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Circle Hereditary Cancer Genetic Test White Paper – last updated 1.11.2018

Executive Summary

Prenetics has developed a targeted next generation sequencing (NGS) based test for hereditary cancer. We developed this test using Illumina's NGS platform by analyzing 35 hereditary cancer genes. This test is designed to identify cancer-causing mutations for 8 different cancers - breast, ovarian, prostate, uterine, colorectal, pancreatic, stomach cancers and melanoma. In this test, we sequence the protein-coding regions of the 35 genes. We have also developed a bioinformatics pipeline that utilizes standard practices in the field. The test has a high analytical validity for the detection of single nucleotide variants and small insertions and deletions (indels). Upon testing 2976 variants across 58 samples, the analytical accuracy of the test is 99.8%.

Introduction

Understanding the genetic basis of cancer risk is a major international endeavor that started in 1980s. The identification of mutations in the genes BRCA1 and BRCA2 in the 1990s was a major turning point in the acceleration of research in hereditary cancer. Advent of next generation sequencing (NGS) in late 2000's has further accelerated the discovery of many cancer susceptibility genes. More than 100 cancer susceptibility genes that are associated with cancer risk have been discovered (Stadler et al 2014) and more genes are being discovered continuously (Sokolenko et al 2015).

While discovery of such new cancer genes is a critical first step, additional clinical studies are needed to independently validate these discoveries. However, development of such clinical evidence for the new genes typically lags behind the discovery of these genes. Based on our assessment of strength of available clinical evidence, we have generated a hereditary cancer panel including 35 genes.

In order to assess strength of clinical evidence for the genes included in our cancer panel, we assess the following sources: a) Testing of the cancer genes as recommended by professional guidelines (e.g., from National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO)), b) Genes found to be valid cancer genes by systematic reviews, c) Genes in which pathogenic mutations have been reported by multiple research studies or reputed resources such as Clingen.

Based on the above criteria, we selected 35 genes related to 8 cancers - breast, ovarian, prostate, uterine, colorectal, pancreatic, stomach cancers and melanoma. In order to analytically validate the panel, we tested our panel using reference samples. Below, we provide the detailed methods and results of our validation process.

Materials & Methods

Prenetics has developed a next generation sequencing (NGS) based hereditary cancer test and has followed a process of established NGS laboratory protocols and custom bioinformatics analysis to generate the test results. Below, we briefly describe our procedures: Genomic DNA is extracted from saliva sample by standard extraction method. Extracted DNA is fragmented and prepared into NGS libraries compatible with the Illumina platform. The Nimblegen SeqCap Target Enrichment technology is applied to enrich 35 genes selected based on their association with different cancers. The target enriched DNA fragments are analyzed by utilizing 2X150 paired-end

sequencing method with an Illumina MiSeq Sequencer with at least 50X average coverage to ensure data quality. Quality control procedures are in-place along the process to ensure sample identification, high quality of DNA isolation, library preparation, target capture and sequencing. Each sequencing test includes one fully characterized positive control. The standard bioinformatics analysis pipeline is used to analyze sequencing data with reference to genome GRCh37 (hg19) for sequence alignment. Our pipeline includes BWA alignment (0.7.15) and GATK (4.0) best practices. Low quality and duplicated reads are removed and variants are detected by following a well-established bioinformatics variants calling pipeline. Variants are classified by following the standards and guidelines for sequence variants interpretation of the American College of Medical genetics and Genomics (ACMG). Variant annotation is performed by using the ANNOVAR framework. Our pipeline is built using a Python library called Snakemake (Koster et al 2012). Snakemake is a workflow management system that is designed to create reproducible and scalable data analyses.

Variants are classified into five categories, including the pathogenic, likely pathogenic, variant of uncertain significance (VUS), likely benign, and benign. Pathogenic and likely pathogenic variants identified by NGS undergo additional confirmatory test using Sanger sequencing before getting reported. All VUS results are reviewed bi-annually for updates in the scientific literatures and notifications will be sent if there are changes to the classification of reported variants.

