Seizures, benign neonatal, 1[9, 11] | Observational clinical trial[4], Interventional clinical trials[5]: Treatment with different AEDs (n=19) and other options are discussed by Kuersten et al. 2020[16] |
| *POLG* | Mitochondrial DNA depletion syndrome 4A (Alpers type), Mitochondrial DNA depletion syndrome 4B (MNGIE type), Mitochondrial recessive ataxia syndrome (includes SANDO and SCAE), Progressive external ophthalmoplegia, autosomal dominant 1, Progressive external ophthalmoplegia, autosomal recessive 1 | Specific AEDs are suggested to be avoided according to the variant and disease type[17] |
| *CLN6* | Ceroid lipofuscinosis, neuronal, 6[11] | Observational clinical trial recruiting[4]; Interventional clinical trials[4] |
| *SLC6A1* | Myoclonic-atonic epilepsy[11] | Evidence of response to Ketogenic diet[18]; Observational clinical trial[4] |
| *WDR45* | Neurodegeneration with brain iron accumulation 5[11] | Observational and Interventional clinical trials[4] |
| *ALDH3A2* | Sjogren-Larsson syndrome[11] | Interventional clinical trial[5] |
| *KCTD7* | Ceroid lipofuscinosis, neuronal 14, Epilepsy, progressive myoclonic 3, with or without intracellular inclusions[11] | Treatment with different AEDs and other options are discussed by Kousi et al. 2012[19] |
| *ARID1B* | Coffin-Siris syndrome 1[11] | Observational and interventional clinical trial[4] |
| *PRRT2* | Convulsions, familial infantile, with paroxysmal choreoathetosis, Episodic kinesigenic dyskinesia 1[11] | Treatment with carbamazepine showed benefit and is discussed by Chen et al. 2011[20] |
| *HNRNPU* | Epileptic encephalopathy, early infantile, 54 | Treatment with different AEDs are discussed by Yates et al. 2017 and Bramswig et al. 2017[21,22]; Observational clinical trial[4] |
| *SLC2A1* | GLUT1 deficiency syndrome, Stomatin-deficient cryohydrocytosis with neurologic defects[11] | Evidence of response to Ketogenic diet[23]; Interventional clinical trials[4] |
| *CLTC* | Mental retardation, autosomal dominant 56 | Evidence of response to MAO-A selegiline inhibitor[24] |
| *ANKRD11* | KBG syndrome | Evidence of response to specific AEDs[25] |


**1**. National Library of Medicine - National Institutes of Health. https://www.nlm.nih.gov/. **2**. https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm555613.htm. **3**. Johnson et al. *Nat Rev Neurol* 2019;15(3):161–178. **4**. ClinicalTrials.gov. https://clinicaltrials.gov/. **5**. EU Clinical Trials Register. https://www.clinicaltrialsregister.eu/. **6**. Gomathi M et al. *J Autism Dev Disord* 2020;50(8):2740-2764. **7.** Russo S. et al. Neurogenetics 2009;10(3): 241–50. **8.** The MalaCards human disease database. Available: https://www.malacards.org/ **9**. Sanders SJ et al. 2018. *Trends Neurosci* 2018;41(7):442–56. **10**. Adam MP et al. 1993 GeneReviews®. University of Washington, Seattle, WA. **11**. OMIM https://www.ncbi.nlm.nih.gov/omim. **12**. Dunbar, M et al. *Mol Genet Metab* 2014;112(4):259–74. **13**. Lotte J. et al. *Seizure* 2016; 35:106–110. **14**. Tüngler V. et al. *Neuropediatrics* 2017;48(S 01):S1–45. **15**. Wolking S et al. *Neurology* 2019;92(11):e1238-e1249. **16**. Kuersten M. et al. *Eur J Med Genet* 2020;63(1):103628. **17**. Li S et al. 2015. *Hepatology* 2015;61(54):1730-9. **18**. Palmer S et al. *Pediatr Neurol* 2016;64:77-79. **19**. Kousi M et al. *J Med Genet* 2012; 49(6):391-9. **20**. Chen WJ et al. *Nat Genet* 2011; 43(12):1252-5. **21**. Yates TM et al. *Am J Med Genet A* 2017;173(11):3003-3012. **22**. Bramswig NC et al. *Hum Genet* 2017;136(7):821-834. **23.** Pérez-Dueñas B et al. *Arch Neurol* 2009;66(11):1410-4. **24**. Manti F et al. *Parkinsonism Relat Disord* 2019;61:207-210. **25.** Lo-Castro A et al. *Am J Med Genet B Neuropsychiatr Genet* 2013 Jan;162B(1):17-23.

# Conclusions

- This study demonstrates a high diagnostic yield (19.5%) in pediatric patients with first unprovoked seizure after 2 years of age and at least one other neurological abnormality
- These findings support the addition of *TPP1* and genes linked to other NCLs and inborn errors of metabolism presenting with epilepsy to diagnostic NGS-based epilepsy panels
- In this cohort, CLN2 diagnosis was achieved 1–2 years earlier than average age of diagnosis reported in studies of the natural history of the disease
- More than 60% of patients who received a molecular diagnosis had a disorder with a targeted treatment, evidence for optimizing pharmaceutical treatment, or on-going clinical trials available
- Overall, this study highlights the importance of the early application of genetic testing in children presenting with seizures after 2 years of age for the efficient identification of disorders with targeted management available

Nickel M et al. Lancet Child Adolesc Health 2018;2(8):582–90.