Northgate Children's Genetics Center

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PEDIATRIC GENETICS — CLINICAL CONSULTATION AND GENETIC TEST RESULTS

Whole Exome Sequencing Report: CTNNB1 Neurodevelopmental Disorder

Patient (Child):	[Sample Child]	**MRN:**	NCG-0000001
Date of Birth:	August 3, 2021 (Age: 3 years, 5 months)	**Date of Report:**	January 14, 2025
Sex:	Female	**Date of Visit:**	October 22, 2024
Parents / Guardians:	[Sample Parent 1] and [Sample Parent 2]	**Referring Physician:**	Dr. [Sample Pediatrician], MD
Attending Geneticist:	Dr. [Sample Geneticist], MD, PhD Board Certified, Clinical Genetics	**Genetic Counselor:**	[Sample Counselor], MS, CGC

REASON FOR REFERRAL

[Sample Child] is a 3-year-old girl referred by her developmental pediatrician for genetic evaluation in the context of global developmental delay, absent speech, truncal hypotonia, lower limb spasticity, and strabismus identified over the first two years of life. She had previously been evaluated for autism spectrum disorder (ASD) and cerebral palsy (CP); neither diagnosis was felt to fully account for her clinical picture. Parental concern first arose at the 9-month well-child visit when she had not yet achieved sitting without support. Whole exome sequencing (WES) was recommended following a non-diagnostic chromosomal microarray (CMA) in June 2024.

DEVELOPMENTAL AND MEDICAL HISTORY

Pregnancy and birth history:

Uncomplicated dichorionic diamniotic twin pregnancy. [Sample Child] is Twin B. Birth weight 2.61 kg (10th percentile), length 47 cm (15th percentile), head circumference 31.8 cm (3rd percentile — microcephaly noted at birth). APGAR scores 8 and 9 at 1 and 5 minutes. No NICU admission. Twin A is developmentally typical with no reported concerns.

Developmental milestones:

Milestone	Expected Age	Achieved Age	Status
Social smile	6–8 weeks	8 weeks	Normal
Head control	3–4 months	5 months	Mildly delayed
Rolling (front to back)	4 months	7 months	Delayed
Sitting without support	6–8 months	18 months	Significantly delayed
Pulling to stand	9–12 months	Not yet achieved	Not achieved
Walking independently	12–15 months	Not yet achieved	Not achieved (age 3y5m)

First words	12 months	No words produced	Absent
Two-word phrases	24 months	No words produced	Absent
Pincer grasp	9–10 months	18 months	Delayed
Pointing to objects	12 months	28 months	Significantly delayed

Medical history:

Recurrent otitis media (4 episodes, bilateral pressure equalization tubes placed at 18 months). Strabismus (esotropia) diagnosed at 14 months; corrective glasses prescribed, ophthalmology follow-up ongoing. Constipation (managed with dietary modification and PEG 3350). Feeding difficulties in infancy requiring thickened feeds; swallowing study at 10 months showed mild oral-phase dysphagia, resolved by 24 months. Sleep disturbance (frequent night waking, difficulty with sleep initiation). No seizures to date; EEG at 24 months within normal limits. No cardiac anomalies on echocardiogram.

Family history:

Non-consanguineous parents. No family history of intellectual disability, developmental delay, seizure disorders, or chromosomal abnormalities. Maternal and paternal grandparents healthy. Twin sibling (Twin A, male) developmentally typical. Parental testing performed as part of this workup — see Genetic Results below.

