Contemporary aetiologies of medical complexity in children: a cohort study

Children with medical complexity (CMC) are a priority population in paediatric medicine.[1–3] CMC have at least one chronic condition, technology dependence, multiple subspecialist involvement and substantial healthcare utilisation.[2 3] They account for >30% of all paediatric healthcare spending despite comprising <1% of the total paediatric population.[3] In a prior retrospective study (2010–2014), uptake of genetic testing was high.[4] Rare genetic conditions are collectively common[5] and often associated with medical complexity and/or serious neurological impairment.[1 5] The contemporary aetiological landscape of childhood medical complexity is uncharted however.

We conducted a retrospective chart review of CMC enrolled in a local Complex Care Program over a >10-year period (01 January 2010–01 November 2020) (online supplemental figure 1).[6] We extracted and critically reviewed phenotype and genetic testing data (online supplemental methods).

For 802 CMC, the median year of birth was 2013 (range 1999–2020) and 56% were male. At least one genetic test was performed in 88% (n=706). An additional 4% (n=31) met current clinical criteria for genetic testing because of unexplained major congenital anomalies or growth/development differences. Putative non-genetic causes accounted for the remaining 8% (n=65; online supplemental figure 1).

Over half the CMC had a primary genetic diagnosis (53.9%, 95% CI: 50.3% to 57.4%) (online supplemental table 1). In nine cases, this was a partial genetic diagnosis (online supplemental table 1). Eleven children each had two genetic diagnoses contributing to their phenotype (online supplemental table 1). These counts do not include CMC with clinical diagnoses of genetic conditions for which there is no confirmatory test (eg, Aicardi syndrome), or genetic diagnoses likely unrelated to their major morbidities (eg, Klinefelter syndrome).

There were 265 different primary genetic diagnoses, arising from all major categories of genetic variation (figure 1A and online supplemental figure 2). Only nine conditions were present in five or more CMC (figure 1B), and 211 conditions were each observed in a single individual/family (online supplemental table 1). Aside from Down syndrome, all conditions were rare diseases. Genome sequencing[1] as a single genetic test could have detected an estimated 99% of the diagnoses (online supplemental table 1). Recurrence risks for parents varied from <1% to 50% or higher (figure 1C), underscoring the potential importance of identifying the precise molecular genetic cause(s) of their child's medical complexity. A minority of conditions had specialised treatments either already available or in clinical trials (figure 1D). Genetic therapies were available clinically for two conditions (spinal

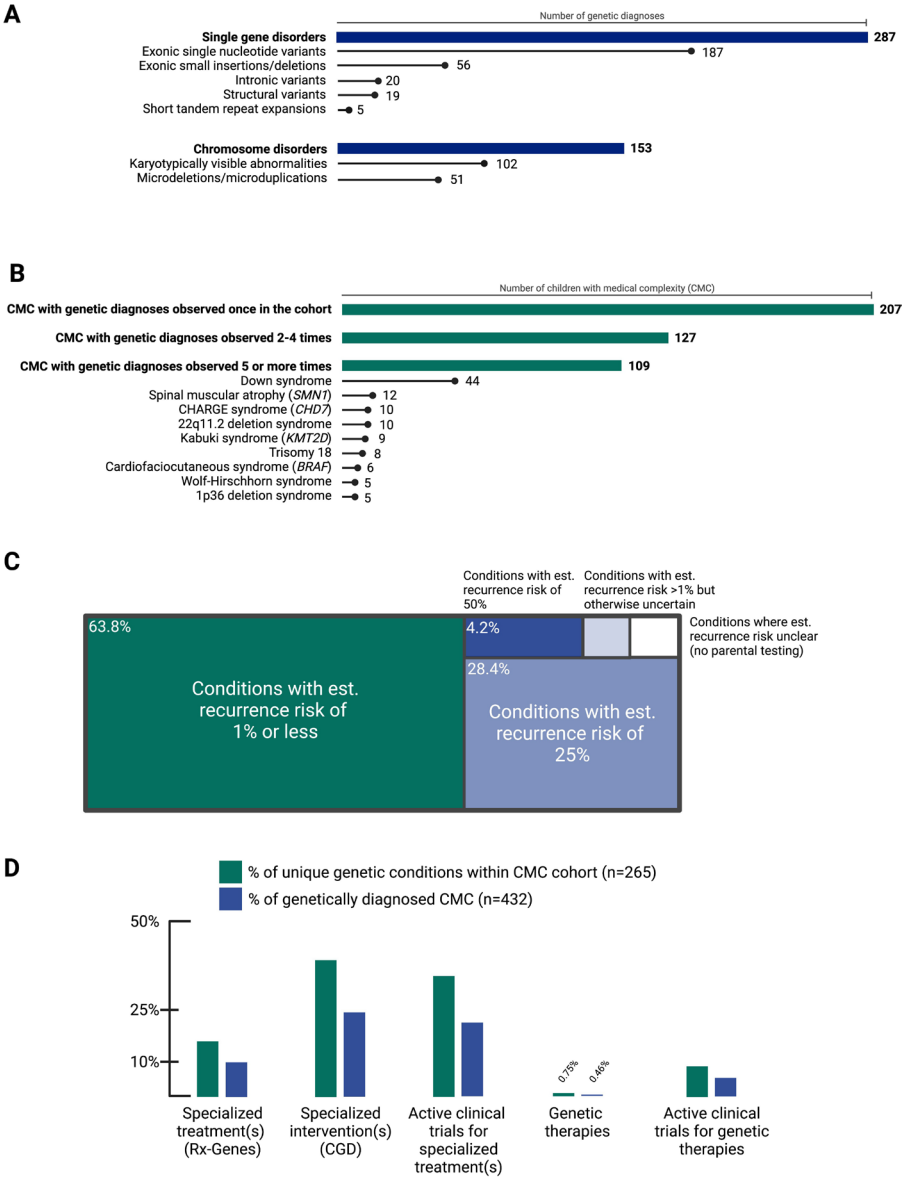

Figure 1 Individually rare genetic conditions are a collectively important contributor to childhood medical complexity. (A) Bar chart displaying counts of primary genetic diagnoses in the children with medical complexity (CMC) study cohort, by variant type(s). For situations of compound heterozygosity where the two variants were of different types (eg, one exonic single nucleotide variant and one intronic variant), each variant was assigned a weight of 0.5. Microdeletions and microduplications were defined as copy number imbalances <5 Mb in size. The 'other' category (not shown) includes three imprinting disorders and one mitochondrial DNA disorder. (B) Bar chart of 443 primary genetic diagnoses in 432 CMC, by frequency category in the cohort. Frequency in this cohort is not necessarily representative of incidence or prevalence in the general population, because of the definition of CMC and potentially the referral criteria for the SickKids Complex Care Program (online supplemental methods). (C) Treemap chart summarising estimated recurrence risk to parents for genetic diagnoses identified in their child with medical complexity. We included only one individual ('proband') from each family, thereby excluding six individuals from five families with the same diagnosis as the proband. The diagnoses for which the estimated recurrence risk to parents was >1% but otherwise uncertain, and for which the estimated recurrence risk to parents was unclear because parental testing was not performed, are annotated in online supplemental table 1. (D) Bar chart of current landscape of specialist treatment options and interventions for genetic conditions in the study cohort, from querying the Rx-Genes online compendium (rx-genes.com), the Clinical Genomic Database (CGD; research.nhgri.nih.gov/CGD/), the ClinicalTrials.gov database and the European Union Clinical Trials Register (all accessed in September 2022). 'Genetic therapies' encapsulates, for example, gene replacement, gene editing and antisense oligonucleotides. Created with BioRender.com.

muscular atrophy and metachromatic leukodystrophy; figure 1D).

Most children in this cohort of 802 Canadian CMC had a known or suspected underlying genetic condition. Studies relying solely on diagnostic codes from administrative or health systems data can underestimate the collective burden of rare genetic diseases. For example, a recent population-scale study estimated prevalence rates in CMC of 'genetic conditions' or 'congenital/genetic (disorders)' ranging from 4.5% to 36.4%.[2] The diversity of genetic diagnoses in the CMC population appears unmatched by any other clinically defined group in paediatrics. One limitation of our study is that ascertainment was via structured Complex Care Clinics in a large urban setting, in a high-income country with a publicly funded healthcare system. Detailed phenotyping and access to advanced genetic testing were necessary to reveal the breadth of genetic disease in this cohort. Conversely, more comprehensive genetic testing like genome-wide sequencing was not performed in many children in this study cohort (online supplemental figure 1). Those CMC who remained undiagnosed after one or more genetic tests may ultimately be found to have rare or novel genetic conditions detectable by genome-wide sequencing.[1]

In summary, these findings provide a detailed picture of the aetiological landscape of childhood medical complexity. Diagnostic and therapeutic odysseys are common in the CMC population. Recognising the collective impact of rare genetic diseases is important when setting healthcare and research priorities.