Our hereditary cancer test is designed to assess clinically relevant mutations in 35 genes associated with hereditary risk for breast, ovarian, colorectal, melanoma, pancreatic, prostate, uterine and stomach cancer (detailed in Supplement Table 1) through the detection of single nucleotide variants and small insertions and deletions (Indel; up to 15-25bp) located in the DNA coding sequences, nearby flanking regions (+/- 20 bp flanking of each exon) and known splice regions in the genes targeted by the cancer panel. These genes include *APC, ATM, BAP1, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, EPCAM, GREM1, MEN1, MITF, MLH1, MRE11A, MSH2, MSH6, MUTYH, NBN, PALB2, PMS1, PMS2, POLD1, POLE, PTEN, RAD50, RAD51C, RAD51D, SMAD4, STK11, TP53,* and *XRCC2*. These genes are assessed for variants within all coding exons. This panel is not intended to analyze the following types of variations: gross rearrangements and deep intronic variation, Alu element insertions, certain homopolymers such as those in PMS1 and other unknown abnormalities. The pattern of variant types varies with the genes and this test detects a high but variable percentage of known and unknown variants of the classes stated. Novel sequence changes in the promoter regions and other non-coding regions will not be detected by this test.

Our validation strategy is governed by the guidelines for NGS from the ACMG (Rehm et al 2013) and the College of American Pathologist (CAP). The validation studies are designed to provide a good representation of possible variant types across the 35 gene in our cancer panel. These groups included well-characterized cell lines and/or DNA specimens, previously extracted from blood from individuals whose genetic variants had been previously characterized by the 1000 Genome Project (The 1000 Genome Project Consortium; Sudmant et al 2015)

Validation Results

1) Descriptive statistics of variants from reference materials

A total of 58 reference materials are selected based on the availability of high quality variant calls and recommendations by the National Institute of Standards and Technology (NIST) (Zook et al 2014). Variant calls in these reference materials were compared to 1000 Genome Project and

Illumina Platinum Genomes (The 1000 Genome Project Consortium; Sudmant et al 2015; Eberie et al 2017).

Table 1. Descriptive variant statistics from reference materials, organized by individual samples.

Specimen	Number of variants		Total	Specimen	Number of variants		Total	Specimen	Number of variants		Total
	SNVs	Indels			SNVs	Indels			SNVs	Indels	
HG00625	48	1	49	HG00701	51	1	52	NA18561	54	2	56
HG00626	54	0	54	HG00704	59	1	60	NA18562	57	0	57
HG00628	46	1	47	HG00705	49	1	50	NA18563	40	0	40
HG00629	48	0	48	HG00707	51	1	52	NA18572	57	0	57
HG00634	61	1	62	HG00708	61	0	61	NA18603	53	2	55
HG00650	49	0	49	HG02521	56	0	56	NA18605	57	0	57
HG00651	58	2	60	HG02522	59	1	60	NA18606	46	1	47
HG00653	35	1	36	NA12878	53	1	54	NA18608	45	1	46
HG00654	57	0	57	NA12889	53	1	54	NA18609	56	1	57
HG00656	58	1	59	NA12890	39	1	40	NA18611	55	0	55
HG00657	39	0	39	NA18530	50	0	50	NA18612	46	0	46
HG00662	49	1	50	NA18534	54	1	55	NA18613	53	1	54
HG00663	55	1	56	NA18536	36	1	37	NA18620	52	0	52
HG00671	55	1	56	NA18543	40	1	41	NA18621	46	1	47
HG00672	36	1	37	NA18544	48	1	49	NA18622	43	1	44
HG00683	57	0	57	NA18546	46	0	46	NA18623	58	0	58
HG00684	65	1	66	NA18548	60	0	60	NA18624	50	1	51
HG00689	46	1	47	NA18549	50	1	51	NA18629	50	0	50
HG00690	48	1	49	NA18557	54	1	55	Subtotal	918	11	929
HG00698	43	1	44	NA18558	41	1	42	**TOTAL**	**2935**	**41**	**2976**
Subtotal	1007	15	1022	Subtotal	1010	15	1025				

