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Clinical factors associated with genetic diagnosis in suspected neurogenetic disorders in a tertiary care clinic

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Author Contributions

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Ethics Declaration

Research approval was granted by the UCLA Medical Institutional Review Board 3. A total of 110 patients and/or their legal guardians provided informed consent for prospective collection of clinical data (UCLA IRB#: 14-001908). With an IRB-approved waiver of consent, the charts of an additional 206 patients were retrospectively reviewed (UCLA IRB#: 19-000121).

Conflict of Interest

Sunil Mehta acted as a paid consultant to Mirium Pharmaceuticals. All other authors declare no conflicts of interest.

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Abstract

Purpose: This study aimed to identify phenotypic factors associated with genetic diagnoses in patients with neurodevelopmental disorders and generate a decision tree to assist clinicians in identifying patients most likely to receive a positive result on genetic testing.

Methods: We retrospectively reviewed the charts of 316 patients evaluated in a neurodevelopmental clinic between 2014 and 2019. Patients were categorized based on genetic test results. Analyses were performed to identify variables that discriminate between patients with and without a genetic diagnosis.

Results: Patients with a genetic diagnosis were more likely to be female and have a history of motor delay, hypotonia, congenital heart disease, and early intervention. Classification and regression tree analysis revealed that 75% of patients with motor delay had a genetic diagnosis. In patients without motor delay, hypotonia, age of walking, and age at initial evaluation were important indicators of a genetic diagnosis.

Conclusion: Our findings suggest that motor delay and hypotonia are associated with genetic diagnoses in children with neurodevelopmental disorders. The decision tree highlights patient subsets at greater risk and suggests possible phenotypic screens. Future studies could develop validated decision trees based on phenotypic data to assist clinicians in stratifying patients for genetic testing.

Keywords

Genetic diagnosis; Genetic testing; Motor delay; Neurodevelopmental disorders; Neurogenetics

Introduction

Neurodevelopmental disorders (NDDs), such as global developmental delay, autism spectrum disorder (ASD), and intellectual disability, have high heritability (ie, the proportion of variation in a trait within a population that can be attributed to genetic differences among individuals) and affect individuals across their life span.[1] With rapid advances in genetic testing, an increasing number of individuals with NDDs can now receive a genetic diagnosis.[2] Hundreds of genetic variants have been implicated in NDDs, including chromosomal rearrangements, insertions and deletions, copy-number variants (CNVs), and single-nucleotide variants (SNVs).[2] Genetic testing for NDDs with chromosomal microarray (CMA) to identify CNVs results in a diagnostic yield of 10% to 20%, whereas the addition of exome sequencing (ES) to identify SNVs results in a diagnostic yield of >40%.[3]

Genetic analysis has previously been performed as part of large-scale genomic research studies, which include patients with a range of complexity levels of NDDs, from very

mild to more severe, identified through broad-based recruitment strategies.[4,5] Genotype-phenotype analyses within these cohorts demonstrate that individuals with heterogeneous NDDs and a genetic diagnosis have an increased frequency of medical comorbidities, such as impaired gastrointestinal motility,[6] epilepsy,[7,8] heart disease,[9,10] and kidney/urinary problems,[10,11] compared with individuals with NDDs without a genetic diagnosis. Likewise, individuals with ASD and a genetic diagnosis are significantly more likely to have a history of motor delay relative to IQ-matched controls with ASD without a genetic diagnosis.[12,13] Our clinic patients differ from these previous cohorts because we specifically select for individuals with high-complexity known or suspected neurogenetic disorders that would benefit from subspecialist management in an outpatient, multidisciplinary, tertiary care clinic. Therefore, our study is susceptible to sampling bias for patients with NDDs of enhanced medical and psychiatric complexity, whereas previous studies were susceptible to self-selection bias. That is, study individuals chose to participate in genomics research studies based on their own motivations or interests.[14] Strict selection criteria (eg, exclusion of individuals with very low mental functioning or a history of birth trauma[4]) may also have biased these genomic research cohorts toward lower complexity subjects.

