Boston Children's Hospital | Children's Rare Disease Collaborative

2025 ANNUAL REPORT

Program Expansion and Mission

The Children's Rare Disease Collaborative (CRDC) at Boston Children's Hospital (BCH) expanded significantly in 2025, supporting 75 rare disease studies comprising more than 300 specific rare diseases across 26 clinical units. Its integrated research–clinical genomic ecosystem now includes data from over 21,000 families comprising more than 47,000 sequenced individuals and continues to enable rapid translation of genomic findings into clinical care.

Diagnostic Yield and Impact

Approximately 35% of patients analyzed through the CRDC receive a confirmed or likely genetic diagnosis. These findings improve patient management, inform prognosis, and guide targeted therapeutic strategies across pediatric specialties.

Pediatric Rare Disease Summit Launch

In 2025, the CRDC supported the inaugural Pediatric Rare Disease Summit for patient families, a major new initiative designed to bridge scientific advances with lived experience. More than 220 family members, clinicians, and researchers participated, bringing together the diverse community that contributes to the CRDC's success.

Focus on Empowerment and Education

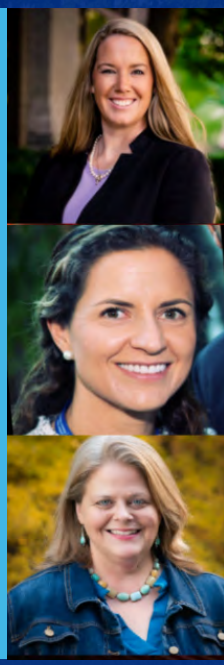
The summit provided families with direct updates from CRDC investigators on emerging genomics, therapy development, and evolving models of care. Sessions emphasized navigating the diagnostic journey, advocating for precision therapies, and understanding how genomic findings can inform long-term care planning.

Community Building and Support Networks

Families reported that the summit strengthened connection with others facing similar challenges and improved access to care resources. The event helped establish a more unified rare disease community and laid the groundwork for ongoing annual programming and expanded family-centered initiatives.

2026 Pediatric Rare Disease Summit

After the Summit, three family members (Ellie A. Hammer, Lucia Huerta, and Erin Ward) emerged as leaders of the newly formed CRDC Patient and Family Advisory Council. They are working with the larger group of patient families and coordinating with us to plan the 2026 Summit, which will take place on October 9th, 2026 at the Martin Conference Center at Harvard Medical School.



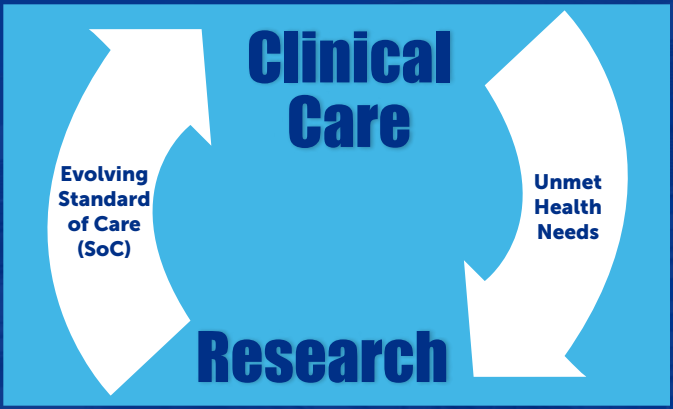
IPCHiP Retreat

The International Precision Child Health Partnership (IPCHiP) consortium fosters collaboration across its member sites: BCH, SickKids (Toronto, Canada), Murdoch Children's Research Institute (MCRI, Melbourne, Australia), and University College London Great Ormond Street Institute of Child Health (UCL GOS ICH, London, United Kingdom). Research leadership includes Nancy Andrews, Piotr Sliz, and Alan Beggs at BCH, along with Stephen Scherer, Chief of Research at SickKids, Kathryn North, Director of MCRI and Helen Cross, Director of UCL GOS ICH. At this year's retreat, BCH highlights included Sarah Morton and Alissa D'Gama presenting on the progress of their studies, as well as discussions by Piotr Sliz and Shira Rockowitz on the IPCHiP vision for international data-sharing platforms.

BCH–UAE Mini Research Symposium on Pediatric Genomics & Rare Diseases

The BCH-UAE Mini Research Symposium featured an engaging presentation from Mohamed Salem Alameri, Acting Director, Genome and Biobank Division of the Department of Health in Abu Dhabi, which highlighted the increasing role of the Emirati Genome Program and the potential for sharing data from the Emirati Genome Program more globally. Mohamad's presentation was followed by two exciting panel sessions that emphasized translating genomic findings to therapies. Panelists Mandana Arbab, who previously completed a postdoctoral fellowship in the lab of David Liu, and Tim Yu, who previously joined us at the Pediatric Rare Disease Summit with Daniel Bauer, discussed the feasibility of using RNA vs DNA therapeutics.

