# Constitutional or biallelic? Settling on a name for a recessively inherited cancer susceptibility syndrome

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COMMUNICATIONS

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Homozygous or compound heterozygous, that is, biallelic, germ-line mutations in one of the four mismatch repair (MMR) genes cause a rare condition that has only recently been recognised as a distinct childhood cancer susceptibility syndrome. As such there is still a lack of awareness of the condition among paediatric oncologists. Timely recognition of the condition that results in an extraordinarily high cancer risk also has far-reaching consequences for other family members. It is therefore important that the medical and scientific community reaches agreement on a standard name for this condition, because the use of different names could potentially create confusion. It is for this reason that we wish to comment on a new designation for this recessively inherited condition that was proposed in a recent paper by Shlien *et al*.[1]

Retrospectively, it now seems almost certain (although not proven genetically) that the first patients with this cancer syndrome were described by Turcot *et al*.[2] However, analysis of, so far, some 150 patients with biallelic inactivating mutations in one of the four MMR genes, *MLH1*, *MSH2*, *MSH6* and *PMS2*, shows that tumour spectrum of this cancer predisposition syndrome is much broader than that of Turcot syndrome.[3] Therefore, the comprehensive designation 'mismatch repair-deficiency syndrome' that alluded to the underlying pathogenic mechanism of the condition became the most widely used name. In a review article summarising the then current understanding of the condition, this designation originally coined by Scott *et al*[4] was extended to 'constitutional mismatch repair-deficiency' in order to avoid possible confusion with the somatic mismatch repair-deficiency found in Lynch syndrome-related tumours and sporadic tumours associated with *MLH1* hypermethylation.[5] The amended name, 'constitutional mismatch repair-deficiency', has now been used in approximately 30 publications. Moreover, the senior author of the Shlien *et al* publication, Uri Tabori, founded and leads the international consortium originally named the 'constitutional mismatch repair deficiency consortium'.[6]

We therefore find it difficult to understand why this condition should now be renamed to 'biallelic mismatch repair deficiency' syndrome. MMR deficiency may be limited to somatic neoplastic cells or may already be present at the zygote stage and consequently affect all cells of an individual, explaining the term 'constitutional', whereas 'biallelic' simply refers to the MMR gene mutation status that causes the condition—but such biallelic mutations could be germ-line or somatic in origin. Moreover, 'mismatch repair deficiency' is a phenotype, whereas 'biallelic' refers to the genotype. Hence, the specification 'constitutional' is far more precise. Furthermore, the term used by OMIM to describe the condition, 'mismatch repair cancer syndrome' (OMIM #276300), the use of which is in fact limited to OMIM, also lacks the essential designation that indeed *deficiency* of MMR capacity leads to cancer predisposition. Based on the above, we would argue that 'constitutional mismatch repair deficiency' (recently abbreviated to CMMRD, rather than CMMR-D, for improved ease of use) is the most appropriate name for the syndrome and we strongly advocate that the medical and scientific community continues to adhere to its use in all future reports.

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