Here, we investigate phenotypic factors associated with a genetic diagnosis in patients with NDDs from a high-complexity clinical sample recruited at the UCLA Care and Research in Neurogenetics (CARING) Clinic, a tertiary care neurogenetics clinic to (1) examine clinical features that have been identified in previous community cohorts, (2) identify novel factors associated with a genetic diagnosis specific to patients with NDDs in an academic health care system clinic setting, and (3) generate a classification tree that may assist clinicians in identifying which set of factors, among patients with NDDs, are most effective in discriminating between those with and without a positive result on genetic testing.

Materials and Methods

Study design

Research approval was granted by the University of California Los Angeles (UCLA) Medical Institutional Review Board (IRB) 3.

A total of 110 patients and/or their legal guardians provided informed consent for prospective collection of clinical data (UCLA IRB#: 14-001908). With an IRB-approved waiver of consent, the charts of an additional 206 patients were retrospectively reviewed (UCLA IRB#: 19-000121). Upon manual extraction from the UCLA electronic health record (EHR) (D.J.A., N.R.W.), all patient data were coded into an encrypted database. Seventy patients were excluded from final analysis because they never received genetic testing because of lack of completion of ordered tests or lack of insurance authorization for genetic tests (Figure 1). Patients were included in one of the study cohorts if they had a known or suspected neurogenetic disorder and had completed at least 1 genetic test, such as CMA, fragile X testing, mitochondrial DNA testing, single-gene sequencing, or ES, with test results available to the study team. ES generally did not report CNVs. We extracted variants and their classification (ie, pathogenic, likely pathogenic, likely benign, or as variant(s) of uncertain significance [VUS]) from clinical reports. Patients with negative findings on

genetic testing were included in the study as well because they had a suspected, but not confirmed, neurogenetic disorder.

We delineated 3 cohorts based on genetic test results (Figure 1): (1) the pathogenic or likely pathogenic (P/LP) cohort included patients whose genetic testing revealed a P/LP variant or other definitive molecular diagnosis; (2) the negative cohort included patients whose genetic test revealed no P/LP variants but could have had likely benign variants, VUS, or no reported variants regardless of type of testing; and (3) the ES negative cohort was a subset of the negative cohort and included only those patients who had ES completed without a P/LP or VUS variant identified. In creating this third cohort with more stringent negative criteria, we ensured that all included patients did not have a P/LP SNV within a gene-coding region. This allowed us to ensure that individuals in the negative comparator cohort were accurately classified and that associations between a genetic diagnosis and clinical factors were not confounded by misclassification of individuals with P/LP SNVs within the negative cohort.

Potential confounding factors included the following sociodemographic variables: sex, age of presentation to the UCLA CARING Clinic, ethnicity, and socioeconomic status as measured by area deprivation index (ADI) (Table 1) and the relative frequency of NDD diagnoses (Table 2). The ADI represents a neighborhood's level of socioeconomic deprivation and is associated with health outcomes.[15] ADI was determined from the reported address of residence in the EHR. The independent variables of interest that we examined included the ages of sitting, walking, first word, and first phrase and a history of the following: motor delay, hypotonia, language delay, neurological diagnosis, seizures, congenital heart disease, attention-deficit/hyperactivity disorder, macrocephaly, microcephaly, head circumference percentile, and early intervention. Patients were coded as having a history of motor delay if 1 or more clinician documented them as such in the EHR, or if 1 or more gross milestones were reported to occur after 8 months for sitting, 12 months for crawling, and 16 months for walking based on the 97th percentiles reported for normative data by the World Health Organization.[16] Similarly, patients were coded as having a history of language delay if 1 or more clinicians documented them as such in the EHR or if 1 or more expressive language milestones were reported to occur after 12 months for first words and 24 months for first phrases (ie, combined words) based on the Act Early Centers for Disease Control and Prevention Recommendations.[17] A history of early intervention was coded if a patient received services and/or supports for developmental disabilities before the age of 3.[18] Macrocephaly was assigned when a patient's occipitofrontal circumference was greater than 2 standard deviations above the mean for his or her given age and sex (ie, >97th percentile); microcephaly was assigned when a patient's occipitofrontal circumference was greater than 2 standard deviations below the mean for his or her given age and sex (ie, <3rd percentile).[19]