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REFERENCES

1 Costain G, Walker S, Marano M, *et al*. Genome sequencing as a diagnostic test in children with unexplained medical complexity. *JAMA Netw Open* 2020;3:e2018109.
2 Leyenaar JK, Schaefer AP, Freyleue SD, *et al*. Prevalence of children with medical complexity and associations with health care utilization and in-hospital mortality. *JAMA Pediatr* 2022;176:e220687.
3 Cohen E, Berry JG, Camacho X, *et al*. Patterns and costs of health care use of children with medical complexity. *Pediatrics* 2012;130:e1463–70.
4 Oei K, Hayeems RZ, Ungar WJ, *et al*. Genetic testing among children in a complex care program. *Children* 2017;4:42.
5 Ferreira CR. The burden of rare diseases. *Am J Med Genet A* 2019;179:885–92.
6 Pan A, Scodellaro S, Khan T, *et al*. Pharmacogenetic profiling via genome sequencing in children with medical complexity. *Pediatr Res* 2022. doi:10.1038/s41390-022-02313-3. [Epub ahead of print: 27 Sep 2022].

SUPPLEMENTAL FILE

Contemporary etiologies of medical complexity in children: a cohort study

Bushra Haque, Tayyaba Khan, Inna Ushcatz, Meredith Curtis, Amy Pan, Wendy Wu, Julia Orkin, Gregory Costain

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Supplemental Methods

Overview of the SickKids® Complex Care Program

The Canadian province of Ontario has a population of approximately 14.5 million, of whom an estimated 0.67% of all children and youth fulfill criteria for medical complexity.[1 2] Canada's healthcare system is federally funded and provincially delivered, with single-payer universal coverage for medically necessary healthcare services.[2] The Complex Care Program at the Hospital for Sick Children (SickKids®) was established in 2006 to help children and families with rare or undiagnosed complex chronic diseases (www.sickkids.ca/en/care-services/clinical-departments/complex-care/). Later, a provincial policy strategy known as Complex Care for Kids Ontario (CCKO) was launched in 2015 to expand integrated care for children with medical complexity (CMC) across Ontario (www.pcmch.on.ca/complex-care-for-kids-ontario/).[3] The standard operational definition for CMC used by the SickKids Complex Care Program is described in detail elsewhere.[4] As described previously,[5] CMC are eligible for enrolment in the SickKids Complex Care Program provided they meet all the following criteria:

"(1) are below 16 years of age,

(2) require care coordination,

(3) have a primary care provider that will remain actively involved in their care,

(4) are actively followed by a SickKids subspecialist,

(5) are not already part of a comprehensive multi-disciplinary program (e.g., cystic fibrosis).

They must also have a severe underlying chronic health condition, have a life expectancy of at least 6 months, require the involvement of multiple healthcare practitioners and be technology dependent and/or users of high intensity care."[5]

Overview of clinical genetic testing practices in Ontario, Canada

Standards and options for genetic testing in our region evolved over the study period. State-of-the-art medically indicated diagnostic genetic testing has long been available to Ontarians via the publicly funded Ontario Health Insurance Plan (OHIP), regardless of whether the testing is performed by a clinically certified laboratory in the province or only available via a commercial laboratory in another country. The latter is funded by an individual's OHIP through the Ministry of Health and Long-term Care's Out-of-Country Prior Approval Program. Chromosomal microarray analysis (CMA) was rapidly adopted in the clinic in the mid 2000s. By 2010, local clinical practice reflected international consensus guidelines that CMA should be a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies.[6] CMA remains the most common genetic test performed in CMC.[5 7 8] Translational research studies beginning in the mid 2010s facilitated access to genome-wide sequencing for CMC and other patients at SickKids.[7 9 10] Around 2014, clinical genetic testing options expanded beyond targeted molecular diagnosis to include broad "genome-wide" sequencing.[11 12] By 2015, there was recognition from the Canadian College of Medical Geneticists (CCMG) that, "clinical genome-wide sequencing is an appropriate approach in the diagnostic assessment of a patient for whom there is suspicion of a significant monogenic disease that is associated with a high degree of genetic heterogeneity, or where specific genetic tests have failed to provide a diagnosis."[13] Ontario-specific estimates of the size of the paediatric population meeting criteria for this testing were published in 2020.[11] In line with recommendations from the American College of Medical Genetics & Genomics (ACMG),[14] clinical genome-wide sequencing is now a standard of care investigation for most CMC who remain undiagnosed after CMA.[7 12]

Figure S1. Study workflow diagram.
Genetic tests organized for the n=802 CMC included, but were not limited to, chromosomal microarray analysis (n=460), karyotype (n=251), next-generation sequencing gene panel testing (n=205), single gene sequencing (n=202), and clinical exome sequencing (n=184; not including research-based exome or genome sequencing). The 65 CMC who did not meet criteria for genetic testing at our center, or where this was uncertain, had a total of 70 different putative non-genetic explanations for their major comorbidities.

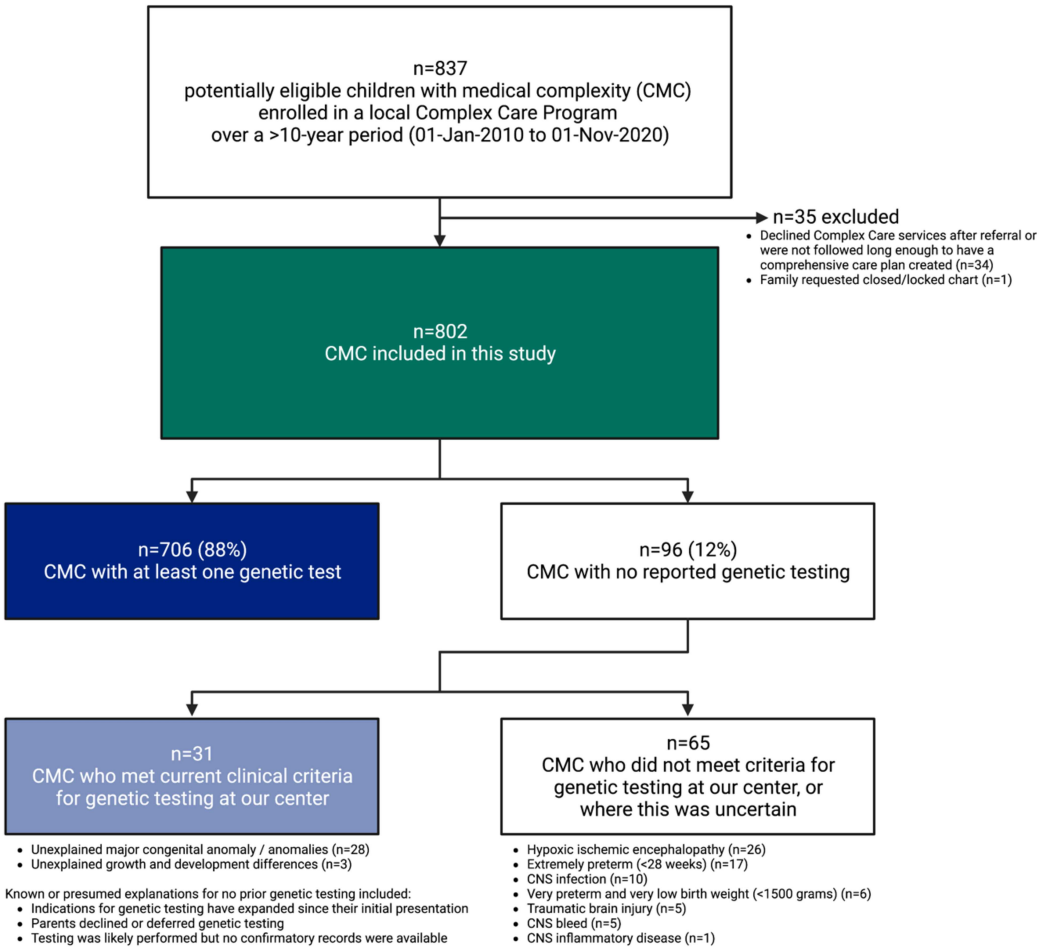

Figure S2. The etiologic landscape of childhood medical complexity has high genetic heterogeneity.
Circos plot of unique chromosomal and single gene variation contributing to medical complexity in a single-center cohort of n=802 CMC. Outer ring: rectangles indicate regions of copy number change associated with genetic diagnoses. Inner ring: lines indicate locations of single genes associated with genetic diagnoses. Innermost rings: single gene variation subdivided into exonic sequence variants (SNVs and indels; circles), intronic variants (triangles), small structural variants (squares), and short tandem repeat expansions (plus mark). A minority of variants in the first category, and most or all the variants in the latter three categories, would not have been detectable by exome sequencing. Created with Circa (http://omgenomics.com/circa). All genetic diagnoses are listed in Table S1.

Table S1. Genetic diagnoses in a cohort of children with medical complexity (CMC).