PHYSICAL EXAMINATION

Anthropometrics	Weight: 13.2 kg (25th %ile). Height: 93 cm (10th %ile). Head circumference: 46.1 cm (<3rd %ile — microcephaly, -2.8 SD).
General	Alert, interactive, non-verbal. Friendly affect. Makes eye contact inconsistently. No apparent distress.
Craniofacial	Microcephaly as noted. Broad, flat nasal bridge. Thin upper lip vermillion. Long philtrum. Mildly upslanting palpebral fissures. Low-set, posteriorly rotated ears. Sparse hair at frontal hairline.
Eyes	Esotropia (right eye). Corrective lenses in place. Fundoscopic exam limited; ophthalmology to evaluate for exudative vitreoretinopathy (FEVR) — see plan.
Musculoskeletal	No scoliosis. Mild bilateral hip dysplasia on clinical exam — hip X-ray ordered. Hands: mild brachydactyly. Mild Achilles tendon tightness bilaterally.
Neurological — Tone	Marked truncal hypotonia: cannot maintain seated posture without support for >30 seconds. Lower extremity hypertonia/spasticity bilaterally, R > L. Upper extremity tone mildly reduced.
Neurological — Reflexes	Patellar reflexes 3+ bilaterally. Ankle clonus present on right (3 beats). Plantar response: extensor right, equivocal left.
Neurological — Movement	Dystonic posturing of bilateral upper extremities with excitement. No ataxia observed. No tremor at rest.
Behavior (observed)	High startle response to auditory stimuli. Hand-flapping noted x2 during exam. No functional communication observed. Responds to name inconsistently.
Skin	Pale, slightly translucent skin. No cafe-au-lait spots. No ash-leaf macules. No neurocutaneous findings.
Cardiac / Abdomen	Regular rate and rhythm. No murmur. Abdomen soft, non-distended. No organomegaly.

PRIOR DIAGNOSTIC WORKUP (SUMMARY)

Test	Date	Result / Interpretation
Chromosomal Microarray (CMA)	June 2024	No pathogenic copy number variants identified. Normal female karyotype (46,XX).
Fragile X (FMR1) PCR	June 2024	Normal — no CGG repeat expansion.
Metabolic screen (amino acids, organic acids, acylcarnitines)	March 2024	Within normal limits. No metabolic disorder identified.
Brain MRI with and without contrast	September 2024	Mild diffuse cortical volume reduction. Thin corpus callosum (body and splenium). Delayed
EEG (24-hour ambulatory)	October 2023	No epileptiform activity. Normal sleep architecture.
Echocardiogram	August 2022	Structurally normal heart. No congenital cardiac anomaly.
Ophthalmology evaluation	March 2024	Esotropia confirmed. Hyperopic refractive error. Retinal periphery not fully visualized — dila
Autism evaluation (ADOS-2, ADI-R)	January 2024	Features of ASD present but evaluators noted atypical profile not fully consistent with prima
Developmental Pediatrics (Bayley-4)	February 2024	Cognitive composite: 55 (profound delay). Language composite: <40 (floor). Motor compos

GENETIC TEST RESULTS — WHOLE EXOME SEQUENCING

Laboratory: Northgate Molecular Genetics Laboratory (CLIA: 00D0000000)

Test performed: Trio Whole Exome Sequencing (proband + both parents)

Specimen type: Peripheral blood (all three individuals)

Date received: October 28, 2024 | **Date reported:** January 14, 2025

POSITIVE RESULT — PATHOGENIC VARIANT IDENTIFIED

Field	Detail
Gene	CTNNB1 (Beta-catenin; MIM #116806)
Chromosomal location	Chromosome 3p22.1
Variant (HGVS notation)	c.1048C>T (NM_001904.4)
Protein change	p.Arg350* (Arginine to Stop codon at position 350)
Variant type	Nonsense / loss-of-function (premature stop codon)
Zygosity	Heterozygous
Classification	**PATHOGENIC (ACMG/AMP criteria: PVS1, PS2, PM2)**
De novo status	**CONFIRMED DE NOVO — variant absent in both parents (trio analysis)**
Associated condition	CTNNB1 Neurodevelopmental Disorder (CTNNB1-NDD) / Neurodevelopmental Disorder with Spastic Dip
Inheritance	Autosomal dominant

Population frequency	Absent from gnomAD (not observed in >250,000 alleles)

This heterozygous nonsense variant (c.1048C>T; p.Arg350*) results in a premature stop codon within exon 8 of the CTNNB1 gene, predicted to cause nonsense-mediated mRNA decay (NMD) and consequent loss of beta-catenin protein function. Loss-of-function variants in CTNNB1 are well-established as causative for CTNNB1-NDD. Trio analysis confirmed this variant arose de novo — it was not inherited from either parent. This finding provides a definitive molecular diagnosis explaining [Sample Child]'s clinical presentation.