Statistical analyses

To investigate associations between genetic diagnosis and clinical characteristics, we used a 2-step analytical approach. First, we conducted χ^2 tests for all binary clinical variables and 2-sample Wilcoxon tests for continuous variables to identify potentially significant associations. Full results of the preliminary analyses are provided in the supplemental

materials for transparency (Supplemental Tables 1 and 2). This preliminary analysis served as an exploratory step to guide our subsequent modeling. To maintain statistical power and reduce the risk of overfitting, given our sample size constraints, we then performed a logistic regression analysis incorporating only the clinical characteristics that showed the strongest associations in the initial analyses. Regression was performed between (1) the P/LP cohort (2) the negative cohort (Figure 2A), and (3) the ES negative cohort (Figure 2B). We present means and standard deviations for continuous variables and counts and relative frequencies for categorical variables. This approach allowed us to focus on the most salient features while preserving model stability. The logistic regression models were controlled for age (in months), ethnicity, and ADI. We considered each clinical characteristic individually and developed regression models using genetic diagnosis as the primary outcome variable. We then used classification and regression tree analysis (CART) to identify combinations of sociodemographic and clinical variables that effectively discriminate between patients with and without a genetic diagnosis. The CART procedure was performed on the entire data set of patients whose genetic testing results were available ($N = 246$). All analyses were performed in SAS 9.4 (SAS Institute) and RStudio (2023). CART was performed using the R package “rpart” (Therneau and Atkinson, 2022).

Results

Cohort description

Referrals to the UCLA CARING Clinic came from physicians within and outside an academic health system, patient advocacy groups (eg, Dup15Q Alliance), and research studies for patients with known or suspected neurogenetic disorders. As the clinic became known in the community, an increasing number of families were self-referred. Of the 316 patients evaluated in a multidisciplinary academic health system clinic between January 1, 2014, and January 1, 2019, 246 patients had completed genetic testing with results available in the EHR and were included in this study. Of those who had completed genetic testing, 153 of 246 (62%) received all their testing before clinic referral, 47 of 246 (19%) received some testing before the clinic and some additional testing after referral, whereas 46 of 246 (19%) patients received all of their testing after referral. Of this group of 246 patients with completed genetic testing, 152 (61.8%) patients were found to have a P/LP variant, and 94 (38%) patients were found to have no variants, benign variants, or VUS (ie, the negative testing cohort). For the P/LP cohort, patients had 62 different genetic diagnoses, with 12 genetic diagnoses being shared by 2 or more patients (ie, recurrent genetic diagnoses) and 50 different genetic diagnoses each being present in only a single patient (ie, nonrecurrent genetic diagnoses).

The negative cohort underwent the following tests: CMA (76 patients), FMR1 CGG repeat analysis (21 patients), metabolic testing (10 patients), PTEN testing (4 patients), mitochondrial DNA testing (3 patients), and MECP2 testing (2 patients). From this negative cohort, 33 patients also underwent ES, which we used as an additional negative control group. Of the ES negative cohort, 25 of 33 patients (76%) had undergone CMA before ES. In the negative cohort, the most common prior test was CMA (76 of 94 patients), with ES frequently recommended but not completed. On average, patients who did not receive

ES lived in neighborhoods with significantly higher ADI (ADI of ES noncompleters vs ES completers: 9.9 vs 6.7, $t = -2.6$, $P = .009$) and were more likely to have uncertain insurance status, meaning that no insurance could be found on file in the EHR (10% of noncompleters vs 3% of completers).

Patients with a P/LP variant were more likely to be female (47% compared with 20% and 12% in the negative and ES negative [$P < .001$]). The average age of presentation in the study group was 9.4 years (range: 2 months-36.7 years). There was no significant difference in age of presentation between the 3 cohorts. There were similar proportions of patients self-identifying as White, Black or African-American, Asian, and Hispanic across the 3 cohorts, with White being the predominant ethnicity (Table 1).

