Estimating Patient Prevalence for Neurodevelopmental Disorders: The Emerging Face of FOXG1 Syndrome

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Abstract

Background and objectives: Understanding the scale of unmet need for specific severe neurodevelopmental disorders (NDD) remains very challenging, in part due to the many overlapping clinical features associated with global and developmental delays, and the variability of epilepsy phenotypes. FOXG1 Syndrome is a prime example of this challenge and requires definitive genetic diagnosis to be identified. We provide the first prevalence estimates of FOXG1 Syndrome based on genetic surveys of severe NDD patients.

Methods: We conducted a systematic literature review and meta-analysis of studies performing genetic testing panels on cohorts of severe NDD within the last ten years. We compiled 13 studies (after omitting one outlier enriched for FOXG1 patients), totaling nearly 36,000 severe NDD pediatric patients.

Results: The proportion of severe NDD attributed to FOXG1 was 0.20% [95% CI: 0.16 – 0.25%]. For comparison, MECP2 and CDKL5 patients accounted for 0.55% [95% CI: 0.48 – 0.64%] and 0.34% [95% CI: 0.28 – 0.40%], respectively. This corresponds to an estimated prevalence of 0.6 – 2.2 FOXG1 patients per 100,000 children or ~420 – 1600 pediatric patients in the United States. The estimated prevalence of CDKL5 patients was 1.8 – 6.6 cases per 100,000 female children, and the estimated prevalence of MECP2 patients was 3.5 – 13.2 cases per 100,000 female children.

Conclusions: FOXG1 Syndrome was previously considered an ultra-rare indication potentially occurring in ~1 per million children. Our analysis based on genetic testing demonstrates the FOXG1 patient population is expected to be approximately one third the size of MECP2 patients largely associated with Rett Disease. Uncoupled from Rett Disease clinical criteria, both FOXG1 Syndrome and CDKL5 Deficiency represent distinct and sizable patient populations. This shows the value of genetic testing in diagnosing these diseases and paints a more up-to-date picture of the scale of unmet need, that will support further drug development strategies.

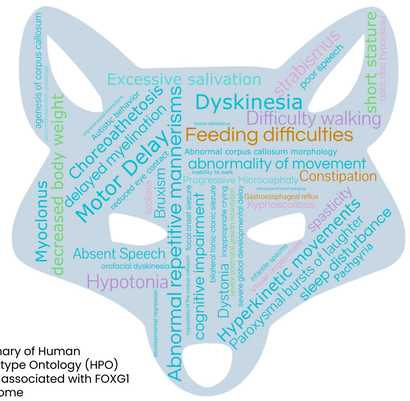
Plain Language Summary

In this study, we tackled the challenge of determining the prevalence of a rare disease called FOXG1 Syndrome. By reviewing genetic data from around 36,000 patients with severe neurodevelopmental disorders, we found that FOXG1 Syndrome is more common than previously thought. Our estimates suggest there are currently between 420 and 1600 children with FOXG1 Syndrome in the United States. Surprisingly, this places FOXG1 Syndrome in a comparable range to other rare diseases like Rett Disease (MECP2) and CDKL5 Deficiency. This research sheds light on the true prevalence of FOXG1 Syndrome, offering valuable insights for healthcare planning and strategies for new drug development.

Methods

Systematic literature review: We used a deductive strategy, searching for "FOXG1" and related terms and excluding cancer, neoplasm, oncology and related MESH terms in Pubmed. We further filtered on human studies to generate the initial scoping pool of 282 papers. Iterative literature search was also supported by AI tools (www.semanticscholar.org) using a training set of included papers.

About FOXG1 Syndrome



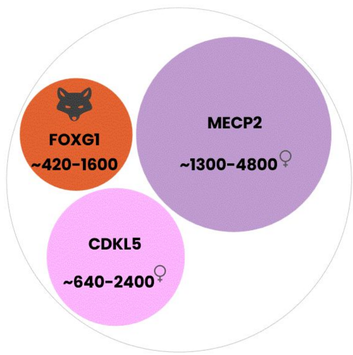
Summary of Human Phenotype Ontology (HPO) terms associated with FOXG1 Syndrome

FOXG1 Syndrome is characterized by:

- Severe global developmental delay
- Microcephaly
- Speech and motor dysfunction
- Often associated with epileptic seizures
- Autosomal dominant (*de novo*) variants in the FOXG1 gene, resulting in haploinsufficiency
- FOXG1 encodes for the Forkhead Box G1, regulating transcription in the neurogenic niche and in fully differentiated adult neurons
- Genetic testing is required for definitive diagnosis