ABOUT CTNNB1 NEURODEVELOPMENTAL DISORDER

The CTNNB1 gene encodes beta-catenin, a protein that plays two critical roles in the developing brain: it regulates cell-to-cell adhesion (keeping cells connected properly) and acts as a key signal transducer in the Wnt signaling pathway (controlling how cells communicate and differentiate during development). When one copy of CTNNB1 loses function — as in [Sample Child]'s case — the brain does not develop normally, particularly affecting motor control pathways, speech and language networks, and visual development.

CTNNB1-NDD is an ultra-rare autosomal dominant disorder; approximately 200–300 individuals have been diagnosed worldwide as of 2024, though the true prevalence is estimated at 1 in 50,000 births. It was first described in 2012, and many older individuals with this condition remain undiagnosed or were previously diagnosed with cerebral palsy or idiopathic intellectual disability. The condition is almost always caused by de novo variants — meaning it is not inherited from a parent but arises as a new genetic change — as confirmed in [Sample Child]'s case.

Core features of CTNNB1-NDD (variability is wide):

Feature	Frequency	Notes
Intellectual disability (mild to profound)	~100%	Cognitive impairment is universal; severity varies considerably
Absent or very limited speech	~70–80%	Most children do not develop functional spoken language; AAC critical
Truncal hypotonia (low trunk muscle tone)	~90%	Present from infancy; contributes to motor delay
Lower limb spasticity	~85%	Legs more affected than arms; scissor gait if walking achieved
Microcephaly	~75%	Often present at birth or develops in first year
Strabismus / refractive error	~60%	Esotropia most common; glasses often required
Exudative vitreoretinopathy (FEVR)	~39%	Incomplete retinal blood vessel development; can cause vision loss if untreated
Behavioral challenges (ASD features, ADHD, aggression)	~50%	Sensory processing differences common; ASD overlap frequently seen
Dystonia	~40%	Involuntary muscle contractions, especially with movement/excitement
Feeding difficulties (infancy)	~40%	Oral-phase dysphagia; may require NG tube or modified feeds
Seizures	~20–30%	Not present in all patients; EEG monitoring recommended
Scoliosis	~15%	Monitoring recommended as child grows

MANAGEMENT PLAN AND RECOMMENDATIONS

Ophthalmology — URGENT: Referral placed to Pediatric Ophthalmology for dilated retinal examination with RetCam imaging to evaluate for Familial Exudative Vitreoretinopathy (FEVR). FEVR affects approximately 39% of children with CTNNB1-NDD and can cause progressive vision loss or retinal detachment if untreated. Early identification and treatment (laser photocoagulation or anti-VEGF therapy) can preserve vision. This appointment

should be prioritized within the next 4–6 weeks.

Neurology: Referral to Pediatric Neurology for ongoing seizure surveillance and spasticity management. Although [Sample Child] has had no seizures to date, the risk is 20–30% in CTNNB1-NDD. Parents counseled on seizure recognition and first aid. Repeat EEG recommended at age 4. Botulinum toxin injections or baclofen may be considered for lower limb spasticity if functional mobility is impacted as she grows.

Speech-Language Pathology (SLP): Given absent speech at age 3.5, augmentative and alternative communication (AAC) evaluation is strongly recommended as an immediate priority. Research consistently shows early AAC introduction improves both communication and — importantly — does not inhibit speech development. Referral to AAC specialist placed. PECS (Picture Exchange Communication System) and high-tech AAC devices (e.g., Tobii Dynavox) should be explored. Continued feeding therapy support as needed.

