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Evaluation of epilepsy in 8p-related disorders

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ABSTRACT

8p-related disorders are genetic conditions associated with chromosomal rearrangements on the short arm of chromosome 8. This study aimed to characterize the epilepsy phenotype in patients with 8p-related disorders seen at Children's Hospital Colorado (CHCO) and/or recorded in the Project 8p Foundation Natural History Study. Key objectives included determining epilepsy prevalence, typical age of seizure onset, efficacy of treatment, and EEG features. A retrospective chart review was conducted for patients seen in the CHCO Neurogenetics Multidisciplinary Clinic and Project 8p Database. Clinical data including demographics, genotype, epilepsy history, and EEG findings were collected. The cohort included 162 unique patients with 8p-related disorders (42 at CHCO, 120 from the Project 8p Natural History Study). Overall, 32 % of patients (53/162) had experienced at least one lifetime seizure: 37 % (30/81) of those with Invdupdel(8p), 35 % (16/46) with 8p deletions, and 15 % (4/26) with 8p duplications. Average age of seizure onset was 3.4 years, with a range from neonatal onset to 16.9 years of age. Among CHCO patients with epilepsy (14/42, 33 %), only one had intractable epilepsy, while 9 became seizure-free, including 5 off medications. EEG abnormalities were present in 18/42, 43 % of the CHCO patients. This study provides the first detailed analysis of epilepsy in a large cohort of patients with 8p-related disorders. While epilepsy is relatively common, it is typically well controlled. Genotype-specific patterns emerged, with Invdupdel(8p) associated with the highest epilepsy prevalence and 8p duplication with the lowest. Further research in larger cohorts is warranted to validate these findings.

1. Introduction

8p-related disorders are a group of genetic conditions caused by rearrangements on chromosome 8p which share a common neurologic phenotype. Rearrangements are known to occur in 8p due in part to repeated sequences known as the Olfactory Receptor gene clusters

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(Giglio et al., 2001). These repetitive regions can lead to recurring chromosomal abnormalities involving 8p, including isolated deletions, isolated duplications, and inverted duplication/deletions (Invdupdel) (Giglio et al., 2001; Fisch et al., 2011). Estimated incidence of Invdupdel (8p) is 1 in 10,000–30,000 live births, making it the most common Invdupdel described in humans (Vibert et al., 2022). While epilepsy has been reported to occur in 34 %-55 % of patients with 8p-related disorder (Okur et al., 2021; Vibert et al., 2022; Burnside et al., 2013) and a range of seizure types have been described in this population, no prior study has focused on in-depth characterization of seizure patterns and prevalence in the 8p population. Given the incomplete penetrance of seizures in individuals with 8p rearrangements, predicting the risk of epilepsy in 8p disorders is critically important.

Several descriptive studies have analyzed the phenotype of 8p duplications, 8p deletions and Invdupdel(8p) (Okur et al., 2021; Santucci et al., 2025; Fisch et al., 2011; Vibert et al., 2022; Lo Bianco et al., 2020; Barber et al., 2013). The phenotype for these conditions can include structural brain and cardiac abnormalities, intellectual disability, autism, epilepsy, macrocephaly, microcephaly, hypotonia, hypertonia, motor delays, cortical vision impairments (CVI), and gastrointestinal issues, amongst other challenges (Santucci et al., 2025).

In this study we aimed to characterize the epilepsy phenotype of the cohort of 8p-related disorder patients seen at Children's Hospital Colorado (CHCO) and through the Project 8p Natural History Study. In particular, it was important to capture epilepsy prevalence and typical seizure age of onset for the cohorts. We were then able to look further into seizure type characterization, medication use and intractability, and EEG findings in the CHCO cohort. Additionally, we also wanted to characterize any differences in epilepsy presentation and severity between InvDelDup(8p), isolated deletions, and isolated duplications of 8p. This study is intended to serve as a resource for future prospective studies to evaluate epilepsy emergence in this high-need population.

2. Materials and methods

2.1. Children's colorado cohort

A retrospective chart review was completed on all patients who were seen and consented in the Neurogenetic clinic with 8p-related disorders from 2020 to 2025 (IRB protocol 16–0152). Utilizing standardized history/examination forms, clinical data was collected including demographics, detailed genotype, epilepsy history, and EEG findings. Data was entered into a secure RedCap data base.

