Profiling Seizures in Rare Diseases:
A Cross-Disease and Symptom-Based Analysis Using RARE-X Data

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BACKGROUND

Seizures & Rare Diseases: Seizures frequently occur in many rare diseases, complicating both diagnosis and management. Epilepsy, defined by recurring seizures, is a chronic neurological disorder caused by abnormal neuronal activity. Genetic mutations often influence the onset and progression of epilepsy, leading to diverse presentations and associated comorbidities. Understanding the full spectrum of seizure occurrence across different rare conditions is essential due to these complexities.

RARE-X: As the research arm of the non-profit rare disease organization Global Genes, RARE-X has developed a platform that empowers patients and patient advocacy groups (PAGs) to contribute data to support therapeutic research. Unlike traditional disease-specific approaches, RARE-X collects patient-reported data based on shared and unique symptoms.

Collaborating with over 100 PAGs, RARE-X represents more than 70 rare disorders and has enrolled around 7,000 participants. With 70% of the conditions involving neurological symptoms and 50-60% classified as neurodevelopmental disorders, RARE-X uses a hypothesis-agnostic approach to capture comprehensive data and enable cross-disease comparisons, uncovering patterns that might otherwise remain undetected.

OBJECTIVE

The objective of this proof-of-concept study was to conduct a cross-disease analysis of seizures in rare diseases using RARE-X data. We grouped the conditions based on the presence of seizures, which led to the selection of a diverse set of disorders, including neurodevelopmental conditions as well as other conditions where patients report seizures.

The conditions were then divided into two cohorts based on seizure frequency: High Seizure (HS: 50-85%) and Low Seizure (LS: 1-33%). These cohorts included 610 and 1,030 participants, respectively, encompassing a total of 246 patients with seizures and 299 without.

To explore the potential benefits of cross-disease comparisons, we focused on one condition (STXBP1). We first described the frequency of seizures within this group and the distribution of other prominent symptoms. Next, we compared the phenotypic profiles observed in STXBP1 to those of the HS and LS seizure cohorts.

Heatmaps were used to show the frequency of seizures in relation to selected neurodevelopmental symptoms, providing an overview of symptom co-occurrence across conditions. To further assess how the RARE-X data compared with external references, we reviewed the frequency of seizures for these 10 conditions as reported in the Genetic and Rare Diseases (GARD) database, which is managed by the NIH.

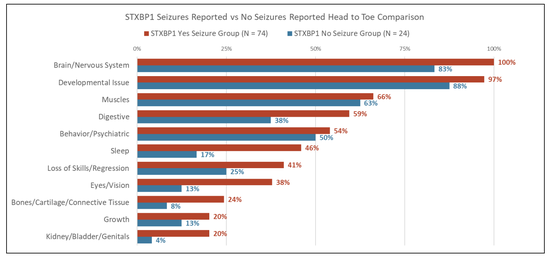
RESULTS

A. Seizure Frequencies in RARE-X and GARD

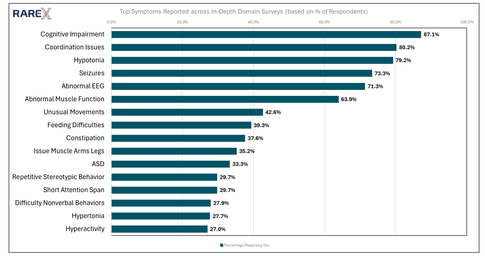
Group	Rare Disease	Enrollment-RARE-X	% Reporting Seizure-RARE-X	GARD (Seizure)
Low Seizure (LS)	Leber Hereditary Optic Neuropathy (LHON)	254	1.30%	Not Reported
	Wiedemann-Steiner Syndrome (WSS)	206	8.70%	Occasional
	FOXP1	211	10.10%	Occasional
	HCU	106	10.90%	Disease Not Listed
	Kleefstra	150	23.30%	Occasional
	Malan	103	32.70%	Occasional
High Seizure (HS)	CACNA1A	129	53.10%	Disease Not Listed
	STXBP1	174	73.20%	Disease Not Listed
	CHD2	200	84.30%	Disease Not Listed
	SYNGAP1	107	84.90%	Very Frequent

