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MULTICENTRE APPROACH TO IMPROVE THE IDENTIFICATION AND MANEGEMENT OF CMMRD PATIENTS IN SPAIN

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Introduction:

Constitutional mismatch repair deficiency (CMMRD) is a rare and devastating childhood-onset cancer predisposition syndrome caused by biallelic germline pathogenic variants in mismatch repair (MMR) genes (*PMS2, MSH6*, *MLH1*, *MSH2*). An accurate and prompt diagnosis is essential to implement genetic counseling, cancer surveillance and effective treatments. However, clinical diagnosis of CMMRD is particularly challenging due to its extremely low prevalence, the broad spectrum of associated tumors, and its overlapping phenotype with other hereditary cancer syndromes. Furthermore, CMMRD genetic diagnosis is hampered by difficulties in *PMS2* analysis and by the identification of MMR variants of unknown significance.

Objective:

The overarching goal of our study is to improve CMMRD identification in Spain as well as clinical management of carrier patients.

Methodology:

We have promoted the creation of an interdisciplinary group of experts in CMMRD from 21 medical centres across different Spanish regions. CMMRD-suspected patients have been recruited. Highly sensitive assessment of microsatellite instability (MSI) in blood samples using hs-MSI approach was used to confirm CMMRD diagnosis. Clinical data and biological samples from confirmed CMMRD cases (including blood and other fluids, non-malignant tissue and tumours) were collected at diagnosis and during surveillance. Tumours diagnosed during follow-up were analysed using TruSight Oncology *500 assay.*

Results:

Thirteen CMMRD suspected patients have been identified by participating centers. CMMRD diagnosis have been confirmed in five of them (1 *PMS2*, 2 *MSH6*, 1 *MSH2*, 1 *MLH1*), presenting positive hs-MSI scores in blood. Our

findings increase the number of CMMRD patients in our country to 14 patients, belonging to 11 families of different geographic origin. The following 201 samples were collected from the patients: 33 blood, 19 urine, 14 oral mucosa, 57 normal tissue, and 39 tumors. The twelve tumors analyzed (Burkitt lymphomas, lymphoblastic lymphomas T, Wilms tumor, high grade gliomas and hepatoblastoma) presented high levels of hs-MSI scores (from 12.9 to 51.41). Mutational profiling in a subset of four high grade gliomas identified specific drivers and actionable mutations in all of them. All tumors showed high tumor mutational burden (>10mutations/MB), being two of them ultrahypermutated (>100 mutations/Mb). As a parallel strategy to improve CMMRD identification, we have started a national-wide population screening of CMMRD in paediatric patients diagnosed with high grade glioma or T-cell lymphoma.

Conclusions:

The constitution of a multi-center multidisciplinary network of CMMRD experts have made possible the identification of new CMMRD patients and the establishment of a national-wide screening of CMMRD. Further molecular analysis in prospectively collected samples may help to design future screening strategies in this syndrome.