Study ID	Molecular diagnosis (gene)	Variant type(s)	Inheritance	Comment code (p.20)
001	kabuki syndrome 1 (KMT2D)	single gene disorder (snv)	de novo autosomal dominant	9,10
002	nicolaides-baraitser syndrome (SMARCA2)	single gene disorder (snv)	de novo autosomal dominant	9
003	spinal muscular atrophy (SMN1)	single gene disorder (structural variant)	autosomal recessive (homozygous)	9,10,11
004	22q11.2 deletion syndrome	microdeletion	de novo autosomal dominant	10
005	hyperinsulinemic hypoglycemia, familial, 1 (ABCC8)	single gene disorder (snv)	autosomal recessive (compound heterozygous)	9,10
006	acrodysostosis 1, with or without hormone resistance (PRKAR1A)	single gene disorder (snv)	inherited autosomal dominant	9
007	trisomy 18	karyotypically visible abnormality	other	
008	chromosome 1p36 deletion syndrome	microdeletion	de novo autosomal dominant	
009	partial monosomy 17, partial trisomy 19	karyotypically visible abnormality	other (unbalanced translocation)	7
010	22q11.2 deletion syndrome	microdeletion	de novo autosomal dominant	10
011	glycogen storage disease 1a (G6PC1)	single gene disorder (snv)	autosomal recessive (compound heterozygous)	9,10,12
012	down syndrome	karyotypically visible abnormality	other	10
013	loeys-dietz syndrome 2 (TGFBR2)	single gene disorder (snv)	de novo autosomal dominant	9
014	hypotonia, infantile, with psychomotor retardation and characteristic facies 2 (UNC80)	single gene disorder (snv)	autosomal recessive (homozygous)	
015	charge syndrome (CHD7)	single gene disorder (indel)	de novo autosomal dominant	9
016	central hypoventilation syndrome, congenital, 1, with or without hirschsprung disease (PHOX2B)	short tandem repeat disorder	de novo autosomal dominant	9,10
017	miller-dieker lissencephaly syndrome	microdeletion	de novo autosomal dominant	
018	wiedemann-steiner syndrome (KMT2A)	single gene disorder (snv)	de novo autosomal dominant	
019	down syndrome	karyotypically visible abnormality	other	10
020	crouzon syndrome (FGFR2)	single gene disorder (snv)	inherited autosomal dominant	9
021	kabuki syndrome 1 (KMT2D)	single gene disorder (snv)	de novo autosomal dominant	9,10
022	cardiofaciocutaneous syndrome (BRAF)	single gene disorder (snv)	de novo autosomal dominant	9
023	smith-lemli-opitz syndrome (DHCR7)	single gene disorder (snv)	autosomal recessive (homozygous)	9,10

024	chromosome 2q34.3 deletion	karyotypically visible abnormality	de novo autosomal dominant	
025	down syndrome	karyotypically visible abnormality	other	10
026	spinal muscular atrophy (SMN1)	single gene disorder (structural variant)	autosomal recessive (homozygous)	9,10,11
027	down syndrome	karyotypically visible abnormality	other	10
028	cockayne syndrome, type b (ERCC6)	single gene disorder (snv, indel)	autosomal recessive (compound heterozygous)	5,9
029	chromosome 2q33 deletion syndrome	microdeletion	de novo autosomal dominant	
030	muscular dystrophy-dystroglycanopathy (congenital with brain and eye anomalies), type a, 5 (FKRP)	single gene disorder (snv, indel)	autosomal recessive (compound heterozygous)	9,12
031	down syndrome	karyotypically visible abnormality	other	10
032	down syndrome	karyotypically visible abnormality	other	10
033	cockayne syndrome, type b (ERCC6)	single gene disorder (snv, indel)	autosomal recessive (compound heterozygous)	4,9
034	metachromatic leukodystrophy (ARSA)	single gene disorder (snv)	autosomal recessive (compound heterozygous)	9,10,11,12
035	down syndrome	karyotypically visible abnormality	other	10
036	down syndrome	karyotypically visible abnormality	other	10
037	22q11.2 deletion syndrome	microdeletion	de novo autosomal dominant	10
038	chromosome 10q22.3-q23.2 deletion syndrome	microdeletion	de novo autosomal dominant	
039	bartter syndrome, type 4a (BSND)	single gene disorder (indel)	autosomal recessive (homozygous)	9
040	lowe syndrome (OCRL)	single gene disorder (snv)	inherited x-linked	9
041	down syndrome	karyotypically visible abnormality	other	10
042	partial trisomy 6	karyotypically visible abnormality	de novo autosomal dominant	
043	3-m syndrome 1 (CUL7)	single gene disorder (snv)	autosomal recessive (compound heterozygous)	
044	cardiofaciocutaneous syndrome 2 (KRAS)	single gene disorder (snv)	de novo autosomal dominant	9
045	williams-beuren syndrome	microdeletion	de novo autosomal dominant	10
046	pontocerebellar hypoplasia type 2a (TSEN54)	single gene disorder (snv)	autosomal recessive (homozygous)	
047	partial monosomy 11, partial trisomy 7	karyotypically visible abnormality	other (unbalanced translocation)	7
048	osteogenesis imperfecta, type xv (WNT1)	single gene disorder (indel)	autosomal recessive (homozygous)	10

049	charge syndrome (CHD7)	single gene disorder (snv)	de novo autosomal dominant	9
050	adams-oliver syndrome 5 (NOTCH1)	single gene disorder (indel)	de novo autosomal dominant	9
051	down syndrome	karyotypically visible abnormality	other	10
052	22q11.2 deletion syndrome	microdeletion	de novo autosomal dominant	10
053	cutis laxa, autosomal recessive, type IIIA (ALDH18A1)	single gene disorder (snv)	autosomal recessive (compound heterozygous)	
054	down syndrome	karyotypically visible abnormality	other	10
055	neurodevelopmental disorder with microcephaly, hypotonia, and variable brain anomalies (PRUNE1)	single gene disorder (snv)	autosomal recessive (homozygous)	4
056	nemaline myopathy 3 (ACTA1)	single gene disorder (snv)	de novo autosomal dominant	
057	heterotopia, periventricular, 1 (FLNA)	single gene disorder (indel)	inherited x-linked	9
058	charge syndrome (CHD7)	single gene disorder (indel)	de novo autosomal dominant	4,9
059	chromosome 2q37 deletion syndrome	microdeletion	de novo autosomal dominant	
060	chromosome 12p13.1-p12.3 deletion	microdeletion	de novo autosomal dominant	
061	aicardi-goutieres syndrome 3 (RNASEH2C)	single gene disorder (snv)	autosomal recessive (compound heterozygous)	5,9,10
062	trisomy 18	karyotypically visible abnormality	other	
063	down syndrome	karyotypically visible abnormality	other	10
064	PIK3CA-related overgrowth spectrum (PIK3CA)	single gene disorder (snv)	de novo autosomal dominant	9,10
065	chromosome 13q33-q34 deletion syndrome	microdeletion	de novo autosomal dominant	
066	marfan syndrome (FBN1)	single gene disorder (structural variant)	de novo autosomal dominant	9,10
067	isodicentric chromosome 15	karyotypically visible abnormality	other	
068	down syndrome	karyotypically visible abnormality	other	10
069	4q deletion syndrome	karyotypically visible abnormality	de novo autosomal dominant	
070	down syndrome	karyotypically visible abnormality	other	10
071	trisomy 18	karyotypically visible abnormality	other	
072	partial monosomy 2, partial trisomy 10	karyotypically visible abnormality	other (unbalanced translocation)	7
073	rubinstein-taybi syndrome 1 (CREBBP)	single gene disorder (indel)	de novo autosomal dominant	9

074	down syndrome	karyotypically visible abnormality	other	10
075	renal cysts and diabetes syndrome (HNF1B)	single gene disorder (snv)	de novo autosomal dominant	9
076	kabuki syndrome 1 (KMT2D)	single gene disorder (indel)	de novo autosomal dominant	9,10
077	mitochondrial dna depletion syndrome 14 (encephalocardiomyopathic type) (OPA1)	single gene disorder (snv)	autosomal recessive (homozygous)	9
078	turner syndrome	karyotypically visible abnormality	other	2,10
079	rubinstein-taybi syndrome 1 (CREBBP)	single gene disorder (snv)	de novo autosomal dominant	4,9
080	kniest dysplasia (COL2A1)	single gene disorder (indel)	de novo autosomal dominant	1,5,9
080	chromosome 2p16.3 deletion	microdeletion	inherited autosomal dominant	1
081	kabuki syndrome 1 (KMT2D)	single gene disorder (indel)	de novo autosomal dominant	9,10
082	down syndrome	karyotypically visible abnormality	other	10
083	nemaline myopathy 2 (NEB)	single gene disorder (structural variant)	autosomal recessive (homozygous)	
084	ehlers-danlos syndrome, musculocontractural type 1 (CHST14)	single gene disorder (snv)	autosomal recessive (homozygous)	9
085	noonan syndrome 8 (RIT1)	single gene disorder (snv)	de novo autosomal dominant	9,10
086	cornelia de lange syndrome 3 (SMC3)	single gene disorder (snv)	de novo autosomal dominant	9
087	cpt deficiency, hepatic, type 1A (CPT1A)	single gene disorder (snv)	autosomal recessive (homozygous)	4,9,10
088	developmental and epileptic encephalopathy 13 (SCN8A)	single gene disorder (snv)	de novo autosomal dominant	9,10
089	down syndrome	karyotypically visible abnormality	other	10
090	schinzel-giedion midface retraction syndrome (SETBP1)	single gene disorder (snv)	de novo autosomal dominant	9
091	cri-du-chat syndrome	karyotypically visible abnormality	de novo autosomal dominant	
092	marfan syndrome (FBN1)	single gene disorder (snv)	inherited autosomal dominant	9,10
093	charge syndrome (CHD7)	single gene disorder (indel)	de novo autosomal dominant	9
094	down syndrome	karyotypically visible abnormality	other	10
095	spastic paraplegia 4 (SPAST)	single gene disorder (snv)	de novo autosomal dominant	10
096	partial monosomy 10, partial trisomy 15	karyotypically visible abnormality	other (unbalanced translocation)	7
097	mucopolysaccharidosis 1h (IDUA)	single gene disorder (snv)	autosomal recessive (homozygous)	3,9,10