B. RARE-X Data: Disease Specific Profile (STXBP1)

STXBP1 (Yes vs No Seizures) - Head to Toe Survey

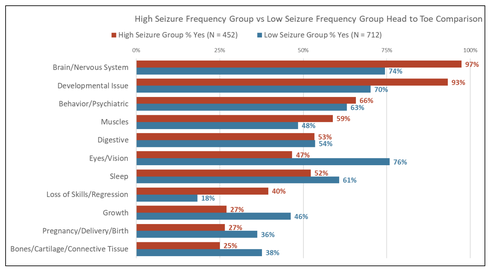


Top Symptoms Reported - Domain Surveys (Based on % of Respondents)

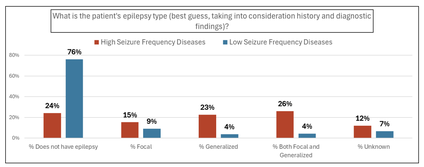


C. RARE-X Data: Cross-Disease Profile (HS vs. LS)

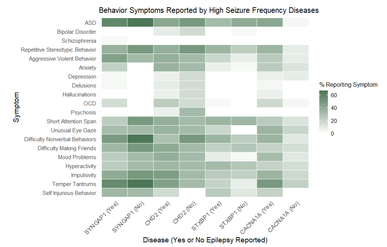
Head to Toe Survey

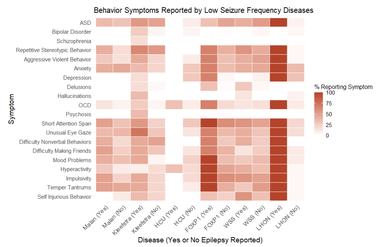


Epilepsy Type



Behavior and Psychiatric Symptoms by Disease





Diagnosis	Unusual Eye Gaze %		Anxiety %		Short Attention Span %		ASD %		Repetitive Stereotypic Behavior %		Psychosis %		Difficulty Nonverbal Behaviors %		Mood Problems %		Temper Tantrums %		Self Injurious Behavior %	
Epilepsy Reported	YES	NO	YES	NO	YES	NO	YES	NO	YES	NO	YES	NO	YES	NO	YES	NO	YES	NO	YES	NO
Kleefstra	73	30	36	22	55	24	55	49	64	54	36	0	45	49	45	5	45	22	36	22
Malan	36	38	43	46	50	32	36	32	43	18	0	0	43	20	43	34	50	46	0	11
WSS	43	31	43	46	57	49	43	53	57	44	0	0	43	27	29	36	29	52	57	33
CACNA1A	36	20	25	13	25	13	43	4	36	9	0	0	36	11	32	11	50	22	21	0
CHD2	37	33	37	33	39	33	43	50	39	50	7	33	30	50	39	33	46	33	17	0
STXBP1	19	0	7	3	36	35	33	41	36	24	0	0	36	24	9	3	21	8	25	11
SYNGAP1	32	33	22	0	24	50	59	67	38	50	0	0	49	67	24	33	57	67	35	33

Disease groups with at least 6 subjects in each epilepsy subgroup are included in this table. Groups where the percentage difference in specific symptoms between 'Yes' and 'No' subgroups is at least 20 percentage points (e.g., 50% vs 30%) are highlighted in:

-Red (greater in 'Yes')

-Blue (greater in 'No')

DISCUSSIONS & ACKNOWLEDGEMENTS

• Comparing RARE-X data with GARD revealed notable differences in the frequency of epilepsy. Additionally, some of the conditions included in RARE-X were not listed in GARD, highlighting the platform's ability to capture a broader spectrum of rare disorders and enhance real-world data collection.

• Our study showed how RARE-X's symptom-based data collection enables valuable cross-disease comparisons, which are crucial in rare diseases where small sample sizes can obscure key patterns. By leveraging patient-reported data, we gain insights into the frequency, co-occurrence, and impact of seizures, guiding more effective research and treatment strategies.

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