Genotype-phenotype analysis

We aimed to determine which specific patient characteristics were associated with the presence of P/LP variant in patients with suspected neurogenetic disorder. Utilizing logistic regression (as depicted in Table 3, Figure 2), we discovered that patients with a history of motor delay had an increase in the odds of having a P/LP variant compared with those without a history of motor delay. This heightened risk was maintained in comparison with both control cohorts (negative cohort: odds ratio [OR] = 4.3, $P \leq .0001$; ES negative cohort: OR = 6.0, $P = .0001$). Furthermore, for every 1-month delay in the age of walking noted by the caregiver, a patient's odds of carrying a P/LP variant increased 5% to 11%. A history of hypotonia (OR = 5.6, $P \leq .0001$; OR = 4.7, $P = .0019$), congenital heart disease (OR = 3.9, $P = .003$; OR = 11.30, $P = .02$), and early intervention (OR = 2.1, $P = .01$; OR = 2.4, $P = .05$) were all similarly associated with increased odds of having a P/LP variant. In comparison with the ES negative cohort, a history of language delay also emerged as significantly associated with a P/LP variant (OR = 3.2, $P = .03$).

Patient classification

In CART analysis, the final tree (Figure 3) achieved a robust overall correct classification rate of 76% among an analytical sample of $N = 246$, albeit with a cross-validated error rate of 32%. The primary (parent) node emerging from this analysis was motor delay. Notably, 62% of our analytical sample had a history of motor delay, and among these patients, this node alone correctly classified 75% (114/152) as having a P/LP variant or genetic diagnosis.

In the subset of patients who did not report a history of motor delay, among those who were biologically female, we identified 70% (16/23) as also having a genetic diagnosis. The ensuing node identified was hypotonia, followed by the age of walking and the age at the initial evaluation at the CARING Clinic (Figure 3). In biologically male patients with a confirmed history of hypotonia, 78% (7/9) of those who commenced walking at 13 to 16 months had received a genetic diagnosis, compared with 29% (2/7) of their counterparts who began walking before 13 months. For biologically male patients without a known history of hypotonia, 81% (42/52) of those evaluated at the CARING Clinic before reaching 24.3 years of age did not have a genetic diagnosis. The final subset, comprising biologically male patients without a history of hypotonia, who received their initial evaluation at the CARING

Clinic at or after 24.3 years of age, was limited in number. However, all members of this group (100%; 3/3) had a P/LP variant.

Discussion

Consistent with previous reports,[12,13] we found that female sex was associated with increased likelihood of having a genetic diagnosis, likely reflecting the higher mutational burden required for females to manifest NDDs.[20] Motor delay and hypotonia also emerged as being strongly associated with a genetic diagnosis, with a 5% to 11% increase in the likelihood of a P/LP variant associated with each 1-month delay in walking. This finding aligns with previous studies showing a 17% increased risk per 1-month delay and suggests that hypotonia should prompt clinicians to carefully screen for motor impairment and consider genetic testing.[13]

Congenital heart disease was significantly associated with genetic diagnosis in our sample, consistent with prior reports.[21] Interestingly, epilepsy did not emerge as a significant covariate, possibly due to insufficient power or referral bias related to the presence of neurology in our multidisciplinary clinic leading to an enrichment of patients with pure epilepsy without other features of neurogenetic disorders. We did not observe differences between our 2 negative cohorts, suggesting that the negative cohort was not substantially diluted by patients without ES who carried undetected SNVs, potentially reflecting the ability of genetics experts to identify patients with high pretest probability of a positive finding and more aggressively pursuing ES. Notably, patients who did not complete ES lived in neighborhoods with higher ADI scores, a measure of socioeconomic deprivation, and were more likely to have uncertain insurance status, highlighting ongoing challenges with equitable access to genetic testing. Although professional societies recommend testing for all patients with NDDs,[22–24] the optimal approach to prioritization in resource-limited settings remains unclear.