098	mucopolysaccharidosis 1h (IDUA)	single gene disorder (snv)	autosomal recessive (homozygous)	3,9,10
099	kabuki syndrome 1 (KMT2D)	single gene disorder (snv)	de novo autosomal dominant	4,9,10
100	segawa syndrome (TH)	single gene disorder (snv)	autosomal recessive (compound heterozygous)	9
101	schimmelpenning-feuerstein-mims syndrome (KRAS)	single gene disorder (indel)	other (de novo mosaic)	
102	intellectual developmental disorder, x-linked, syndrome, snijders blok type (DDX3X)	single gene disorder (snv)	de novo x-linked	
103	osteopathia striata with cranial sclerosis (AMER1)	single gene disorder (snv)	x-linked (inheritance unknown)	7
104	chromosome 13q14 deletion syndrome	karyotypically visible abnormality	de novo autosomal dominant	
105	pfeiffer syndrome (FGFR2)	single gene disorder (snv)	de novo autosomal dominant	9
106	microcephalic osteodysplastic primordial dwarfism, type 2 (PCNT)	single gene disorder (snv)	autosomal recessive (homozygous)	
107	pallister-killian syndrome	karyotypically visible abnormality	other	
108	joubert syndrome 28 (MKS1)	single gene disorder (snv, indel)	autosomal recessive (compound heterozygous)	
109	myotonic dystrophy 1 (DMPK)	short tandem repeat disorder	autosomal dominant with anticipation	9,10
110	ataxia-telangiectasia (ATM)	single gene disorder (indel)	autosomal recessive (homozygous)	9,10
111	miller-dieker lissencephaly syndrome	microdeletion	de novo autosomal dominant	
112	menkes disease (ATP7A)	single gene disorder (indel)	inherited x-linked	9,10
113	adrenoleukodystrophy (ABCD1)	single gene disorder (indel)	inherited x-linked	1,5,9,10
113	22q11.2 deletion syndrome	microdeletion	de novo autosomal dominant	1,10
114	trisomy 18	karyotypically visible abnormality	other	
115	chromosome 10q24 deletion	microdeletion	de novo autosomal dominant	
116	pontocerebellar hypoplasia, type 1b (EXOSC3)	single gene disorder (snv)	autosomal recessive (compound heterozygous)	5
117	charge syndrome (CHD7)	single gene disorder (indel)	de novo autosomal dominant	9
118	charge syndrome (CHD7)	single gene disorder (snv)	de novo autosomal dominant	9
119	cortical dysplasia, complex, with other brain malformations 3 (KIF2A)	single gene disorder (snv)	de novo autosomal dominant	
120	spastic ataxia 5 (AFG3L2)	single gene disorder (snv)	autosomal recessive (compound heterozygous)	
121	pelizaeus-merzbacher disease (PLP1)	single gene disorder (snv)	inherited x-linked	10

122	pierpont syndrome (TBL1XR1)	single gene disorder (snv)	de novo autosomal dominant	
123	miller-dieker lissencephaly syndrome	microdeletion	de novo autosomal dominant	
124	down syndrome	karyotypically visible abnormality	other	10
125	down syndrome	karyotypically visible abnormality	other	10
126	spinal muscular atrophy (SMN1)	single gene disorder (structural variant)	autosomal recessive (homozygous)	9,10,11
127	kabuki syndrome 1 (KMT2D)	single gene disorder (snv)	de novo autosomal dominant	9,10
128	dravet syndrome (SCN1A)	single gene disorder (snv)	de novo autosomal dominant	9,10
129	metachromatic leukodystrophy (ARSA)	single gene disorder (snv)	autosomal recessive (homozygous)	9,10,11,12
130	wolfram-like syndrome, autosomal dominant (WFS1)	single gene disorder (snv)	de novo autosomal dominant	9,10
131	pelizaeus-merzbacher disease	microduplication	inherited x-linked	
132	down syndrome	karyotypically visible abnormality	other	10
133	trisomy 13	karyotypically visible abnormality	other	
134	miller-dieker lissencephaly syndrome	microdeletion	de novo autosomal dominant	
135	partial monosomy 10, partial trisomy 5	karyotypically visible abnormality	other (balanced chromosomal translocation in a parent)	6
136	partial trisomy 10	karyotypically visible abnormality	de novo autosomal dominant	
137	developmental and epileptic encephalopathy 4 (STXBP1)	single gene disorder (structural variant)	de novo autosomal dominant	10
138	congenital heart defects, multiple types, 4 (NR2F2)	single gene disorder (snv)	de novo autosomal dominant	9
139	chromosome 3q26-q29 duplication	karyotypically visible abnormality	de novo autosomal dominant	
140	kleefstra syndrome 1	microdeletion	de novo autosomal dominant	
141	partial monosomy 16, partial trisomy 2	karyotypically visible abnormality	other (balanced chromosomal translocation in a parent)	6
142	sandhoff disease (HEXB)	single gene disorder (structural variant, snv)	autosomal recessive (compound heterozygous)	10
143	developmental and epileptic encephalopathy 48 (AP3B2)	single gene disorder (snv)	autosomal recessive (homozygous)	3,10
144	cardiofaciocutaneous syndrome (BRAF)	single gene disorder (snv)	de novo autosomal dominant	9
145	fumarase deficiency (FH)	single gene disorder (snv)	autosomal recessive (compound heterozygous)	9,10
146	developmental and epileptic encephalopathy 26 (KCNB1)	single gene disorder (snv)	de novo autosomal dominant	10

147	neurodegeneration with brain iron accumulation 1 (PANK2)	single gene disorder (indel)	autosomal recessive (homozygous)	10
148	down syndrome	karyotypically visible abnormality	other	10
149	jacobsen syndrome	karyotypically visible abnormality	de novo autosomal dominant	
150	brain small vessel disease with or without ocular anomalies (COL4A1)	single gene disorder (snv)	de novo autosomal dominant	4,9
151	pontocerebellar hypoplasia, type 1b (EXOSC3)	single gene disorder (snv)	autosomal recessive (homozygous)	3
152	pontocerebellar hypoplasia, type 1b (EXOSC3)	single gene disorder (snv)	autosomal recessive (homozygous)	3
153	dravet syndrome (SCN1A)	single gene disorder (snv)	de novo autosomal dominant	9,10
154	chromosome 18p deletion syndrome	karyotypically visible abnormality	de novo autosomal dominant	
155	22q13.2-q13.31 deletion (incl. EP300)	microdeletion	de novo autosomal dominant	
156	lissencephaly 3 (TUBA1A)	single gene disorder (snv)	de novo autosomal dominant	
157	niemann-pick disease, type c2 (NPC2)	single gene disorder (snv)	autosomal recessive (homozygous)	4,9,10
158	rett syndrome (MECP2)	single gene disorder (snv)	de novo x-linked	10
159	spinal muscular atrophy, lower extremity-predominant 1 (DYNC1H1)	single gene disorder (snv)	de novo autosomal dominant	
160	pontocerebellar hypoplasia, type 1b (EXOSC3)	single gene disorder (snv)	autosomal recessive (homozygous)	3
161	ceroid lipofuscinosis, neuronal, 1 (PPT1)	single gene disorder (snv)	autosomal recessive (compound heterozygous)	10
162	chromosome 1p36 deletion syndrome	karyotypically visible abnormality	de novo autosomal dominant	
163	deafness, dystonia, and cerebral hypomyelination (BCAP31)	single gene disorder (indel)	inherited x-linked	
164	angelman syndrome	microdeletion	de novo autosomal dominant	10
165	chromosome 1p36 deletion syndrome	microdeletion	de novo autosomal dominant	
166	ceroid lipofuscinosis, neuronal, 3 (CLN3)	single gene disorder (structural variant)	autosomal recessive (homozygous)	9,10,12
167	8q12.3q13.3 deletion (EYA1)	karyotypically visible abnormality	de novo autosomal dominant	
168	friedreich ataxia (FXN)	short tandem repeat disorder	autosomal recessive (homozygous)	9,10
169	pelizaeus-merzbacher disease (PLP1)	single gene disorder (snv)	de novo x-linked	
170	dysautonomia, familial (ELP1)	single gene disorder (snv)	autosomal recessive (compound heterozygous)	5,10
171	spinocerebellar ataxia, autosomal recessive 16 (STUB1)	single gene disorder (snv)	autosomal recessive (homozygous)	10

