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# Gene discovery for complex diseases using exomic sequencing: identifying pancreatic cancer susceptibility genes

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Traditional methods of gene discovery, candidate gene and linkage approaches, have yielded very few pancreatic cancer susceptibility loci, such that genetic basis of ~90% of the familial clustering of pancreatic cancer is unknown. The recent advances and cost reductions in genome sequencing have enabled us to identify pancreatic cancer susceptibility genes through exomic sequencing patients with a family history of pancreatic cancer. Individuals that have an inherited tumor suppressor gene often lose the wild- type allele through loss of heterozygosity or somatic mutation. Therefore, we examined a patient's tumor and germ-line DNA for genes with evidence of both inherited and somatic variants that were likely to result in the absence of a functional protein in the patient's tumor. We also analyzed data on normal genetic variation in published databases and in individuals without pancreatic cancer. These analyses identified *PALB2* as candidate pancreatic cancer gene. The role of *PALB2* in familial pancreatic cancer was validated by studying an additional 96 pancreatic cancer patients. Large-scale follow-up studies of over 500 familial pancreatic cancer patients are currently underway.

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