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

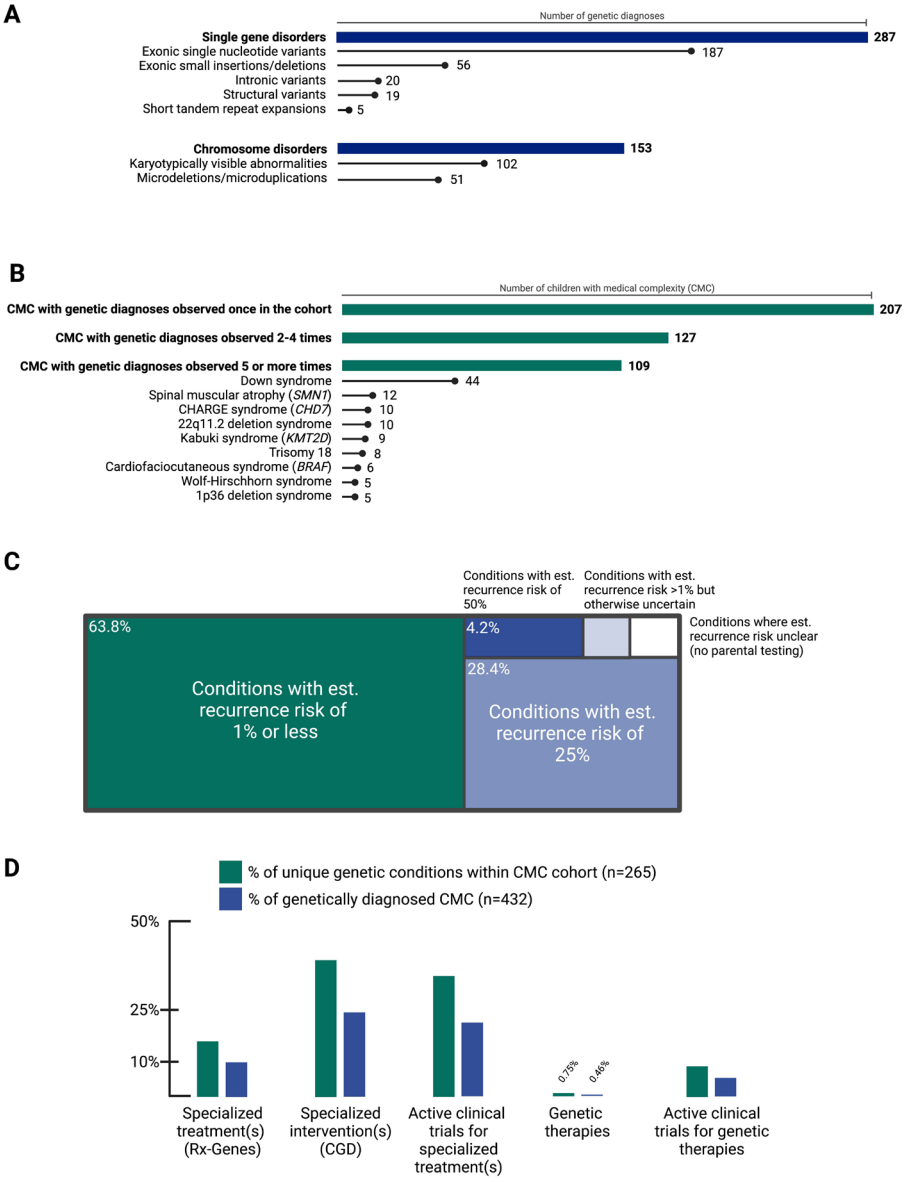

Figure 1 Individually rare genetic conditions are a collectively important contributor to childhood medical complexity. (A) Bar chart displaying counts of primary genetic diagnoses in the children with medical complexity (CMC) study cohort, by variant type(s). For situations of compound heterozygosity 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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