2.2. Project 8p natural history study cohort

The Chromosome 8p Natural History Study is a global, retrospective, and prospective natural history study designed to collect and analyze data on individuals diagnosed with or suspected of having Chromosome 8p rearrangements. The study aims to characterize the phenotypic spectrum, identify genotype-phenotype correlations, facilitate clinical trial readiness, and establish a biorepository for biospecimens linked to patient phenotypic data. The study is administered by Project 8p Foundation in collaboration with multiple academic and research institutions. The study protocol was approved by an Institutional Review Board (IRB approval number NB200051), and informed consent is obtained from all participants or their legal guardians prior to enrollment. Participants have the right to withdraw at any time, and data security and confidentiality measures are strictly adhered to in compliance with HIPAA and GDPR regulations. Project 8p Natural History Study participants are recruited globally through patient advocacy networks, clinician referrals, social media campaigns, and collaborations with research institutions. Eligible participants include individuals of any age diagnosed with Chromosome 8p rearrangements, their biological relatives, and age-matched unaffected controls.

Enrollment occurs via the Project 8p Natural History Study website (www.project8p.org), where participants provide consent and complete self-reported surveys. Participants can opt to share medical records, genetic reports, and biospecimens for further research. Participants are periodically contacted for data updates and additional research opportunities.

All participants (or their legal guardians) provided informed consent via the registry platform before enrolling. Data collection encompassed demographic, clinical, and genetic information, gathered through modular online surveys that addressed specific 8p rearrangements (e.g., deletions, duplications), reported health symptoms, disease burden, and caregiver experiences. For this study, we retrospectively collected data from all patients with registry entries from years 2021–2025.

2.3. Statistical analysis

Descriptive statistical analysis was then performed on the group as a whole and each sub-group (deletion, duplication, and inverted duplication/deletion) including mean, median, and range.

3. Results

3.1. Description of Populations

42 patients with 8p were seen at Children's Hospital Colorado from 2020 to 2025. CHCO patients are seen annually in the clinic. Since the clinic began in 2020, many patients have had several follow-up appointments, although new patients continue to be seen each year. 120 unique patients were also identified from the Chromosome 8p Natural History database. Duplicate patients were eliminated; if a patient was seen at CHCO and in the 8p natural history study, their data was included under "CHCO". Both cohorts were organized by genotype with demographic characteristics outlined. (Table 1)

Genotype, presence/absence of epilepsy, and age of seizure onset were extracted from both data sets. More in-depth characterization of seizure types, seizure medications and epilepsy severity/seizure freedom were only reported for the CHCO cohort.

3.2. Epilepsy description

Overall, 32 % of patients (53/162) had experienced at least one lifetime seizure. Average age of seizure onset was 3.4 years, with a range from neonatal onset to 16.9 years of age(Fig. 1). Febrile seizures occurred in 7 of the 53 patients who reported seizures across both cohorts (13 %): 6 cases in the natural history study and 1 case in the CHCO cohort. Because the natural history study database is based on parent-reported information, additional epilepsy descriptors (e.g., seizure types, medication usage) could not be independently verified and were consequently excluded.

Upon review of the CHCO cohort, 14 patients had had at least one

Table 1
Characteristics of both cohorts (Children's Hospital Colorado and Project 8p Database).

Characteristic	Children's Hospital Colorado	Project 8p Natural History Study	Total
Total number of patients	42	120	162
Average age and (age range)	10.7 years (7 months – 42 years)	10.6 years (3 months – 46 years)	
Inv/Del/Dup	22/42 (52 %)	59/120 (49 %)	81/162 (50 %)
Deletion Only	12/42 (28 %)	34/120 (28 %)	46/162 (28 %)
Duplication Only	7/42 (17 %)	18/120 (15 %)	25/162 (15 %)
Trisomy or Ring	1/42 (2 %)	5/120 (4 %)	6/162 (4 %)