Physical and Occupational Therapy: Continued intensive PT for gross motor development, lower extremity strengthening, and spasticity management. Gait analysis when ambulation is achieved. OT for fine motor skill development, sensory processing, and adaptive equipment. Aquatic therapy may be beneficial. Current therapy frequency (PT 3x/week, OT 2x/week) appears appropriate and should be maintained.

Educational / Early Intervention: Regional Center services should be reviewed and updated to reflect new diagnosis. [Sample Child] is likely eligible for specialized preschool placement with intensive support. An individualized education program (IEP) meeting is recommended with the new genetic diagnosis as supporting documentation. School team to be provided a copy of this report with parental consent.

Cardiology: No cardiac anomaly was identified on prior echo; routine cardiology follow-up is not indicated at this time. Parents should be aware that congenital heart defects have been reported rarely in CTNNB1-NDD; if any new cardiac symptoms arise, evaluation should be sought.

Orthopedics: Hip X-ray ordered at today's visit given clinical finding of mild hip dysplasia. Orthopedic referral pending results. Monitoring for scoliosis at each annual genetics visit.

Genetic Counseling — Recurrence Risk: The de novo nature of this variant means that neither parent carries the mutation. The recurrence risk for a future sibling is estimated at approximately 1% (due to the very small possibility of parental germline mosaicism — where a parent's egg or sperm cells carry the variant at low levels even though their blood test was negative). Parental testing confirmed both parents are negative in peripheral blood. Prenatal diagnosis (via CVS or amniocentesis) or preimplantation genetic testing (PGT-M) is available for future pregnancies if desired. Genetic counseling session to be scheduled to discuss family planning in detail.

Research and Community: We strongly encourage enrollment in the CTNNB1 patient registry (curectnnb1.org / CTNNB1 Connect & Cure). Natural history data from registered families directly informs research and drug development for this condition. Citizen Health is also a recommended platform for organizing [Sample Child]'s medical records and connecting with other CTNNB1 families — given the rarity of this condition, community connection is often one of the most valuable resources families find. The CTNNB1 Foundation and Simons Searchlight research program also welcome family participation.

PROGNOSIS AND NATURAL HISTORY

CTNNB1-NDD is a lifelong condition. It is not progressive in the neurodegenerative sense — the underlying genetic cause does not worsen over time — but because development is ongoing, new challenges may emerge as developmental expectations increase with age. Life expectancy is not well established but is not believed to be significantly shortened in the absence of serious complications (severe respiratory illness, refractory epilepsy). Many children with CTNNB1-NDD make meaningful developmental progress with consistent, intensive early intervention.

Walking is achieved by some but not all children — estimates vary but roughly 50–60% of children with CTNNB1-NDD eventually achieve some degree of independent ambulation, though often with an atypical gait and frequently with assistive devices. Functional communication through AAC is achievable for many. Adult outcomes are not yet well characterized given the recency of the diagnosis, but a growing number of adults are now identified and followed through specialty clinics.

FOLLOW-UP

Return to Northgate Children's Genetics Center in **12 months** for annual genetics review, or sooner if new concerns arise. Ophthalmology appointment to be scheduled within 4–6 weeks — please contact our office if you have not heard from them within 2 weeks. Neurology appointment expected within 6–8 weeks.

[Sample Parent 1] and [Sample Parent 2] were present for the full results disclosure and management discussion. This is an enormous amount of information to receive, and we want you to know that our team is here to support you. Our genetic counselor, [Sample Counselor], is available for follow-up calls and can help coordinate referrals, connect you with family support resources, and answer questions as they arise. Please do not hesitate to reach out.

Electronically signed by: **Dr. [Sample Geneticist], MD, PhD**
Board Certified, Clinical Genetics Northgate Children's Genetics Center Date: January 14, 2025

Report dictated: January 14, 2025 Document ID: NCG-GEN-20250114-0000001 Copies sent to: • Dr. [Sample Pediatrician] (PCP) • [Sample Parent 1] and [Sample Parent 2] • Regional Center (with consent)