2) Independent confirmation of variants

The 35-gene cancer genetic test was validated using 58 specimens selected from the 1000 genome project (Coriell Institute for Medical Research). All functional types of variants are included for this analysis. The results of our cancer panel was compared against the previously identified variants in 1000 genomes project which allowed the assessment of test accuracy. Low-confidence variants in 1000 genomes project were independently confirmed by Sanger sequencing. Table 2 below provides the results of this analysis organized by genes.

Table 2. Overview of results for 2976 variants.

Gene	Total variants	True Positives	False Positives	False Negatives
APC	395	395	0	0
ATM	73	73	0	0
BAP1	11	11	0	0
BARD1	178	178	0	0
BMPR1A	52	52	0	0
BRCA1	229	229	0	0
BRCA2	359	359	0	1
BRIP1	174	174	0	0
CDH1	69	69	0	0
CDKN2A	76	76	0	0
CHEK2	12	12	0	0
EPCAM	73	73	0	0
GREM1	24	24	0	0
MEN1	154	154	0	0
MITF	1	1	0	0
MLH1	17	17	0	0
MRE11A	90	90	0	0
MSH2	61	61	0	0
MSH6	54	54	0	0
MUTYH	43	43	0	0
NBN	180	180	0	0
PALB2	26	26	0	0
PMS1	31	31	0	0
PMS2	232	232	0	4*
POLD1	51	51	0	0
POLE	211	211	0	0
PTEN	6	6	0	0
RAD50	2	2	0	0

RAD51C	7	7	0	0
RAD51D	29	29	0	0
STK11	7	7	0	0
TP53	48	48	0	0
XRCC2	1	1	0	0
TOTAL	**2976**	**2976**	**0**	**5**

*4 variants at the position Chr7:6013153 in PMS2 is a false negative. But, this is in a pseudogene region and is also a benign variant.

Interpretation and Conclusion

Our cancer panel achieves an analytical accuracy of 99.8% for single nucleotide variants and small indels (<25bp) based on the above validation study results. Sensitivity to detect insertions and deletions larger than 25bp but smaller than a full exon may be marginally reduced. Overall, the test has a high analytical validity for the detection of single nucleotide variants and small insertions and deletions.

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Supplement

Supplemental Table 1: Known associations between genes in our cancer panel and cancer type

Gene	Breast	Ovarian	Uterine	Colorectal	Melanoma	Pancreatic	Stomach	Prostate*
APC				•		•	•	
ATM	•			•		•	•	•
BAP1					•			
BARD1	•	•						
BMPR1A				•		•	•	
BRCA1	•	•				•		•
BRCA2	•	•			•	•		•
BRIP1	•	•						
CDH1	•			•			•	
CDK4					•			
CDKN2A					•	•		
CHEK2	•	•		•				•
EPCAM		•	•	•		•	•	
GREM1				•				
MEN1						•	•	
MITF					•			
MLH1		•	•	•		•	•	
MRE11A	•	•		•				
MSH2		•	•	•		•	•	
MSH6		•	•	•		•	•	
MUTYH	•		•	•			•	
NBN	•	•						•
PALB2	•	•				•		•
PMS1				•				
PMS2		•	•	•		•	•	•
POLD1				•				
POLE				•				
PTEN	•		•	•	•			
RAD50	•	•						
RAD51C	•	•						
RAD51D	•	•						
SMAD4				•		•	•	
STK11	•	•	•	•		•	•	
TP53	•	•	•	•	•	•	•	•
XRCC2	•	•		•				

This table depicts only primary cancer risks and does not specify other important gene-specific associated cancers.

* Please note that research and screening guidelines for genes associated with hereditary prostate cancer are still in their early stages.