AB033. P003. Identification of germline mutations in cancer predisposition genes in patients with a personal and/or family history of pancreatic cancer

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Background: Pancreatic cancer is estimated to have a familial background in 5–10%. Although the underlying genetic basis for most of the familial clustering remains elusive, multiple known hereditary syndromes and genes are associated with an increased risk of developing pancreatic cancer.

Methods: We performed a retrospective genetic evaluation of 80 cancer patients with a presumed genetic predisposition for pancreatic cancer. The probands were selected from seven strata based on personal or family history of pancreatic cancer, breast and/or ovarian cancer, colon cancer or melanoma. Germline DNA was analyzed using a custom designed HEAT-Seq target panel of 52 (pancreatic) cancer susceptibility genes (Roche) and sequencing was performed on a MiSeq instrument. Detected variants were confirmed with Sanger sequencing.

Results: Fifteen patients (18.75%) were heterozygous for at least one loss of function germline mutation in one of 52 (pancreatic) cancer susceptibility genes. We detected 18 class 5 variants in eleven genes: *BRCA1* (n=1), *BRCA2* (n=2), *ATM* (n=3), *FANCM* (n=2), *PMS2* (n=1), *MSH6* (n=1), *FANCE* (n=1), *FANCD2* (n=1), *CHEK2* (n=2), *MUTYH* (n=2) and *NTHL1* (n=2). In addition, eight missense variants were predicted to affect function by in silico prediction programs in eight patients: *ATM* (n=3), *ERCC4* (n=1), *FANCA* (n=1), *BRIP1* (n=1), *RAD51D* (n=1) and *POT1* (n=1).

Conclusions: These preliminary results obtained in a relatively small cohort of cancer patients eligible for genetic testing because of a personal history of breast/colon/pancreatic cancer or melanoma and at least one close relative with pancreatic cancer, revealed inactivating mutations in cancer predisposition genes in 18.75% of the patients and certainly warrant a further extension of the study cohort. These findings warrant further segregation analysis in the families to evaluate their link with the different cancers and highlight the need for recommendations governing germline multi-gene panel testing of cancer patients with a personal or family history of pancreatic cancer.

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