Our CART analysis suggests the potential utility of motor delay and hypotonia as phenotypic screens to identify patients most likely to benefit from genetic testing, with an overall accuracy rate of 76%. However, we acknowledge that our sample reflects high-complexity patients and that our data are cross-sectional; therefore, we are unable to establish temporal ordering between patient and clinical characteristics and our outcome. Additionally, the model's classification accuracy may have been limited by missing milestone data and unstandardized clinician notes, indicating the need for higher-powered, prospective studies with more complete phenotyping.[25]

In summary, our findings confirm and expand previous work identifying motor delay and hypotonia as key phenotypic differences between individuals with NDDs with and without a genetic diagnosis from ES or other tests more broadly. The decision tree represents a preliminary, exploratory step toward the development of accurate, validated algorithms to guide genetic testing decisions. Future large-scale studies integrating high-quality phenotypic data could enable the creation of clinically useful decision support tools to help stratify patients with NDDs for genetic testing.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability

The data sets generated and/or analyzed during the current study are not publicly available because of patient privacy laws but are available from the corresponding author upon request.

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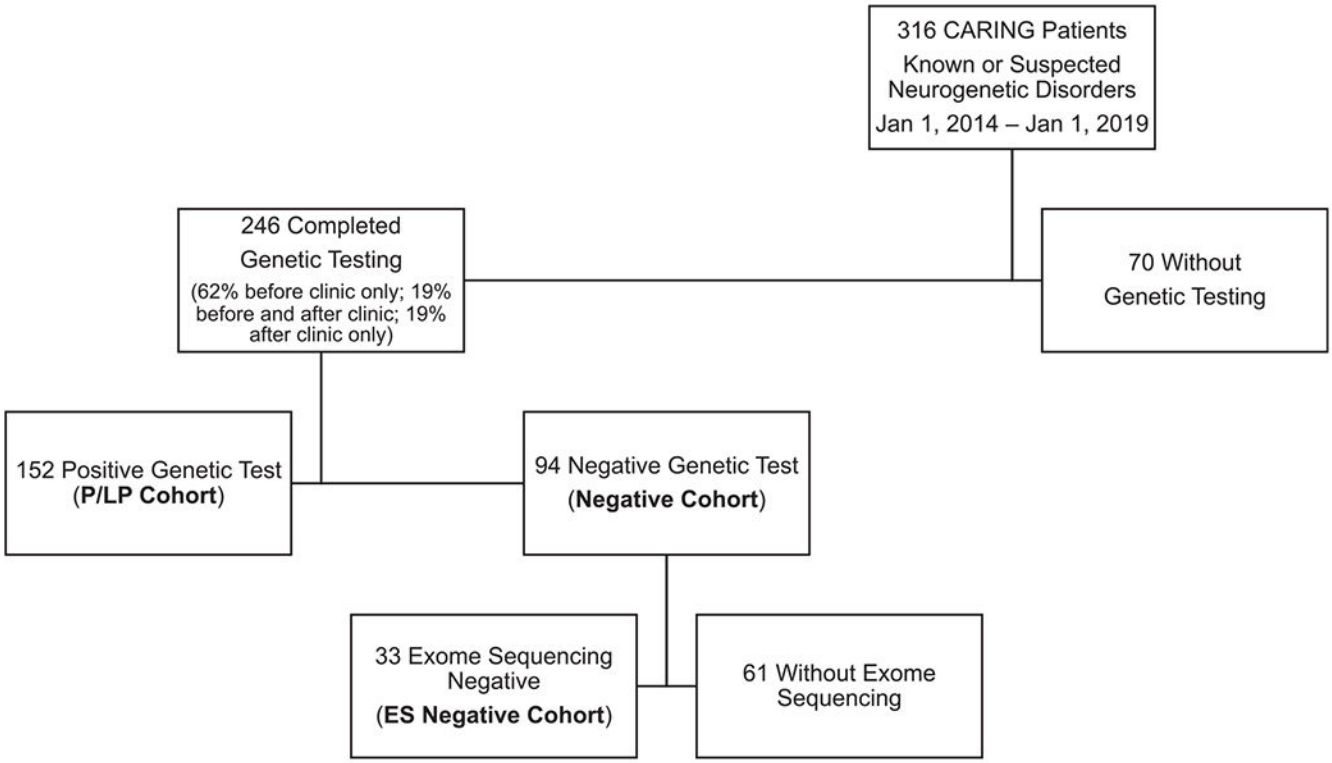

Figure 1. Patient flow in CARING Clinic (2014-2019).
P/LP, pathogenic/likely pathogenic.