172	joubert syndrome 34 (B9D2)	single gene disorder (snv)	autosomal recessive (homozygous)	
173	chromosome 16p13.11 deletion syndrome	microdeletion	de novo autosomal dominant	2
174	glycine encephalopathy (GLDC)	single gene disorder (snv)	autosomal recessive (homozygous)	4,9
175	down syndrome	karyotypically visible abnormality	other	10
176	congenital disorder of glycosylation, type 1p (ALG11)	single gene disorder (snv)	autosomal recessive (homozygous)	9
177	down syndrome	karyotypically visible abnormality	other	10
178	pyruvate dehydrogenase e1-alpha deficiency (PDHA1)	single gene disorder (snv)	de novo x-linked	9
179	spinal muscular atrophy (SMN1)	single gene disorder (structural variant)	autosomal recessive (homozygous)	9,10,11
180	developmental and epileptic encephalopathy 7 (KCNQ2)	single gene disorder (snv)	de novo autosomal dominant	9,10,12
181	3p- syndrome	karyotypically visible abnormality	de novo autosomal dominant	
182	sotos syndrome 1 (NSD1)	single gene disorder (snv)	de novo autosomal dominant	9
183	wolf-hirschhorn syndrome	karyotypically visible abnormality	de novo autosomal dominant	
184	kbg syndrome (ANKRD11)	single gene disorder (structural variant)	de novo autosomal dominant	
185	cat eye syndrome	karyotypically visible abnormality	de novo autosomal dominant	
186	brown-vialetto-van laere syndrome 1 (SLC52A3)	single gene disorder (snv)	autosomal recessive (homozygous)	9
187	short stature, onychodysplasia, facial dysmorphism, and hypotrichosis (POC1A)	single gene disorder (indel)	autosomal recessive (homozygous)	
188	chromosome 1p36 deletion syndrome	microdeletion	de novo autosomal dominant	
189	neuromuscular disease, congenital (RYR1)	single gene disorder (snv)	autosomal recessive (compound heterozygous)	9,10
190	cardiofaciocutaneous syndrome 3 (MAP2K1)	single gene disorder (snv)	de novo autosomal dominant	9
191	invdupdel(8p) syndrome	karyotypically visible abnormality	de novo autosomal dominant	
192	chromosome 13q12.11 deletion	microdeletion	de novo autosomal dominant	
193	developmental and epileptic encephalopathy 14 (KCNT1)	single gene disorder (snv)	de novo autosomal dominant	9,10
194	congenital disorder of glycosylation, type 1a (PMM2)	single gene disorder (snv)	autosomal recessive (compound heterozygous)	9,10
195	spasticity, childhood-onset, with hyperglycinemia (GLRX5)	single gene disorder (snv)	autosomal recessive (homozygous)	9
196	LONP1-related disorder (LONP1)	single gene disorder (snv)	autosomal recessive (homozygous)	3

197	kabuki syndrome 1 (KMT2D)	single gene disorder (snv)	de novo autosomal dominant	9,10
198	LONP1-related disorder (LONP1)	single gene disorder (snv)	autosomal recessive (homozygous)	3
199	combined oxidative phosphorylation deficiency 12 (EARS2)	single gene disorder (snv)	autosomal recessive (homozygous)	
200	pallister-killian syndrome	karyotypically visible abnormality	other	
201	costello syndrome (HRAS)	single gene disorder (snv)	de novo autosomal dominant	9
202	trisomy 18	karyotypically visible abnormality	other	
203	mitochondrial dna depletion syndrome 4a (alpers type), autosomal recessive 1 (POLG)	single gene disorder (snv)	autosomal recessive (homozygous)	10
204	kabuki syndrome 1 (KMT2D)	single gene disorder (snv)	de novo autosomal dominant	9,10
205	myotubular myopathy, x-linked (MTM1)	single gene disorder (snv)	x-linked (inheritance unknown)	7,9,10,12
206	menkes disease (ATP7A)	single gene disorder (indel)	inherited x-linked	9,10
207	beckwith-wiedemann syndrome	imprinting disorder	other	8
208	kleefstra syndrome 1	microdeletion	de novo autosomal dominant	
209	cornelia de lange syndrome 1 (NIPBL)	single gene disorder (indel)	de novo autosomal dominant	9
210	ehlers-danlos syndrome, vascular type (COL3A1)	single gene disorder (snv)	inherited autosomal dominant	9,10
211	mosaic trisomy 18	karyotypically visible abnormality	other	
212	alport syndrome 1, x-linked (COL4A5)	single gene disorder (snv)	inherited x-linked	2,9,10
213	developmental and epileptic encephalopathy 11 (SCN2A)	single gene disorder (snv)	de novo autosomal dominant	9,10
214	apert syndrome (FGFR2)	single gene disorder (snv)	de novo autosomal dominant	9
215	down syndrome	karyotypically visible abnormality	other	10
216	partial monosomy 9, partial trisomy 16	karyotypically visible abnormality	other (de novo unbalanced translocation)	
217	tay-sachs disease (HEXA)	single gene disorder (snv, indel)	autosomal recessive (compound heterozygous)	10,12
218	charge syndrome (CHD7)	single gene disorder (indel)	de novo autosomal dominant	9
219	beckwith-wiedemann syndrome	karyotypically visible abnormality	other (balanced chromosomal translocation in a parent)	6
220	developmental and epileptic encephalopathy 1 (ARX)	single gene disorder (snv)	inherited x-linked	10
221	allan-herndon-dudley syndrome (SLC16A2)	single gene disorder (snv)	de novo x-linked	9,10

222	ring chromosome 18	karyotypically visible abnormality	other	
223	coffin-siris syndrome 4 (SMARCA4)	single gene disorder (snv)	de novo autosomal dominant	
224	emanuel syndrome	karyotypically visible abnormality	other (balanced chromosomal translocation in a parent)	6
225	cimdag syndrome (VPS4A)	single gene disorder (snv)	de novo autosomal dominant	9
226	chromosome 5q14.3 deletion syndrome	karyotypically visible abnormality	de novo autosomal dominant	
227	22q11.2 deletion syndrome	microdeletion	de novo autosomal dominant	10
228	cardiofaciocutaneous syndrome (BRAF)	single gene disorder (snv)	de novo autosomal dominant	9
229	rett syndrome (MECP2)	single gene disorder (snv)	de novo x-linked	1,10
229	neurofibromatosis type 1 (NF1)	single gene disorder (indel)	de novo autosomal dominant	1,9,10
230	chromosome 6p26 deletion	karyotypically visible abnormality	de novo autosomal dominant	
231	rett syndrome, congenital variant (FOXG1)	single gene disorder (indel)	de novo autosomal dominant	
232	developmental and epileptic encephalopathy 11 (SCN2A)	single gene disorder (snv)	de novo autosomal dominant	9,10
233	treacher collins syndrome 1 (TCOF1)	single gene disorder (indel)	de novo autosomal dominant	9
234	spinal muscular atrophy (SMN1)	single gene disorder (structural variant)	autosomal recessive (homozygous)	9,10,11
235	mosaic monosomy 21, mosaic ring 21	karyotypically visible abnormality	other	
236	down syndrome	karyotypically visible abnormality	other	10
237	down syndrome	karyotypically visible abnormality	other	10
238	pontocerebellar hypoplasia, type 2e (VPS53)	single gene disorder (snv)	autosomal recessive (compound heterozygous)	
239	developmental and epileptic encephalopathy 7 (KCNQ2)	single gene disorder (snv)	de novo autosomal dominant	9,10,12
240	crigler-najjar syndrome, type 1 (UGT1A1)	single gene disorder (indel)	autosomal recessive (homozygous)	1,9,10,12
240	kindler syndrome (FERMT1)	single gene disorder (snv)	autosomal recessive (homozygous)	1,9,10
241	down syndrome	karyotypically visible abnormality	other	10
242	chromosome 13q deletion syndrome	karyotypically visible abnormality	de novo autosomal dominant	
243	charge syndrome (CHD7)	single gene disorder (indel)	de novo autosomal dominant	9
244	cardiofaciocutaneous syndrome (BRAF)	single gene disorder (snv)	de novo autosomal dominant	9

245	developmental and epileptic encephalopathy 13 (SCN8A)	single gene disorder (snv)	de novo autosomal dominant	9,10
246	partial monosomy 5, partial trisomy 8	karyotypically visible abnormality	other (balanced chromosomal translocation in a parent)	6
247	down syndrome	karyotypically visible abnormality	other	10
248	stuve-wiedemann syndrome (LIFR)	single gene disorder (indel)	autosomal recessive (homozygous)	
249	turner syndrome	karyotypically visible abnormality	other	10
250	developmental and epileptic encephalopathy 91 (PPP3CA)	single gene disorder (snv)	de novo autosomal dominant	10
251	down syndrome	karyotypically visible abnormality	other	1,10
251	retinoblastoma (RB1)	single gene disorder (snv)	de novo autosomal dominant	1,4,9,10
252	cardiofaciocutaneous syndrome (BRAF)	single gene disorder (snv)	de novo autosomal dominant	9
253	22q11.2 deletion syndrome	microdeletion	de novo autosomal dominant	10
254	down syndrome	karyotypically visible abnormality	other	10
255	developmental and epileptic encephalopathy 14 (KCNT1)	single gene disorder (snv)	de novo autosomal dominant	9,10
256	treacher collins syndrome 1 (TCOF1)	single gene disorder (indel)	inherited autosomal dominant	9
257	congenital disorder of glycosylation, type 1t (PGM1)	single gene disorder (snv)	autosomal recessive (homozygous)	9,10
258	trisomy 18	karyotypically visible abnormality	other	
259	partial monosomy 9, partial trisomy 18	karyotypically visible abnormality	other (de novo unbalanced translocation)	
260	neuromuscular disease, congenital (RYR1)	single gene disorder (snv)	de novo autosomal dominant	9,10
261	chromosome 7q36.3 duplication	microduplication	de novo autosomal dominant	1
261	chromosome 9q34.3 deletion	microdeletion	inherited autosomal dominant	1
262	neuromuscular disease, congenital (RYR1)	single gene disorder (snv)	de novo autosomal dominant	9,10
263	myotonic dystrophy 1 (DMPK)	short tandem repeat disorder	autosomal dominant with anticipation	9,10
264	salla disease (SLC17A5)	single gene disorder (snv)	autosomal recessive (compound heterozygous)	4
265	brain small vessel disease with or without ocular anomalies (COL4A1)	single gene disorder (snv)	de novo autosomal dominant	9
266	myasthenic syndrome, congenital, 16 (SCN4A)	single gene disorder (snv)	autosomal recessive (compound heterozygous)	9,10
267	developmental and epileptic encephalopathy 14 (KCNT1)	single gene disorder (snv)	de novo autosomal dominant	9,10

