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Characterization of the germline and somatic mutation profile in familial pancreatic cancer reveals pathogenic germline variants and potentially druggable somatic mutations.

Julie Earl[1,2], Maria E. Castillo[1], Emma Barreto[1], Mercedes Rodríguez-Garrote [1,2], Vanessa Pachón[1,2], Reyes Ferreiro[1], Maria Villamayor[1], David García-Seisdedos[3,] Gloria Muñoz[3] and Alfredo Carrato[1,2,4]

[1]Molecular epidemiology and predictive tumor markers group, Ramón y Cajal Health Research Institute (IRYCIS), Carretera Colmenar Km 9,100. 28034. Madrid, Spain.

[2]Biomedical Research Network in Cancer (CIBERONC)

[3]Translational Genomics Core Facility, Ramón y Cajal Health Research Institute (IRYCIS), Madrid, Spain.

[4]Alcala University, Madrid, Spain

Purpose: Familial pancreatic cancer (FPC) is a rare disorder defined as a family with at least two affected first-degree relatives and appears to be inherited in an autosomal dominant manner. An estimated 4-10% of cases have a familial background with an unknown genetic basis in the majority of cases. The Spanish familial pancreatic cancer registry (Pan-Gen-FAM) was established in 2009 with the principal objective to characterize the phenotypic and genetic background of FPC. This study analyzed the germline and somatic mutation profile in sporadic and familial PDAC cases with the aim to determine the genetic cause of FPC and identify potentially druggable mutations that can be exploited in the clinic.

Materials and methods: Panel sequencing of germline DNA was performed of 35 genes associated with hereditary cancer in 43 PDAC cases from families with an apparent hereditary pancreatic cancer syndrome using the Sureselect technology (Agilent). BEAMing was also performed for the detection of a KRAS mutation in plasma and panel sequencing using the TruSight15 panel (Illumina).

Results: Pathogenic germline variants were identified in 19% (5/26) of PDAC cases from pure FPC families in the genes *MLH1, CDKN2A, POLQ* and *FANCM*. Low frequency potentially pathogenic VUS were also identified in 35% (9/26) of PDAC cases in the genes *FANCC, MLH1, PMS2, CFTR, APC* and *MUTYH*. The concentration of cfDNA in plasma correlated with disease stage and overall survival (OS). The frequency of KRAS mutations detected by BEAMing in plasma was 59% in sporadic cases and 17% in familial cases. Although, TP53 mutations appeared at a similar frequency (61% FPC vs. 71% SP). Mutations were found in the following potentially druggable genes in combination with

TP53: KIT, AKT, PDGFR, ERBB2, PIK3CA and BRAF in familial PDAC and KRAS negative sporadic cases.

Conclusions: The genetic basis of familial pancreatic cancer can be explained in 21% of families by known hereditary cancer genes.

The level of cfDNA in plasma appears to be a prognostic indicator, independently of the detection of tumor specific mutations.

FPC and KRAS negative sporadic cases harbor potentially druggable somatic mutations in combination TP53.