ABSTRACT

Hereditary cancer syndromes are characterized by the predisposition to early-onset or multiple cancers in a person or family. They follow Mendelian inheritance patterns, demonstrate predilections for specific tumor types and can be associated with non-malignant growths or congenital abnormalities. Their stereotyped patterns of disease direct clinical genetic testing and provide guidance for prevention, screening and surveillance interventions. This thesis illustrates the phenotype of tumor types with underlying germline mutations and highlights the utility of understanding the pathologic correlation in order to direct genetic testing and novel gene identification. My PhD studies occurred in a time when there was a rapid change in technology. I began by testing hypotheses about genes that were known to cause hereditary cancer or specific tumors and relied on low-throughput molecular biology. I gained an understanding of the specificity of some genotype-phenotype correlations. Later, I took the opportunity to learn a discovery technique, using high-throughput exome-sequencing to determine the genetic basis of a family's syndrome. My thesis began with testing the hypothesis that a proportion of lobular breast cancers would be due to germline mutations in *CDH1*. Before the data presented in this thesis, it was unclear whether germline mutations in *CDH1* represented a frequent high-risk breast cancer-susceptibility gene. Sequence analysis of a large cohort of women with early-onset or familial lobular breast cancer demonstrated that, without a selective history of diffuse gastric cancer, potentially pathogenic germline mutations in *CDH1* are infrequent. I also investigated the association between granular cell tumors and a multiple congenital anomaly syndrome caused by mutation in the mitogen-activated protein-kinase pathway, and the strong association of germline *BRCA1* and *BRCA2* mutations with high-grade serous epithelial ovarian cancer. With cheaper DNA-sequencing capabilities, it has become possible to capitalize on the distinct phenotypes associated with Mendelian disease, and look for similar novel genetic events in individuals with a shared phenotype to determine the underlying genetic predispositions. This thesis demonstrates a strategy successful in diagnosing a family with Mucolipidosis type III gamma and discusses the strategy for novel gene detection in a hereditary cancer family, gastric adenocarcinoma and proximal polyposis of the stomach.