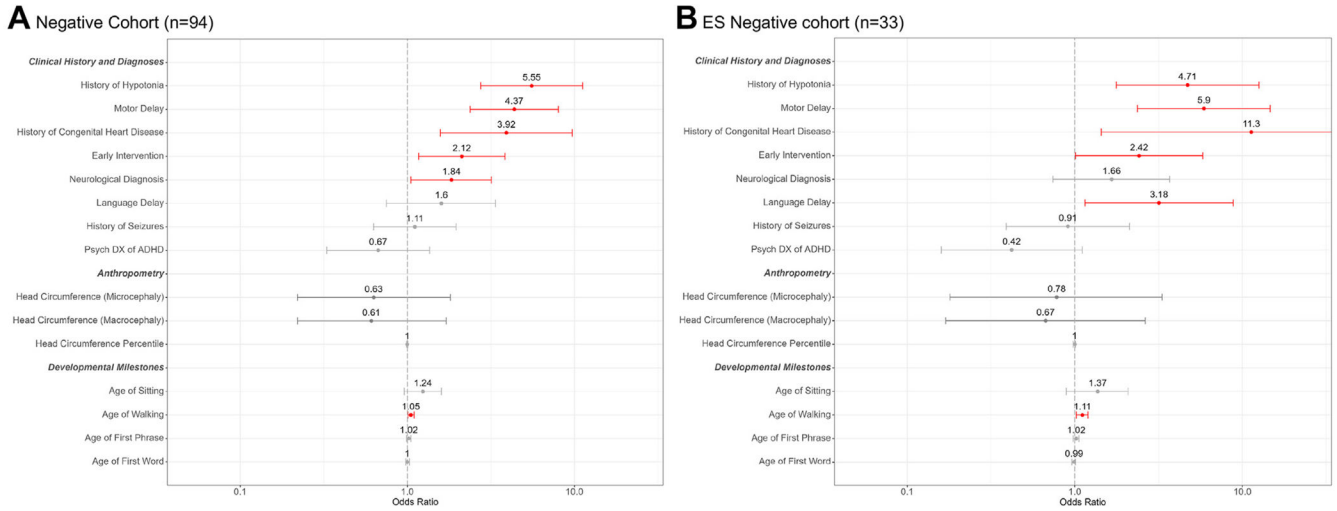

Figure 2. Association of phenotypic factors with having a genetic diagnosis compared with the negative cohort and the ES negative cohort.

A. Negative cohort. B. ES negative cohort, where the association between history of congenital heart disease and genetic diagnosis has a very large upper limit (odds ratio = 11.30, 95% CI 1.44-88.77), likely due to sparsity and/or instability in this estimate. The figure above thus does not show the upper limit to ensure that the rest of the associations can be visualized clearly. ADHD, attention-deficit/hyperactivity disorder; ES, exome sequencing. Red points and confidence intervals indicate factors with statistically significant associations with genetic diagnosis ($p < 0.05$), while gray represents non-significant associations.

