FAMILIAL CANCER CLINICAL UNIT

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CLINICAL, DIAGNOSTIC AND RESEARCH HIGHLIGHTS

Mosaic variegated aneuploidy (MVA). Using WES we found biallelic loss-of-function MAD1 mutations in a 30-year-old female with multiple cancers, together with a constellation of benign neoplasia derived from the 3 embryonic layers, and developmental defects. The patient showed the highest rate in any gene involved in SAC (FIGURE 1) and MAD1 protein absence, a circumstance that is in principle incompatible with embryonic development. In collaboration with other CNIO groups, we are investigating the relationship between aneuploidy and tumorigenesis, trying to identify a second mechanism—a dysfunction in APC/C or in another biological process involved in ensuring chromosome segregation—that could contribute to cell viability or evasion of embryonic lethality.

Deciphering the role of rare variants in Breast Cancer (BC). Earlier in 2021, the 2 largest BC case-control studies published so far confirmed 11 genes associated with BC susceptibility and that therefore should be included in diagnostic testing. All these genes were already considered clinically relevant, except BARD1, whose role in BC susceptibility had not been clearly established until now. Based on these results, we included BARD1 in our diagnostic panel, and we analysed the gene in a large series of 2000 BRCAX Spanish families. We found a strikingly high proportion of large deletions in the gene that suggest the existence of regional differences in the spectrum of mutations in the Spanish population.

Identification of new BC susceptibility genes. We previously identified RECQL5, a member of the RECQL-helicases family, as a new BC susceptibility candidate. More recently, we identified 13 additional candidate genes that are currently being analysed by NGS to evaluate their role in the disease in a large set of 3000 Spanish BC families.

DNA glycosylase inhibitors as a new therapeutic approach in hereditary BC patients. We are exploring the possible therapeutic use of OGG1 glycosylase inhibitors in BC patients. We found that the inactivation of BER by the OGG1 THS487 increases the accumulation of oxidised bases at the telomeres, leading to telomere loss and post-mitotic defects. Moreover, we discovered that THS487 enhances the activity of the PARP1 inhibitor olaparib in BRCA1 deficient cells.

Clinical and diagnostic activity. During 2021, our consultancy at the Fuenlabrada Hospital was visited by 397 patients and 900 genetic studies were performed in the laboratory.

OVERVIEW

Mosaic variegated aneuploidy (MVA) is a rare genetic condition that groups together a number of individuals with constitutional mosaic aneuploidies involving different chromosomes, associated with a constellation of clinical features such as developmental delay, microcephaly, and other congenital defects. Cancer predisposition, especially embryonal tumours, is one of the most important clinical signs of MVA. Among several others, spindle assembly checkpoint (SAC) is an important mechanism involved in the correct segregation of chromosomes, thus preventing the appearance of aneuploidies. To date, 3 SAC genes—BUBB, CEP57, and TRIP13—have been identified as being involved in MVA. Mutations in these genes only account for a proportion of MVA patients. The identification of new genes involved in MVA is not only essential for genetic counselling and for the management of these patients, but also to unravel the complex relationship between aneuploidy and carcinogenesis.

We also continued our research to try to decipher the genetic bases of familial breast and colorectal cancer, and to apply such knowledge to clinical practice through our Familial Cancer Consultancy in the Fuenlabrada University Hospital. In addition to both identifying new genes involved in the susceptibility to these tumours and quantifying the associated risk, we have also been exploring new therapeutic tools that could be useful in the future.

PUBLICATIONS