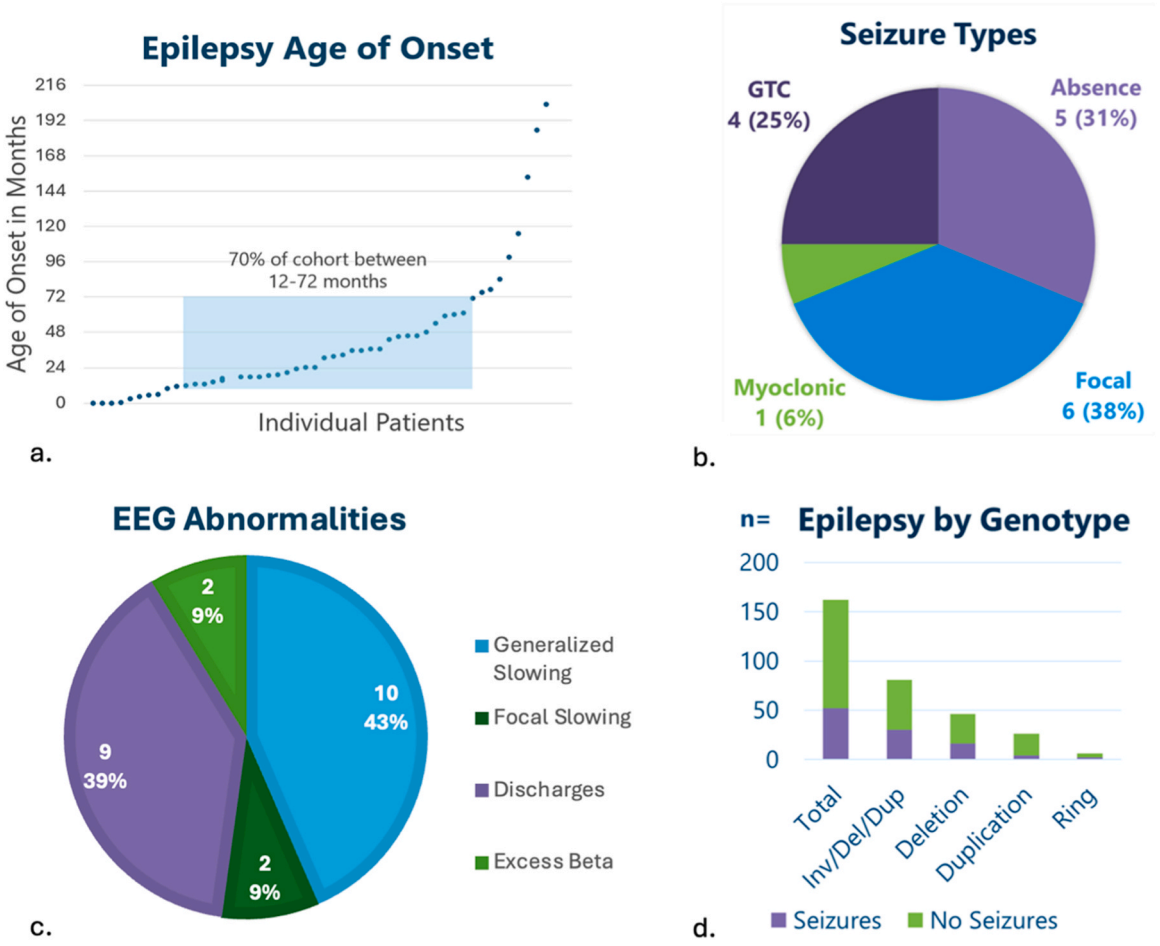

Fig. 1. a) Epilepsy age of onset across both cohorts (53 patients in total) b) Seizure types in the CHCO cohort across the 14 patients with epilepsy c) EEG abnormalities in the CHCO cohort (42 patients in total) d) Epilepsy prevalence by genotype across both cohorts.

lifetime seizure and only one patient met criteria for intractable epilepsy. 9/14 (64 %) patients were seizure free, with 5 out of those 9 being seizure free off medications. Several different unprovoked seizure types were reported, including Generalized Absence, Focal impaired consciousness, Generalized Myoclonic, and Generalized Tonic-Clonic (Fig. 1). Corpus callosum abnormalities were present in 4/14 (29 %) of patients with seizures, a finding also observed at a similar rate across the entire CHCO 8p cohort in 12/42 (29 %) of patients. Importantly, no focal MRI abnormalities that might represent a possible etiology for the seizures were seen. 8/14 (57 %) had generalized epilepsies, 2/14 (14 %) had focal epilepsies, and 4/14 (29 %) had a combined epilepsy. No patient had a clearly defined ILAE syndrome. Seizure medications were also reviewed, with most patients (9/14, 64 %) using only Levetiracetam, 2 patients on Depakote, and the one patient with intractable epilepsy on three medications (Lamotrigine, Cannabidiol, and Brivaracetam). There were no cases of status epilepticus reported in the cohort.