Population-Level Insights



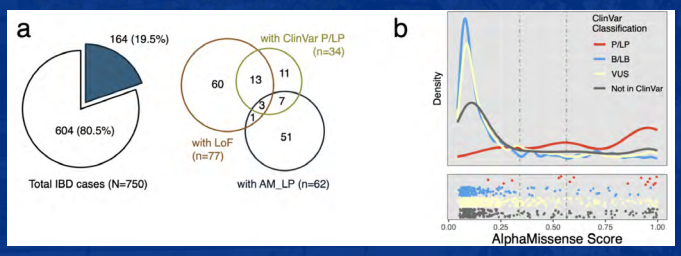
Institutional Genomics Infrastructure

The CRDC's foundational paper, led by Dr. Sliz and colleagues, described a scalable, hospital-wide sequencing platform capable of supporting research, diagnostics, confirmatory testing, and reanalysis. This infrastructure continues to serve as a national model for pediatric precision medicine.

Population-Scale Architecture of Usher Syndrome

A comprehensive genomic analysis led by Dr. Shearer and team quantified the worldwide prevalence of Usher syndrome, the leading cause of deaf-blindness, at approximately 1 in 29,000 individuals. The study identified *USH2A* as the largest contributor to disease burden, highlighted ancestry-specific genetic patterns, and suggested therapeutic strategies such as exon-specific antisense oligonucleotides. CRDC data were used as a non-disease control population.

Evaluation of AI in Variant Interpretation



CRDC data for patients with Inflammatory Bowel Disease (IBD) were used to evaluate the AlphaMissense deep learning model through a collaboration between Dr. Snapper's team in Gastroenterology, Hepatology, and Nutrition and Drs. Kong and Mandl from the Computational Health Informatics Program. The study showed that the model correctly identified fewer than one-third of known pathogenic missense variants, underscoring the continued need for expert clinical interpretation alongside computational tools.

Mechanistic Discovery & Functional Genomics

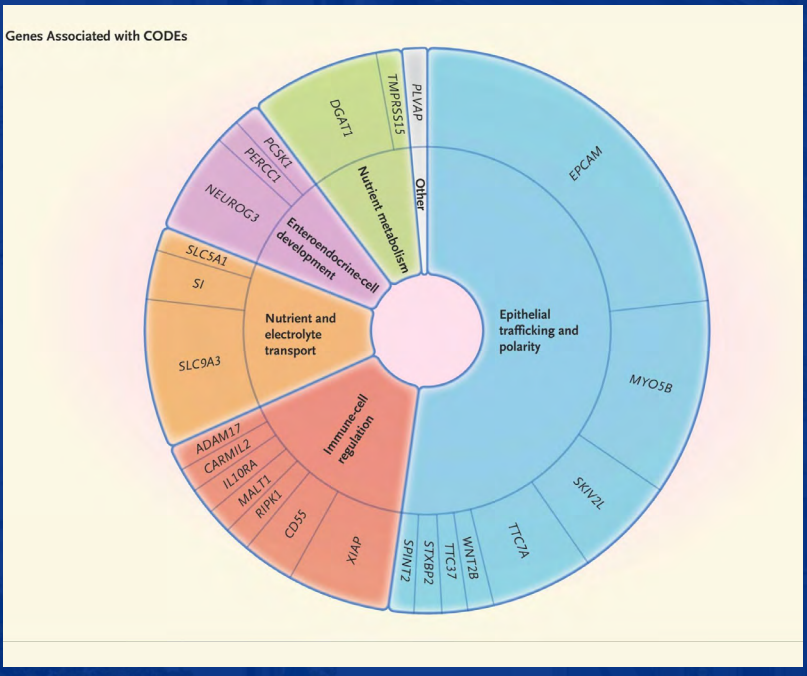
Precision Therapeutics Enabled by Genomics

A child with progranulin deficiency–associated lung and liver fibrosis experienced marked clinical improvement following targeted anti–TNF-α therapy. This multidepartmental effort, led by Drs. Kennedy and Raby in Pulmonary Medicine, demonstrated how CRDC exome sequencing paired with spatial transcriptomics can identify actionable disease mechanisms and guide effective treatment.

