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Clinical and biological landscape of constitutional mismatch–repair deficiency syndrome: an International Replication Repair Deficiency Consortium cohort study

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Abstract

Background: Constitutional mismatch repair deficiency (CMMRD) syndrome is a rare and aggressive cancer predisposition syndrome. Because a scarcity of data on this condition contributes to management challenges and poor outcomes, we aimed to describe the clinical spectrum, cancer biology, and impact of genetics on patient survival in CMMRD.

Methods: In this cohort study, we collected cross-sectional and longitudinal data on all patients with CMMRD, with no age limits, registered with the International Replication Repair Deficiency Consortium (IRRDC) across more than 50 countries. Clinical data were extracted from the IRRDC database, medical records, and physician-completed case record forms. The primary objective was to describe the clinical features, cancer spectrum, and biology of the condition. Secondary objectives included estimations of cancer incidence and of the impact of the specific mismatch-repair gene and

genotype on cancer onset and survival, including after cancer surveillance and immunotherapy interventions.

Findings: We analysed data from 201 patients (103 males, 98 females) enrolled between June 5, 2007 and Sept 9, 2022. Median age at diagnosis of CMMRD or a related cancer was 8.9 years (IQR 5.9-12.6), and median follow-up from diagnosis was 7.2 years (3.6-14.8). Endogamy among minorities and closed communities contributed to high homozygosity within countries with low consanguinity. Frequent dermatological manifestations (117 [93%] of 126 patients with complete data) led to a clinical overlap with neurofibromatosis type 1 (35 [28%] of 126). 339 cancers were reported in 194 (97%) of 201 patients. The cumulative cancer incidence by age 18 years was 90% (95% CI 80-99). Median time between cancer diagnoses for patients with more than one cancer was 1.9 years (IQR 0.8-3.9). Neoplasms developed in 15 organs and included early-onset adult cancers. CNS tumours were the most frequent (173 [51%] cancers), followed by gastrointestinal (75 [22%]), haematological (61 [18%]), and other cancer types (30 [9%]). Patients with CNS tumours had the poorest overall survival rates (39% [95% CI 30-52] at 10 years from diagnosis; log-rank $p < 0.0001$ across four cancer types), followed by those with haematological cancers (67% [55-82]), gastrointestinal cancers (89% [81-97]), and other solid tumours (96% [88-100]). All cancers showed high mutation and microsatellite indel burdens, and pathognomonic mutational signatures. MLH1 or MSH2 variants caused earlier cancer onset than PMS2 or MSH6 variants, and inferior survival (overall survival at age 15 years 63% [95% CI 55-73] for PMS2, 49% [35-68] for MSH6, 19% [6-66] for MLH1, and 0% for MSH2; $p < 0.0001$). Frameshift or truncating variants within the same gene caused earlier cancers and inferior outcomes compared with missense variants ($p < 0.0001$). The greater deleterious effects of MLH1 and MSH2 variants as compared with PMS2 and MSH6 variants persisted despite overall improvements in survival after surveillance or immune checkpoint inhibitor interventions.

Interpretation: The very high cancer burden and unique genomic landscape of CMMRD highlight the benefit of comprehensive assays in timely diagnosis and precision approaches toward surveillance and immunotherapy. These data will guide the clinical management of children and patients who survive into adulthood with CMMRD.

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