3.3. EEG features

EEG was abnormal in 43 % of the patients in the CHCO cohort (18/42). The most common abnormality was generalized background slowing (10/42, 23 %) followed by epileptiform discharges (9/42,21 %) (Fig. 1). 11/14 (79 %) patients with seizures had at least one abnormal EEG in their medical record. In terms of interictal epileptiform discharges, 6/9 (67 %) were focal discharges, of which the most common location was posterior (4/9, 44 %). The remaining patients had generalized discharges (3/9, 33 %). There was no patient who met criteria for developmental epileptic encephalopathy with spike-and-wave activation in sleep (DEE- SWAS) or had a diagnosis of infantile spasms.

3.4. Genotype/phenotype epilepsy correlations

Presence of seizures was broken down by genotype: 37 % (30/81) of those with Invdupdel(8p) had seizures, 35 % (16/46) with 8p deletions, and 16 % (4/25) with 8p duplications (Fig. 1). These percentages were consistent between the CHCO cohort and the Project 8p Natural History Study. The one patient with intractable epilepsy in the CHCO cohort had an 8p distal deletion. We analyzed the relationship between the precise chromosomal breakpoints of copy-number variants and epilepsy, with no significant associations detected.

4. Discussion

This is the first study of its kind looking in depth at epilepsy prevalence, characterization, and severity in 8p-related disorders. This unique study was able to incorporate both clinical data from a cohort of patients seen at Children's Hospital Colorado as well as a cohort of patients in a disease-specific natural history study through a patient advocacy group. Both datasets showed remarkably similar percentages of genotype and epilepsy prevalence. This consistency is key, showing that although the number of patients seen at CHCO is small, the breakdown of patients is representative of the population as a whole.

Epilepsy characterization revealed that while epilepsy is present in many patients with 8p-related disorders, it tends to be well controlled, with many patients achieving seizure freedom and discontinuing medication. In the CHCO cohort, most patients achieved seizure

freedom using Levetiracetam as the first-line medication. However, this cohort is too small to conclude that Levetiracetam is specifically highly effective in this population. It is more likely that Levetiracetam is the most common first-line epilepsy medication used overall, and that the majority of 8p patients respond well to a single agent. Having a larger cohort with detailed medication data would be useful in clarifying this relationship. Age of seizure onset was also consistent across both cohorts as mainly childhood (1–7yo), with few patients having seizure onset neonatally or in adulthood. Our findings support prior reports of absence seizures, febrile seizures, tonic-clonic seizures (Okur et al., 2021) and staring spells (Fisch et al., 2011). To our knowledge, this is the first documentation of myoclonic seizures in the 8p population.

EEG features revealed abnormalities, but none that pointed to a specific ILAE syndrome such as DEE with Spike Wave Activation in Sleep (DEE-SWAS) or Infantile Epileptic Spasms Syndrome (IESS). To our knowledge no specific ILAE epilepsy syndromes have been identified in 8p-related disorders, though there is interest from patient communities in understanding the prevalence of these syndromes in their population. Interestingly, there was a predominance of posterior spikes without a clear structural reason for this finding. More investigation is warranted into specific EEG patterns and epilepsy severity/MRI findings.

There are several limitations to this study. There were differences in methodology and collection across the two datasets. In addition, available sample sizes remain small, which restricts the power to detect meaningful associations. Finally, the average age of these cohorts was 10 years old, limiting generalizability to adolescents and adults.

Overall, this study underscores that while epilepsy is present in this population, it is generally mild in severity and responsive to treatment. Even in a large cohort of 162 patients there were no cases of status epilepticus reported, and only one patient in the CHCO cohort met criteria for intractable epilepsy. While these are encouraging results, further study is needed into the other features of 8p-related disorders that drive severity and how these features relate to the presence or absence of epilepsy.

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CRediT authorship contribution statement

Kaiti Syverson: Writing – review & editing, Software, Formal analysis, Data curation. **Andrea Miele:** Writing – review & editing. **Margarita Saenz:** Writing – review & editing. **Kristina Malik:** Writing – review & editing. **Megan Stringfellow:** Software, Data curation. **Katie Angione:** Writing – original draft, Data curation, Conceptualization. **Megan Abbott:** Writing – original draft, Investigation, Formal analysis, Conceptualization. **Scott Demarest:** Writing – review & editing, Supervision, Resources, Funding acquisition, Conceptualization. **Lauren Chaby:** Writing – review & editing, Formal analysis, Data curation. **Jacob Borello:** Writing – review & editing, Data curation. **Bina Maniar:** Supervision, Data curation, Conceptualization.

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