268	spinal muscular atrophy (SMN1)	single gene disorder (structural variant)	autosomal recessive (homozygous)	9,10,11
269	tuberous sclerosis 2 (TSC2)	single gene disorder (indel)	de novo autosomal dominant	9,10
270	mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (melas) (MT-TL1)	mitochondrial dna disorder	mitochondrial dna disorder	6,10
271	spinal muscular atrophy (SMN1)	single gene disorder (structural variant)	autosomal recessive (homozygous)	9,10,11
272	spinal muscular atrophy (SMN1)	single gene disorder (structural variant)	autosomal recessive (homozygous)	9,10,11
273	DICER1 tumor predisposition (DICER1)	single gene disorder (indel)	inherited autosomal dominant	9
274	kabuki syndrome 1 (KMT2D)	single gene disorder (indel)	de novo autosomal dominant	9,10
275	22q11.2 deletion syndrome	karyotypically visible abnormality	other (balanced chromosomal translocation in a parent)	6,10
276	22q11.2 deletion syndrome	microdeletion	de novo autosomal dominant	2,10
277	mental retardation autosomal recessive 13 (TRAPPC9)	single gene disorder (snv)	autosomal recessive (compound heterozygous)	
278	filippi syndrome (CKAP2L)	single gene disorder (snv)	autosomal recessive (compound heterozygous)	
279	chromosome 19p13.13 deletion syndrome	microdeletion	de novo autosomal dominant	
280	developmental and epileptic encephalopathy 48 (AP3B2)	single gene disorder (snv)	autosomal recessive (homozygous)	3,10
281	allan-herndon-dudley syndrome (SLC16A2)	single gene disorder (indel)	x-linked (inheritance unknown)	7,9,10
282	chromosome 3q26 triplication	microduplication	de novo autosomal dominant	
283	cri-du-chat syndrome	microdeletion	de novo autosomal dominant	
284	noonan syndrome 6 (NRAS)	single gene disorder (snv)	de novo autosomal dominant	9,10
285	UFSP2-related neurodevelopmental disorder (UFSP2)	single gene disorder (snv)	autosomal recessive (homozygous)	
286	developmental and epileptic encephalopathy 3 (SLC25A22)	single gene disorder (snv)	autosomal recessive (homozygous)	10
287	chromosome 3q29 microdeletion syndrome	microdeletion	de novo autosomal dominant	
288	10p15.1-p12.1 deletion (GATA3)	karyotypically visible abnormality	de novo autosomal dominant	
289	chromosome 14q11-q22 deletion syndrome	karyotypically visible abnormality	de novo autosomal dominant	
290	rett syndrome, congenital variant (FOXG1)	single gene disorder (snv)	de novo autosomal dominant	
291	spinal muscular atrophy (SMN1)	single gene disorder (structural variant)	autosomal recessive (homozygous)	9,10,11
292	lissencephaly 1 (PAFAH1B1)	single gene disorder (indel)	de novo autosomal dominant	

293	trisomy 13	karyotypically visible abnormality	other	
294	cardiofaciocutaneous syndrome (BRAF)	single gene disorder (snv)	de novo autosomal dominant	9
295	neurodevelopmental disorder with epilepsy, cataracts, feeding difficulties, and delayed brain myelination (NACC1)	single gene disorder (snv)	de novo autosomal dominant	
296	charge syndrome (CHD7)	single gene disorder (snv)	de novo autosomal dominant	9
297	kbg syndrome (ANKRD11)	single gene disorder (indel)	de novo autosomal dominant	
298	crouzon syndrome (FGFR2)	single gene disorder (snv)	de novo autosomal dominant	9
299	cardiofaciocutaneous syndrome 3 (MAP2K1)	single gene disorder (snv)	de novo autosomal dominant	9
300	spinal muscular atrophy (SMN1)	single gene disorder (structural variant)	autosomal recessive (homozygous)	9,10,11
301	down syndrome	karyotypically visible abnormality	other	10
302	encephalopathy, lethal, due to defective mitochondrial peroxisomal fission 1 (DNM1L)	single gene disorder (snv)	autosomal recessive (homozygous)	
303	sotos syndrome 1 (NSD1)	single gene disorder (indel)	de novo autosomal dominant	9
304	schinzel-giedion midface retraction syndrome (SETBP1)	single gene disorder (snv)	de novo autosomal dominant	9
305	pallister-killian syndrome	karyotypically visible abnormality	other	
306	episodic ataxia/myokymia syndrome (KCNA1)	single gene disorder (snv)	inherited autosomal dominant	1,9
306	microcephalic osteodysplastic primordial dwarfism, type 2 (PCNT)	single gene disorder (snv, indel)	autosomal recessive (compound heterozygous)	1
307	wolf-hirschhorn syndrome	karyotypically visible abnormality	de novo autosomal dominant	
308	down syndrome	karyotypically visible abnormality	other	10
309	masa syndrome (L1CAM)	single gene disorder (snv)	inherited x-linked	
310	developmental and epileptic encephalopathy 7 (KCNQ2)	single gene disorder (snv)	de novo autosomal dominant	9,10,12
311	myotonic dystrophy 1 (DMPK)	short tandem repeat disorder	autosomal dominant with anticipation	9,10
312	cockayne syndrome, type a (ERCC8)	single gene disorder (indel)	autosomal recessive (compound heterozygous)	9,10
313	spinal muscular atrophy (SMN1)	single gene disorder (structural variant, indel)	autosomal recessive (compound heterozygous)	9,10,11
314	developmental and epileptic encephalopathy 11 (SCN2A)	single gene disorder (snv)	de novo autosomal dominant	9,10
315	22q11.2 deletion syndrome	microdeletion	de novo autosomal dominant	10
316	congenital disorder of glycosylation, type 2m (SLC35A2)	single gene disorder (snv)	de novo x-linked	9,10

317	kleefstra syndrome 1	microdeletion	de novo autosomal dominant	
318	down syndrome	karyotypically visible abnormality	other	10
319	wolf-hirschhorn syndrome	karyotypically visible abnormality	de novo autosomal dominant	
320	developmental and epileptic encephalopathy 74 (GABRG2)	single gene disorder (snv)	de novo autosomal dominant	10
321	developmental and epileptic encephalopathy 7 (KCNQ2)	single gene disorder (snv)	de novo autosomal dominant	9,10,12
322	pelizaeus-merzbacher disease (PLP1)	single gene disorder (indel)	inherited x-linked	
323	down syndrome	karyotypically visible abnormality	other	1,10
323	neurofibromatosis type 1 (NF1)	single gene disorder (snv)	de novo autosomal dominant	1,9,10
324	cri-du-chat syndrome	karyotypically visible abnormality	other (de novo unbalanced translocation)	
325	neurofibromatosis type 1 (NF1)	single gene disorder (snv)	inherited autosomal dominant	9,10
326	down syndrome	karyotypically visible abnormality	other	10
327	glycogen storage disease 2 (GAA)	single gene disorder (snv, indel)	autosomal recessive (compound heterozygous)	9,10
328	neurofibromatosis type 1 (NF1)	single gene disorder (indel)	de novo autosomal dominant	9,10
329	7q22.1-q22.3 deletion (incl. SHFM1 locus)	microdeletion	de novo autosomal dominant	
330	glycogen storage disease 2 (GAA)	single gene disorder (snv)	autosomal recessive (homozygous)	4,9,10
331	spinal muscular atrophy, x-linked 2, infantile (UBA1)	single gene disorder (snv)	inherited x-linked	
332	developmental and epileptic encephalopathy 47 (FGF12)	single gene disorder (snv)	de novo autosomal dominant	10
333	rett syndrome (MECP2)	single gene disorder (indel)	de novo x-linked	10
334	congenital disorder of glycosylation, type 1a (PMM2)	single gene disorder (snv)	autosomal recessive (compound heterozygous)	9,10
335	cardiofaciocutaneous syndrome 3 (MAP2K1)	single gene disorder (snv)	de novo autosomal dominant	9
336	mosaic trisomy 9	karyotypically visible abnormality	other	8
337	genitopatellar syndrome (KAT6B)	single gene disorder (snv)	de novo autosomal dominant	9
338	trisomy 18	karyotypically visible abnormality	other	
339	chromosome 3q29 microdeletion syndrome	microdeletion	de novo autosomal dominant	
340	rubinstein-taybi syndrome 1 (CREBBP)	single gene disorder (indel)	de novo autosomal dominant	9