Results

Estimated Number of Pediatric Patients in the United States with Severe Neurodevelopmental Disorders Attributed to MECP2, CDKL5 or FOXG1 Genetic Variants



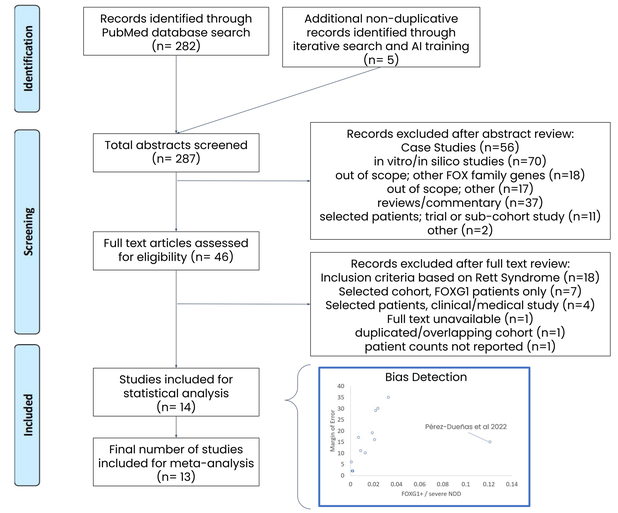
Gene	Estimated Prevalence Range[1]	Previously Reported Prevalence [95%CI]	Associated Disorders (ORPHA codes)
MECP2	3.5-13.2 per 100,000 female children	7.1 [4.8-10.5] per 100,000 female children[2]	Rett Syndrome (778); Atypical Rett Syndrome (3095); Severe neonatal-onset encephalopathy with microcephaly (209370); Autism (106); X-linked intellectual disability-psychosis-macroorchidism syndrome (3077)
CDKL5	1.8 -6.6 per 100,000 female children	4.4 [1.5 -10.3] per 100,000 female children[3]	CDKL5 deficiency (505652); Atypical Rett Syndrome (3095); Early infantile epileptic encephalopathy (1934)
FOXG1	0.6 -2.2 per 100,000 children		FOXG1 Syndrome (561854); Atypical Rett Syndrome (3095); non-specific early-onset epileptic encephalopathy (442835)

1 | Literature based benchmarking indicates severe neurodevelopment disorders occur in 0.3% - 1.1% of all children. See CDC Report from Zablotsky *et al* Pediatrics (2019) and related references.
2 | Petriti *et al*, Global Prevalence of Rett Syndrome: Systematic Review and Meta-analysis. Syst. Rev (2023)
3 | Symonds *et al*, Incidence and phenotypes of childhood-onset genetic epilepsies: a prospective population-based national cohort. Brain (2019)

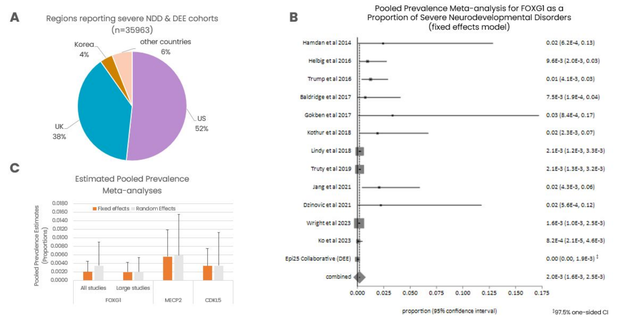
Methods (Continued)

Primary inclusion and exclusion criteria: Patients diagnosed with severe neurodevelopmental disorders AND undergoing genetic testing for at least FOXG1, MECP2 and CDKL5 genes. Excluding patient cohorts selected for trials or other limiting criteria.

PRISMA literature review summary. Initial scoping and iterative review. Bias detection (inset) for papers included for statistical analysis were evaluated for enrichment of FOXG1 patients and excluded from meta-analysis.



Pooled Prevalence Meta-analysis: Pooled prevalence was calculated by inverse variance with fixed effect weighting. Heterogeneity was assessed by I^2 (74.7%; 95% confidence interval: 52.2-84.1% for FOXG1 meta-analysis). For comparison, random effects modeling was also calculated, as well as pooled prevalence proportions with only large studies of 300+ patients per cohort. Software: StatsDirect (v3.3.6)



A | Total number of pooled patients evaluated and country reporting.
B | Forest plot for pooled prevalence meta-analysis for FOXG1 (all studies)
C | Summary results for all meta-analysis conducted, including MECP2 and CDKL5, as a pooled proportion of severe Neurodevelopmental Disorder patients

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