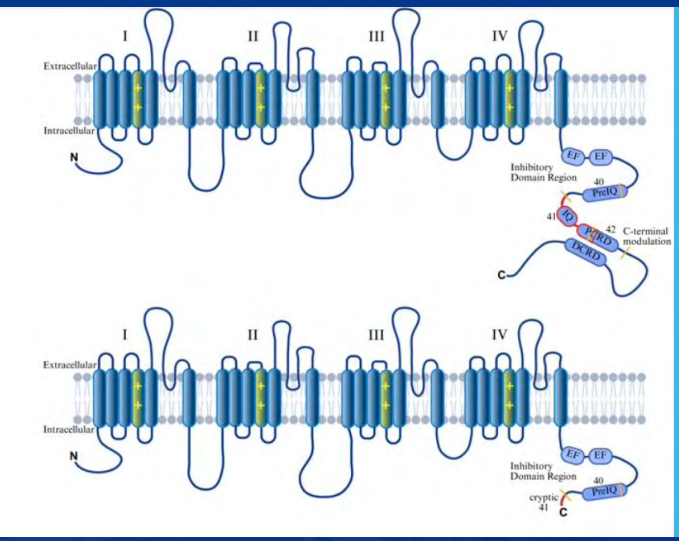
Modifier Gene Discovery in Cystic Fibrosis

Burden testing in rapidly progressive cystic fibrosis identified *SLC26A9* as a key disease modifier influencing lung disease severity in children homozygous for the F508del CFTR mutation, in a collaboration between Dr. Wang (Pulmonary Medicine) and Dr. Agrawal, who moved from BCH to the University of Miami. These findings help explain variability in disease progression and suggest new therapeutic avenues.

Functional Genomics in Congenital Diarrhea and Enteropathy



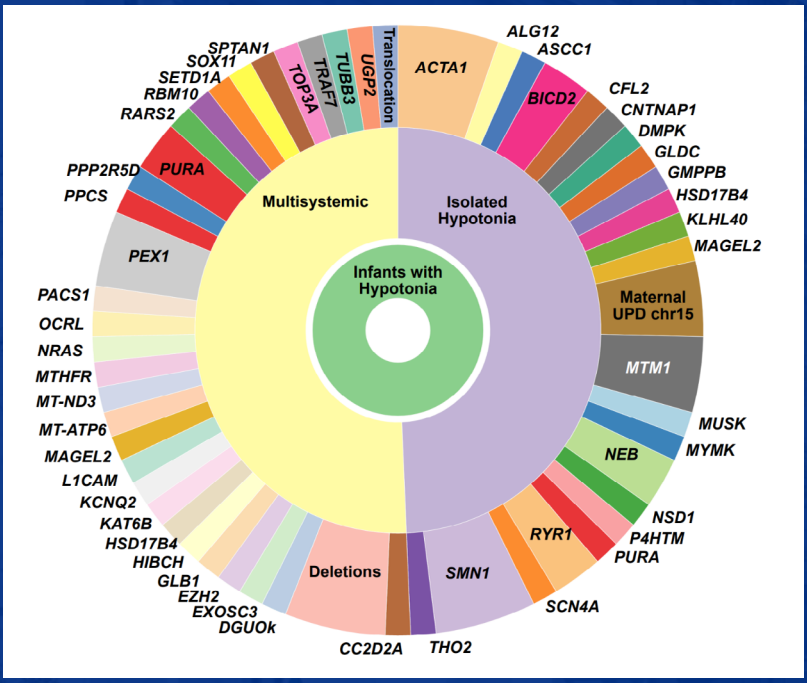
Large-scale genomic analysis of infants with congenital diarrhea and enteropathies, led by Dr. Thiagarajah from Gastroenterology, Hepatology, and Nutrition in collaboration with teams at SickKids and UCLA, identified causal variants in nearly half of affected patients and revealed three novel disease genes—GRWD1, MYO1A, and MON1A. Functional studies using cell systems and zebrafish models demonstrated how defects in protein production, epithelial structure, and intracellular trafficking disrupt intestinal function and drive severe early-onset disease.



Whole-Genome Sequencing for Structural Variant Diagnosis

Whole-genome sequencing identified a novel inverted duplication in CACNA1F in a child with congenital stationary night blindness after nondiagnostic exome testing. This work, led by Dr. Whitman and colleagues, expanded the known pathogenic variant spectrum and highlighted the diagnostic advantage of genome sequencing for complex rearrangements.

Diagnostic Innovation & Sequencing Utility



Complex Genetics of Neonatal Hypotonia

A multicenter NICU study led by Dr. Morton from Newborn Medicine and Dr. Agrawal, who moved from BCH to the University of Miami, in collaboration with IPCHiP partners (SickKids, UCL GOS ICH, and MCRI), demonstrated that exome/genome sequencing yields diagnoses in 60% of infants with unexplained hypotonia. These results frequently altered acute care decisions, prognosis, and family counseling.

Deep Phenotyping and the Genetics of Movement Disorders

Systematic evaluation, led by Dr. Beggs and colleagues, revealed distinct motor and cognitive patterns associated with diverse neurodevelopmental disorders, including tone abnormalities, gait deviation, and progressive motor delays. These findings support earlier genomic evaluation for children with combined motor and cognitive concerns.