341	tuberous sclerosis 2 (TSC2)	single gene disorder (indel)	de novo autosomal dominant	9,10
342	down syndrome	karyotypically visible abnormality	other	10
343	down syndrome	karyotypically visible abnormality	other	10
344	SCN4A-related congenital myopathy (SCN4A)	single gene disorder (snv, indel)	autosomal recessive (compound heterozygous)	9,10
345	charge syndrome (CHD7)	single gene disorder (snv)	de novo autosomal dominant	9
346	ullrich congenital muscular dystrophy (COL6A1)	single gene disorder (snv)	de novo autosomal dominant	10
347	down syndrome	karyotypically visible abnormality	other	10
348	muscular dystrophy-dystroglycanopathy (congenital with brain and eye anomalies), type A, 4 (FKTN)	single gene disorder (snv)	autosomal recessive (homozygous)	9
349	mitochondrial complex 1 deficiency, nuclear type 2 (NDUFS8)	single gene disorder (snv)	autosomal recessive (homozygous)	
350	leukoencephalopathy with vanishing white matter (EIF2B5)	single gene disorder (snv)	autosomal recessive (compound heterozygous)	9
351	infantile neuroaxonal dystrophy 1 (PLA2G6)	single gene disorder (snv)	autosomal recessive (compound heterozygous)	
352	congenital disorder of glycosylation type 1d (ALG3)	single gene disorder (snv)	autosomal recessive (homozygous)	9
353	down syndrome	karyotypically visible abnormality	other	10
354	down syndrome	karyotypically visible abnormality	other	10
355	chromosome 1p36 deletion syndrome	karyotypically visible abnormality	de novo autosomal dominant	
356	MYH7-related myopathy (MYH7)	single gene disorder (snv)	de novo autosomal dominant	9,10
357	schaaf-yang syndrome (MAGEL2)	single gene disorder (snv)	de novo autosomal dominant	9
358	trisomy 18	karyotypically visible abnormality	other	
359	phosphoribosylpyrophosphate synthetase superactivity (PRPS1)	single gene disorder (snv)	inherited x-linked	9
360	wolf-hirschhorn syndrome	karyotypically visible abnormality	de novo autosomal dominant	
361	costello syndrome (HRAS)	single gene disorder (snv)	de novo autosomal dominant	9
362	cockayne syndrome, type b (ERCC6)	single gene disorder (indel)	autosomal recessive (homozygous)	9
363	wieacker-wolff syndrome (ZC4H2)	single gene disorder (snv)	de novo x-linked	
364	down syndrome	karyotypically visible abnormality	other	10
365	menke-hennekam syndrome 1 (CREBBP)	single gene disorder (indel)	de novo autosomal dominant	9

366	developmental and epileptic encephalopathy 5 (SPTAN1)	single gene disorder (snv)	de novo autosomal dominant	10
367	temple syndrome	imprinting disorder	other	
368	chromosome 17q12 deletion syndrome	microdeletion	inherited autosomal dominant	3
369	chromosome 17q12 deletion syndrome	microdeletion	inherited autosomal dominant	3
370	chromosome 2q24 deletion syndrome	microdeletion	de novo autosomal dominant	
371	kagami-ogata syndrome	microdeletion	de novo autosomal dominant	
372	kleefstra syndrome 1	microdeletion	de novo autosomal dominant	
373	spondyloepimetaphyseal dysplasia, faden-alkuraya type (RSPRY1)	single gene disorder (snv)	autosomal recessive (homozygous)	
374	spinal muscular atrophy (SMN1)	single gene disorder (structural variant)	autosomal recessive (homozygous)	9,10,11
375	developmental and epileptic encephalopathy 58 (NTRK2)	single gene disorder (snv)	de novo autosomal dominant	10
376	pyruvate dehydrogenase e1-alpha deficiency (PDHA1)	single gene disorder (snv)	de novo x-linked	9
377	spinal muscular atrophy, lower extremity-predominant 1 (DYNC1H1)	single gene disorder (snv)	de novo autosomal dominant	
378	rett syndrome, congenital variant (FOXG1)	single gene disorder (indel)	de novo autosomal dominant	
379	tuberous sclerosis 2 (TSC2)	single gene disorder (snv)	de novo autosomal dominant	9,10
380	bilateral frontoparietal polymicrogyria (ADGRG1)	single gene disorder (snv)	autosomal recessive (homozygous)	
381	wolf-hirschhorn syndrome	microdeletion	de novo autosomal dominant	
382	chromosome 16p11.2 duplication syndrome	microduplication	inherited autosomal dominant	1
382	chromosome 16p12.2 deletion syndrome	microdeletion	inherited autosomal dominant	1
383	metachromatic leukodystrophy (ARSA)	single gene disorder (snv)	autosomal recessive (homozygous)	9,10,11,12
384	mucopolysaccharidosis ii (IDS)	single gene disorder (structural variant)	x-linked (inheritance unknown)	7,9,10,12
385	brown-vialetto-van laere syndrome 1 (SLC52A3)	single gene disorder (snv)	autosomal recessive (homozygous)	9
386	loeys-dietz syndrome 1 (TGFBR1)	single gene disorder (snv)	de novo autosomal dominant	9
387	mosaic trisomy 22	karyotypically visible abnormality	other	
388	developmental and epileptic encephalopathy 76 (ACTL6B)	single gene disorder (snv)	autosomal recessive (homozygous)	1,10
388	persistent mullerian duct syndrome type 1 (AMH)	single gene disorder (snv)	autosomal recessive (homozygous)	1,9

389	cystinuria (SLC7A9)	single gene disorder (snv)	autosomal dominant (unknown)	2,7,9,10
390	beckwith-wiedemann syndrome	imprinting disorder	other	8
391	hypotonia, infantile, with psychomotor retardation and characteristic facies 3 (TBCK)	single gene disorder (indel)	autosomal recessive (homozygous)	
392	cutis laxa type 2b (PYCR1)	single gene disorder (snv)	autosomal recessive (compound heterozygous)	
393	neurodegeneration with brain iron accumulation 5 (WDR45)	single gene disorder (snv)	de novo x-linked	10
394	williams-beuren syndrome	microdeletion	de novo autosomal dominant	10
395	prader-willi syndrome	microdeletion	de novo autosomal dominant	10
396	koolen-de vries syndrome	microdeletion	de novo autosomal dominant	
397	sucrase-isomaltase deficiency, congenital (SI)	single gene disorder (snv)	autosomal recessive (homozygous)	1,4,9
397	neuronopathy, distal hereditary motor, type VI (IGHMBP2)	single gene disorder (snv)	autosomal recessive (homozygous)	1,9
398	muscular dystrophy-dystroglycanopathy (congenital with mental retardation), type B, 1 (POMT1)	single gene disorder (indel)	autosomal recessive (homozygous)	9
399	ifap syndrome with or without bresheck syndrome (MBTPS2)	single gene disorder (snv)	inherited x-linked	
400	developmental and epileptic encephalopathy 26 (KCNB1)	single gene disorder (snv)	de novo autosomal dominant	10
401	osteogenesis imperfecta, type VIII (P3H1)	single gene disorder (snv)	autosomal recessive (homozygous)	10
402	ceroid lipofuscinosis, neuronal, 6 (CLN6)	single gene disorder (snv)	autosomal recessive (homozygous)	4,12
403	joubert syndrome 20 (TMEM231)	single gene disorder (snv)	autosomal recessive (homozygous)	
404	ceroid lipofuscinosis, neuronal, 7 (MFSD8)	single gene disorder (snv)	autosomal recessive (homozygous)	9
405	down syndrome	karyotypically visible abnormality	other	10
406	sbbyss syndrome (KAT6B)	single gene disorder (indel)	de novo autosomal dominant	9
407	rubinstein-taybi syndrome 2 (EP300)	single gene disorder (snv)	de novo autosomal dominant	9,10
408	deafness, autosomal recessive 1a (GJB2)	single gene disorder (snv)	autosomal recessive (homozygous)	2,9
409	spastic ataxia 8, autosomal recessive, with hypomyelinating leukodystrophy (NKX6-2)	single gene disorder (indel)	autosomal recessive (homozygous)	
410	ectodermal dysplasia 1, hypohidrotic, x-linked (EDA)	single gene disorder (snv)	inherited x-linked	10
411	developmental and epileptic encephalopathy 11 (SCN2A)	single gene disorder (snv)	de novo autosomal dominant	9,10
412	anterior segment dysgenesis 7, with sclerocornea (PXDN)	single gene disorder (snv, indel)	autosomal recessive (compound heterozygous)	2.9