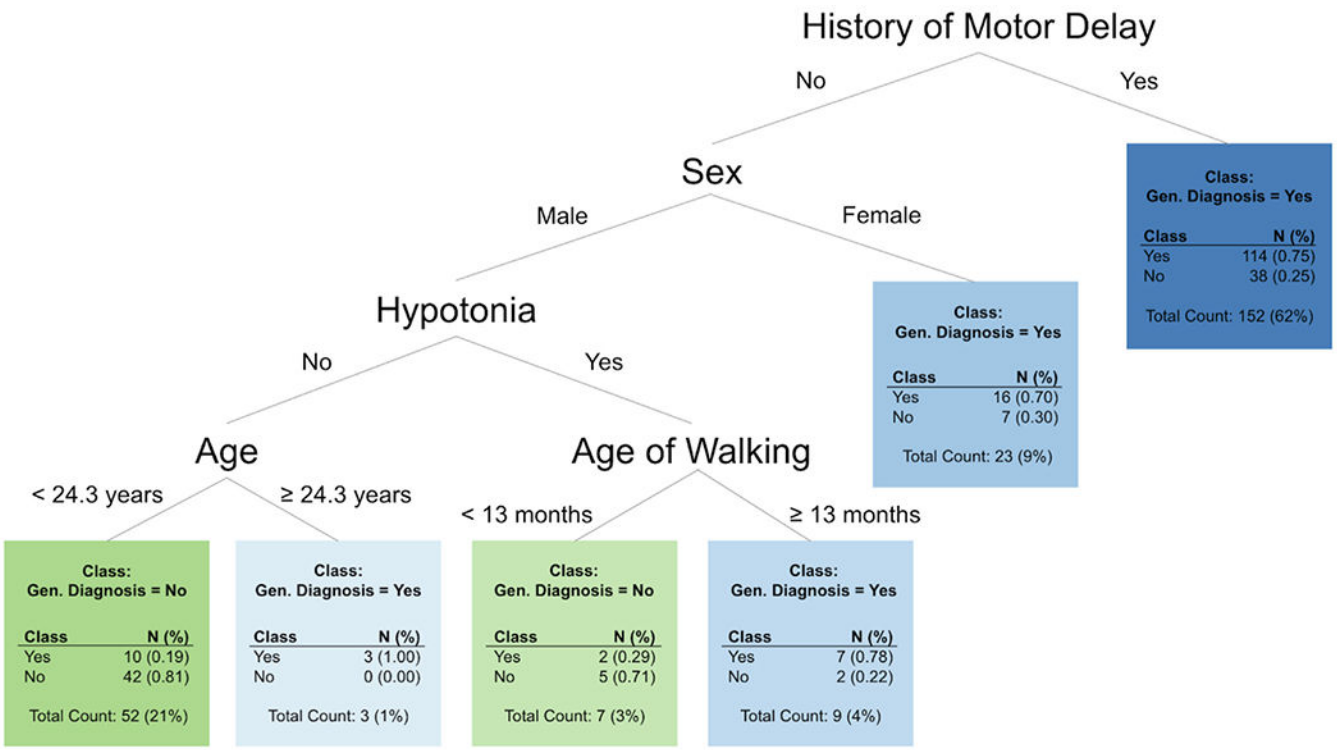

Figure 3. Classification and regression tree analysis of CARING patients who received genetic testing.

Terminal nodes (boxes) shaded in blue represent patient groups classified as having a genetic diagnosis. Groups at high-likelihood for genetic diagnosis are identified by blue-colored boxes. The percentages specify the accuracy of our model's classification at each terminal node (eg, for the "History of Motor Delay = yes" node, our model correctly identified 75% of the patients with a genetic diagnosis at that node). The total counts specify the fraction of the entire data set within each terminal node.

Table 1

Demographic traits of CARING Clinic cohorts

	P/LP Cohort (*n* = 152)			Negative Cohort (*n* = 94)			ES Negative Cohort (*n* = 33)		
Trait	**Median**	**Mean**	**SD**	**Median**	**Mean**	**SD**	**Median**	**Mean**	**SD**
Age (mo)	78.0	111.6	96.6	93.5	112.4	78.7	77.8	100	62.5
ADI	5.0	8.1	8.8	6.0	10.3	11.5	3.0	7.5	9.1
	n		**%**	***n***		**%**	***n***		**%**
Female	71		47.7	19		21.2	4		12.1
Male	81		53.3	75		79.8	29		87.9
White	85		55.9	53		56.4	20		60.6
Hispanic	30		19.7	18		19.1	6		18.2
Asian	20		13.2	16		17.0	6		18.2
Black	1		0.7	1		1.1	0		0
Other or unknown race	16		10.5	6		6.4	1		3.0

ADI, area deprivation index; *ES*, exome sequencing; *n*, number; *P/LP*, pathogenic/likely pathogenic.