Comprehensive Immune Profiling for Primary Immune Regulatory Disorders

Integrated T-cell and autoantibody profiling, led by Dr. Chou and team, identified molecular signatures that refine diagnosis and disease stratification in children with suspected primary immune regulatory disorders, highlighting the growing role of immunogenomics in complex inflammatory disease.

Common and Rare Variant Architecture in Pediatric ADHD

Genome sequencing studies, led by Dr. Doan and colleagues, showed that rare pathogenic variants and common polygenic risk scores independently contribute to ADHD risk. Children carrying rare disruptive variants exhibited lower polygenic risk scores, supporting the existence of distinct genetic pathways underlying similar clinical presentations.

Patient-Centered Phenotypes

Motor Phenotypes in Neurodevelopmental Disorders

Across multiple genetic syndromes, Dr. Srivastava (Neurology) in collaboration with Columbia University, documented a high prevalence of motor abnormalities, including hypotonia, delayed milestones, and cerebral palsy–like features. These findings support proactive motor evaluation and surveillance in children with genetic diagnoses.

Actionable Findings in Cerebral Palsy

Genomic evaluation of cerebral palsy, led by Drs. Srivastava and Poduri, showed that up to 8% of individuals with identified genetic etiologies harbor clinically actionable variants, guiding surveillance, metabolic management, and access to targeted treatments

Pain and Behavioral Phenotyping

Studies of Snijders Blok–Campeau syndrome, a rare genetic condition that affects how the brain develops and can cause learning challenges, limited speech, and low muscle tone, led by Drs. Brownstein (Genetics and Genomics) and Berde (Anesthesia, Critical Care, and Pain Medicine), highlighted variability in pain perception and emphasized the need for individualized behavioral pain scales. This contributes to broader efforts to improve symptom assessment in nonverbal children. This work has also contributed to collaborations with two biotech companies developing novel analgesics and helped establish a 32-center pediatric consortium focused on erythromelalgia.

A Sampling of Collaborative Research in 2025

for a full list please see the CRDC publications website

Discovery of New Genetic Disorders

CRDC-supported sequencing identified multiple novel disease genes, including *ADAT3* and *DNAJB4*, linking impaired tRNA modification to severe neurodevelopmental disorders with abnormal neuronal migration, and chaperone dysfunction to congenital and childhood-onset myopathies marked by early respiratory failure and axial weakness. These discoveries expanded the phenotypic spectrum of both neurodevelopmental and neuromuscular disease and provided new mechanistic frameworks for pathogenesis.

Phenotype Expansions

CRDC-enabled research expanded disease understanding by linking genetic variation to underlying biology rather than isolated clinical features. Studies of *KDM5B*, *SCAF4*, and *TUBA4A* demonstrated how disruptions in chromatin regulation and cytoskeletal function can result in broader, multisystem disease than previously recognized. These genomic insights were strengthened by patient-derived functional models, which revealed genotype-specific inflammatory and signaling defects, including the multisystem consequences of *ITGAV* deficiency. Together, this work highlights how CRDC approaches translate genetic discoveries into clearer disease mechanisms and clinical insight.

2025 New Rare Disease Study Teams

In 2025, the CRDC welcomed 14 new rare disease study teams, reflecting continued growth across clinical specialties.

Eleven teams joined from the Department of Pediatrics, including Drs. Chang and Nigrovic studying non-systemic juvenile idiopathic arthritis; Drs. Crestani and Gaffin focusing on severe asthma; Drs. Henderson and Lee examining systemic juvenile idiopathic arthritis and macrophage activation syndrome; Dr. Chang studying childhood-onset systemic lupus erythematosus; Drs. Bartnikas and Crestani investigating food protein–induced enterocolitis syndrome; Dr. Brownstein studying early-onset interstitial cystitis and bladder pain syndrome; Dr. Bodamer focusing on Mendelian disorders of the epigenetic machinery; Dr. Chung studying congenital diaphragmatic hernia and esophageal atresia; Drs. Zhang and Huang investigating genodermatoses, including epidermolysis bullosa; and Drs. Liang and Balkin (from Plastic and Oral Surgery) studying vascular anomalies.

Two teams joined from Neurology, including Drs. D'Gama and Soul studying neonatal encephalopathy and Dr. Maski studying idiopathic hypersomnia and narcolepsy. One new team joined from Cardiology, led by Dr. Abrams, focusing on inherited arrhythmia syndromes and cardiomyopathies. We look forward to the contributions and success of these teams within the Collaborative.

Summary of 2025 Impact

Overall, the CRDC enabled the discovery of new diseases, clarified mechanisms across biological systems, enhanced diagnostic precision, and facilitated targeted therapies with meaningful clinical benefit. By connecting genomic research to patient care at scale, the CRDC continues to reshape pediatric rare disease medicine.