Short Report

PALB2 mutations in European familial pancreatic cancer families


Recently, PALB2 was reported to be a new pancreatic cancer susceptibility gene as determined by exomic sequencing, as truncating PALB2 mutations were identified in 3 of 96 American patients with familial pancreatic cancer (FPC). Representing the European Registry of Hereditary Pancreatitis and Familial Pancreatic Cancer (EUROPAC) and the German National Case Collection for Familial Pancreatic Cancer (FaPaCa), we evaluated whether truncating mutations could also be detected in European FPC families. We have directly sequenced the 13 exons of the PALB2 gene in affected index patients of 81 FPC families. An index patient was defined as the first medically identified patient, stimulating investigation of other members of the family to discover a possible genetic factor. None of these patients carried a BRCA2 mutation. We identified three (3.7%) truncating PALB2 mutations, each producing different stop codons: R414X, 508-9delAG and 3116delA. Interestingly, each of these three families also had a history of breast cancer. Therefore, PALB2 mutations might be causative for FPC in a small subset of European families, especially in those with an additional occurrence of breast cancer.

Hereditary pancreatic cancer is a rare, but established, inherited tumor predisposition syndrome. Families with FPC have two or more first-degree relatives with pancreatic carcinoma (PC) and do not fulfill the criteria for another inherited syndrome. International and national tumor registries have been established to collect families in order to determine the characteristics and underlying gene defect(s) of FPC. The comprehensive clinical and genetic analyses of FPC families within these registries have revealed important data about FPC. The vertical pattern of cancer observed in the majority of the FPC families is consistent with an autosomal dominant trait. The most commonly mutated gene for FPC is BRCA2 (1–2). However, recent studies indicate that the prevalence of BRCA2 mutations is lower than initially reported (3). Another gene in this pathway is PALB2, which acts as a bridge between BRCA2 and BRCA1 in a complex that is critical for homologous recombination and double-strand break repair (4). Germline PALB2 mutations have previously been associated with Fanconi anemia and breast cancer predisposition (5–7).

Jones et al. recently described the exomic sequencing of PALB2 in patients with FPC (8). They identified truncating mutations in 3 (3.1%) of 96 American FPC patients. Each of these mutations produces a different stop codon. Representing the EUROPAC and the FaPaCa, we evaluated whether truncating mutations could be detected in our FPC families.
Materials and methods

As Europe can be considered to comprise a single large genetic pool, we included families from Germany ($n = 41$), the United Kingdom ($n = 30$), Latvia ($n = 3$), Italy ($n = 3$), Greece ($n = 2$), Hungary ($n = 1$) and Spain ($n = 1$).

To determine whether PALB2 mutations occur in our patients with FPC, we directly sequenced the 13 exons of this gene in affected index pancreatic cancer patients of 81 FPC families, of whom 57 had at least one affected first-degree relative and 24 had at least two affected relatives with PC. None of these patients carried a BRCA2 mutation as evaluated by denaturing high-performance liquid chromatography (DHPLC) analysis and/or direct sequencing of the whole gene. All participants provided written informed consent and the study was approved by the local Ethics Committees of either the Philipps-University, Marburg, or the North West Multi-centre Research Ethics Committee in the United Kingdom.

Results and Discussion

We identified three (3.7%, standard error 2.1%, 95% CI 0.8–10.4%) PALB2 germline mutations, one nonsense and two frameshift mutations, in three families. These mutations are considered to be pathogenic, because each creates a stop codon that is predicted to cause a truncation of the PALB2 protein. Truncating mutations in PALB2 are rare in individuals without cancer; none was reported in 1084 normal participants in a previous study (7).

Family 25-9-00056 was found to carry the mutation c.1240C>T, p.R414X (Fig. 1). This is a nonsense mutation located in exon 4, resulting in truncation at position 414. This family has four cases of PC: three sisters and one brother. Another sister had breast cancer, as did her daughter (Fig. 2). This large family was screened and seven as of yet unaffected members were found to be carriers of this mutation. They are presently enrolled in our prospective PC screening program.

![Fig. 1. PALB2 mutation c.1240 C>T, p.R414X identified in FPC family 25-9-00056. Arrow, mutation; II3, family member identification.](image1.png)
Fig. 2. Pedigree of FPC family 25-9-00056; *, mutation carrier; wt, wild type; y, years; dg, diagnosis. The arrow indicates the index case (II:3).

program (9). The penetrance of the mutation in family 25-9-00056 was estimated by means of a model-maximized logarithm of odds (MOD) score analysis (10) as implemented in the program GENEHUNTER-MODSCORE (11, 12). In the context of this linkage-based method, the parametric logarithm of odds (LOD) score is maximized with respect to the trait-model parameters, i.e. the three penetrances and the disease allele frequency. As the LOD score represents the conditional probability of the observed genotypes given the trait phenotypes (rather than the probability of the observed genotypes and the trait phenotypes), the maximization yields unbiased estimates of these parameters (13). Hence, a MOD-score analysis is an ascertainment-assumption-free method, that is the parameter estimates are independent of the ascertainment scheme and the degree to which affected persons are enriched in the studied sample compared with the general population. Because of the younger age of the persons in the third generation who have a mutation-carrying parent (46 years or younger), we decided to include only individuals of the parental and grandparental generation, to avoid a bias due to an age-of-onset effect. The genotyped persons III:23 and III:24 were nevertheless included, with their phenotype set to unknown, to allow for reconstructing the genotype of their unaffected but untyped father II:9 as far as possible in the calculation. As PALB2 mutations are expected to be extremely rare in the general population, we assumed that one grandparent carries the mutation but not the other, thus excluding a recessive mode of inheritance. With this setting, the MOD-score analysis yielded a dominant disease model with an arbitrary low disease allele frequency, no phenocopies, and a penetrance of 0.24. This estimate represents the cumulative risk of developing PC at an age of 58 years.

Family 25-2-000102 was found to carry the mutation c.508-9delAG, p.R170I, 183X. This deletion located in exon 4 causes a frameshift mutation, resulting in a truncation at amino acid position 183. In this family, the male index patient and his mother were diagnosed with PC at ages 58 and 68 years, respectively. His aunt had breast cancer at age 65 years and another aunt had a brain tumor at age 64 years. Segregation of the PALB2
Palb2 mutations in European FPC families

Conclusions

Therefore, we conclude that Palb2 mutations might contribute to hereditary pancreatic cancer in a small subset of European FPC families, most probably in those with concomitant breast cancer. The prevalence of Palb2 mutations appears to be comparable to that of BRCA2 mutations in FPC families. As we did not analyze exonic deletions, the observed prevalence of Palb2 mutations might even be a modest underestimate.

Although the absolute and relative risk for the development of PC in Palb2 mutation carriers still remains unknown, Palb2 mutation carriers of FPC families have to be considered as high-risk individuals with at least 10- to 32-fold increased risk depending on the number of affected family members (16). According to an expert consensus statement, such high-risk family members should be offered participation in board-approved, prospective screening programs for the early detection and potentially curative operative treatment of PC or even better its precursor lesions (16), as it has been shown that PC screening of high-risk individuals might be effective (9, 17).

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Conflict of interest

The authors have no conflict of interest.

References