Table 2

Neurodevelopmental diagnoses of CARING Clinic cohorts

	P/LP Cohort (*n* = 152)		Negative Cohort (*n* = 94)		ES Negative Cohort (*n* = 33)	
Neurodevelopmental Diagnoses	***n***	**%**	***n***	**%**	***n***	**%**
GDD	119	78.3	57	60.6	18	54.5
ASD	104	68.4	85	90.4	27	81.8
ID	63	41.4	38	40.4	13	39.4

ASD, autism spectrum disorder; *GDD*, global developmental delay; *ID*, intellectual disability; *n*, number; *P/LP*, pathogenic/likely pathogenic.

Table 3

Phenotypic comparison of patients with and without a genetic diagnosis

	P/LP Cohort (*n* = 152)		Negative Cohort (*n* = 94)		ES Negative Cohort (*n* = 33)		P/LP vs Negative		P/LP vs ES Negative	
Trait	***n***	**%**	***n***	**%**	***n***	**%**	**OR (CI)**	***P***	**OR (CI)**	***P***
Early intervention	108	71.1	52	55.3	19	57.6	2.1 (1.2-3.9)	**.01**	2.4 (1.0-5.8)	.05
Gross motor delay	111	73.0	37	39.4	13	39.4	4.3 (2.3-8.0)	**<.0001**	6.0 (2.4-14.7)	**.0001**
Hypotonia	81	53.2	19	20.2	9	27.3	5.6 (2.8-11.2)	**<.0001**	4.7 (1.8-12.6)	**.002**
Language delay	129	84.9	75	79.8	23	69.7	1.6 (0.8-3.4)	.2	3.2 (1.2-8.8)	**.03**
Epilepsy	67	44.1	35	37.2	11	33.3	1.1 (0.6-2.0)	.7	0.9 (0.4-2.1)	.8
Congenital heart disease	30	19.7	8	8.5	1	3.0	3.9 (1.6-9.7)	**.003**	11.3 (1.4-88.8)	**.02**
Macrocephaly	12	7.9	11	11.7	5	15.2	0.6 (0.2-1.7)	.4	0.7 (0.2-2.6)	.6
Microcephaly	13	8.6	9	9.6	4	12.1	0.6 (0.2-1.8)	.4	0.8 (0.2-3.3)	.7
ADHD	22	14.5	22	23.4	10	30.3	0.7 (0.3-1.3)	.3	0.4 (0.2-1.1)	.1
Neurologic diagnosis	99	65.1	47	50.0	17	51.5	1.8 (1.1-3.2)	**.03**	1.7 (0.7-3.7)	.2
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**OR (CI)**	***P***	**OR (CI)**	***P***
Head circumference percentile	48.6	39.6	55.5	40.3	57.2	42.0	1.0 (1.0-1.0)	.9	1.00 (1.0-1.0)	.8
Age of sitting (mo)	10.9	9.6	7.8	2.04	7.4	2.3	1.2 (1.0-1.6)	.1	1.4 (0.9-2.1)	.1
Age of walking (mo)	21.6	12.1	16.9	9.7	15.7	5.2	1.1 (1.0-1.1)	**.03**	1.1 (1.0-1.2)	**.02**
Age of first word (mo)	24.3	18.6	22.4	17.5	24.9	23.8	1.0 (1.0-1.0)	.8	1.0 (1.0-1.0)	.4
Age of first phrase (mo)	43.5	22.4	33.8	18.4	31.3	19.2	1.0 (1.0-1.0)	.2	1.0 (1.0-1.0)	.3

P values < .05 are in bold.

ADHD, attention-deficit/hyperactivity disorder; *CI*, confidence interval; *ES*, exome sequencing; *n*, number; *OR*, odds ratio; *P/LP*, pathogenic/likely pathogenic.