413	rett syndrome, congenital variant (FOXG1)	single gene disorder (indel)	de novo autosomal dominant	
414	intellectual developmental disorder, x-linked, syndromic, hedera type (ATP6AP2)	single gene disorder (indel)	de novo x-linked	5,9
415	noonan syndrome 3 (KRAS)	single gene disorder (snv)	de novo autosomal dominant	9,10
416	developmental and epileptic encephalopathy 50 (CAD)	single gene disorder (snv)	autosomal recessive (homozygous)	9,10
417	PIK3CA-related overgrowth spectrum (PIK3CA)	single gene disorder (snv)	de novo autosomal dominant	9,10
418	hemorrhagic destruction of the brain, subependymal calcification, and cataracts (JAM3)	single gene disorder (snv)	autosomal recessive (compound heterozygous)	4,5
419	intellectual developmental disorder, x-linked syndromic, snyder-robinson type (SMS)	single gene disorder (snv)	de novo x-linked	5,9
420	mirage syndrome (SAMD9)	single gene disorder (snv)	inherited autosomal dominant	9
421	raynaud-claes syndrome (CLCN4)	single gene disorder (snv)	de novo x-linked	
422	fanconi renotubular syndrome 4, with maturity-onset diabetes of the young (HNF4A)	single gene disorder (snv)	inherited autosomal dominant	2,9,10
423	intellectual developmental disorder, x-linked 12 (THOC2)	single gene disorder (snv)	de novo x-linked	
424	developmental and epileptic encephalopathy 4 (STXBP1)	single gene disorder (snv)	de novo autosomal dominant	10
425	FBXW7-related neurodevelopmental disorder (FBXW7)	single gene disorder (snv)	de novo autosomal dominant	
426	kabuki syndrome 2 (KDM6A)	single gene disorder (indel)	inherited x-linked	9
427	pyruvate dehydrogenase e1-alpha deficiency (PDHA1)	single gene disorder (indel)	de novo x-linked	9
428	intellectual developmental disorder and microcephaly with pontine and cerebellar hypoplasia (CASK)	single gene disorder (indel)	de novo x-linked	9
429	cornelia de lange syndrome 5 (HDAC8)	single gene disorder (indel)	de novo x-linked	10
430	neurodevelopmental disorder with structural brain anomalies and dysmorphic facies (RAC3)	single gene disorder (snv)	de novo autosomal dominant	
431	cystic fibrosis (CFTR)	single gene disorder (snv)	autosomal recessive (compound heterozygous)	2,9,10
432	down syndrome	karyotypically visible abnormality	other	10

Comment code legend

Comment code 1: child with two different molecularly confirmed genetic diagnoses.
Comment code 2: child where the genetic diagnosis does not explain all the major phenotypic features (i.e., “partial diagnosis”).
Comment code 3: child whose family member(s) are also in this cohort.
Comment code 4: child’s genetic variant is intronic and disrupts a canonical splice site.
Comment code 5: child’s genetic variant is intronic and not within a canonical splice site.
Comment code 6: estimated recurrence risk to parents is >1% but otherwise uncertain.

Comment code 7: estimated recurrence risk to parents is unclear (parental testing not performed).
Comment code 8: child's genetic variant not detectable by genome sequencing. We concluded that all exonic and intronic single nucleotide variants (SNVs), small insertions/deletions (indels), structural variants (including *SMN1* deletions), short-tandem repeat expansions at known disease loci, non-mosaic chromosome imbalances / copy number variation, uniparental disomy, and mitochondrial DNA variation (heteroplasmy >5%) that was diagnostic in this cohort could have been reliably detected by trio short-read genome sequencing.[15] In four instances of mosaic aneuploidy detected by blood-based testing, we conservatively estimated that genome sequencing might have missed the one instance where the mosaicism fraction was <50%. Two instances of KvDMR hypomethylation causing Beckwith-Wiedemann syndrome would not have been detectable by genome sequencing with current methods. Our observation here is that genome sequencing would have been sufficient (not necessary) to diagnose most conditions in this cohort. As with other molecular tests like chromosomal microarray analysis, follow-up genetic testing would still be required in some instances to, e.g., confirm chromosome structure.
Comment code 9: genetic diagnosis with one or more clinically approved/available specialized treatment(s).
Comment code 10: genetic diagnosis with active clinical trial(s) for one or more specialized treatment(s).
Comment code 11: genetic diagnosis with one or more clinically approved/available genetic therapies (e.g., gene replacement, gene editing, antisense oligonucleotide).
Comment code 12: genetic diagnosis with active clinical trial(s) for one or more genetic therapies (e.g., gene replacement, gene editing, antisense oligonucleotide). There are 14 conditions in this cohort with genetic therapies in clinical trials listed in the ClinicalTrials.gov database and/or the EU Clinical Trials Registry (ClinicalTrials.gov Identifiers: NCT03770572, NCT02725580, NCT03466463, NCT03934268, NCT03517085, NCT05224505, NCT03199469, NCT05152823, NCT04798235, NCT01801709, NCT01560182, NCT02559830, NCT00004454, NCT04571970, NCT04851873, NCT03955679, NCT03837184).

Supplemental References

1. Cohen E, Berry JG, Camacho X, et al. Patterns and costs of health care use of children with medical complexity. *Pediatrics* 2012;130(6):e1463-70. doi: 10.1542/peds.2012-0175 [published Online First: 2012/11/28]
2. Quartarone S, Lin JLL, Orkin J, et al. Implementing a Care Coordination Strategy for Children with Medical Complexity in Ontario, Canada: A Process Evaluation. *Int J Integr Care* 2022;22(2):9. doi: 10.5334/ijic.6073 [published Online First: 20220428]
3. Lin JLL, Quartarone S, Aidarus N, et al. Process Evaluation of a Hub-and-Spoke Model to Deliver Coordinated Care for Children with Medical Complexity across Ontario: Facilitators, Barriers and Lessons Learned. *Healthc Policy* 2021;17(1):104-22. doi: 10.12927/hcpol.2021.26574
4. Orkin J, Chan CY, Fayed N, et al. Complex care for kids Ontario: protocol for a mixed-methods randomised controlled trial of a population-level care coordination initiative for children with medical complexity. *BMJ Open* 2019;9(8):e028121. doi: 10.1136/bmjopen-2018-028121 [published Online First: 20190801]
5. Oei K, Hayeems RZ, Ungar WJ, et al. Genetic Testing among Children in a Complex Care Program. *Children (Basel)* 2017;4(5) doi: 10.3390/children4050042 [published Online First: 2017/05/23]
6. Miller DT, Adam MP, Aradhya S, et al. Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. *Am J Hum Genet* 2010;86(5):749-64. doi: 10.1016/j.ajhg.2010.04.006
7. Costain G, Walker S, Marano M, et al. Genome Sequencing as a Diagnostic Test in Children With Unexplained Medical Complexity. *JAMA Netw Open* 2020;3(9):e2018109. doi: 10.1001/jamanetworkopen.2020.18109 [published Online First: 2020/09/23]
8. Carter MT, Cloutier M, Tsampalieros A, et al. Genetic and metabolic investigations for individuals with neurodevelopmental disorders: A survey of Canadian geneticists' practices. *Am J Med Genet A* 2021;185(6):1757-66. doi: 10.1002/ajmg.a.62167 [published Online First: 20210315]
9. Stavropoulos DJ, Merico D, Jobling R, et al. Whole Genome Sequencing Expands Diagnostic Utility and Improves Clinical Management in Pediatric Medicine. *NPJ Genom Med* 2016;1:15012-. doi: 10.1038/npjgenmed.2015.12 [published Online First: 2016/01/13]
10. Lionel AC, Costain G, Monfared N, et al. Improved diagnostic yield compared with targeted gene sequencing panels suggests a role for whole-genome sequencing as a first-tier genetic test. *Genet Med* 2018;20(4):435-43. doi: 10.1038/gim.2017.119 [published Online First: 2017/08/05]
11. Ontario H. Genome-Wide Sequencing for Unexplained Developmental Disabilities or Multiple Congenital Anomalies: A Health Technology Assessment. *Ont Health Technol Assess Ser* 2020;20(11):1-178. [published Online First: 20200306]
12. Hayeems RZ, Marshall CR, Gillespie MK, et al. Comparing genome sequencing technologies to improve rare disease diagnostics: a protocol for the evaluation of a pilot project, Genome-wide Sequencing Ontario. *CMAJ Open* 2022;10(2):E460-E65. doi: 10.9778/cmajo.20210272 [published Online First: 20220524]
13. Boycott K, Hartley T, Adam S, et al. The clinical application of genome-wide sequencing for monogenic diseases in Canada: Position Statement of the Canadian College of Medical

Geneticists. *J Med Genet* 2015;52(7):431-7. doi: 10.1136/jmedgenet-2015-103144 [published Online First: 20150507]

14. Manickam K, McClain MR, Demmer LA, et al. Exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability: an evidence-based clinical guideline of the American College of Medical Genetics and Genomics (ACMG). *Genet Med* 2021 doi: 10.1038/s41436-021-01242-6 [published Online First: 2021/07/03]
15. Marshall CR, Chowdhury S, Taft RJ, et al. Best practices for the analytical validation of clinical whole-genome sequencing intended for the diagnosis of germline disease. *NPJ Genom Med* 2020;5:47. doi: 10.1038/s41525-020-00154-9 [published Online First: 2020/10/29]