**Nucleic acid extraction**

Whole blood was collected in Becton Dickinson EDTA Vacutainer tubes (Becton Dickinson, NJ). The DNA was isolated from 400 ul of whole blood on the Qiagen QIAsymphony nucleic acid isolation robot using the “Blood\_400\_V6\_DSP” protocol. Saliva samples were collected in Oragene saliva kits containing a stabilizing agent (either OGR-250 or OGR-500; DNA Genotek, Ottawa, Canada). DNA was isolated from 1 ml of saliva on the QIAsymphony using the “Oragene\_CR2358\_ID485\_V2” protocol, a custom protocol for the isolation of DNA from the Oragene kits. DNA was eluted in 100 ul of Qiagen buffer ATE (10 mM Tris, 0.1 mM EDTA, 0.04% azide, pH 8.3). DNA is routinely checked for quality and quantity by Nanodrop spectrophotometer.

Tumor and normal tissue DNA was extracted using Qiagen AllPrep DNA/RNA Mini Kits (Qiagen, CA) according to the manufacturer’s instructions with the following modifications: 30 mg of minced tissue was mixed with 160 μl of buffer RPL plus (Qiagen, CA) 50 μl of 0.9 – 2 mm RNAse-free stainless steel beads (Next Advance, Inc., NY), and homogenized for 3 minutes in a Bullet Blender tissue homogenizer (Next Advance, Inc., NY). Subsequently, 340 μl of buffer RPL plus was added and the samples were homogenized for three minutes, incubated at 37˚C for two minutes, homogenized for three minutes, and pelleted by centrifugation for three minutes. Nucleic acids were then extracted from the supernatant according to the manufacturer’s instructions.

**Whole exome capture and next-generation sequencing**

Genomic DNA (1.5 to 3 μg) was sheared using a Covaris E220 instrument operating SonoLab v6.2.6 according to the manufacturer’s protocol for a 200 bp target peak size. The presence of ~260 bp DNA fragments was verified using an Agilent 2100 Bioanalyzer (Agilent, CA). Sheared DNA (500 to 1,000 ng) was processed into Illumina compatible sequencing libraries with a PrepX ILM DNA Library Kit (Wafergen, Fremont, CA) on an Apollo 324 instrument (Wafergen, CA). Libraries were uniquely barcoded with DNA adapters (BioO Scientific, TX) and amplified using High-Fidelity PCR Master Mix according to manufacturer’s instructions. Equimolar concentrations of QiaQuick (Qiagen, Hilden, Germany) or AMPure XP (Beckman-Coulter, CA) purified libraries were pooled prior to multiplex SeqCap EZ Exome V3.0 (Roche, Basel, Switzerland) hybridization and capture. Adapter ligated library concentrations were determined using KAPA Library quantification kits (KAPA Biosystems, MA) and Agilent 2100 Bioanalyzer analysis. Libraries were sequenced on an Illumina 2500 (Illumina Inc., CA) using 2x100 bp reads in high-output mode.

**Processing of raw sequencing data**

Illumina Fastq files were aligned to the Human Reference Genome (NCVI Build 37) using the Burrows-Wheeler Alignment Tool (BWA) v0.7.3a (1). Picard Tools v1.102 (2) was used to remove duplicate reads and generate BAM files for each sample. Base quality score recalibration and indel realignment was accomplished using the Genome Analysis Tool Kit (GATK) v. 2.7.4 (3).

**“Panel of Normals” creation**

The “panel of normals” was generated using white blood cell whole-exome sequence data from 50 patients with no known hematologic malignancy. “Panel of normals” variants were called using Mutect v1.1.7 implementing the -ArtifactDetectionMode option and the resultant VCFs were combined using the CombineVariants tool in the Genome Analysis ToolKit (GATK) v2.7.4 (3) with the following options: -filteredrecordsmergetype KEEP\_IF\_ANY\_UNFILTERED, -filteredAreUncalled, -genotypeMergeOptions UNIQUIFY. The “panel of normals” filter removes mutations with corresponding alternate alleles in >0.2% of reads at a given site or with corresponding alternate alleles in >0.2% of the samples within the panel of normal (4).

**PCR amplification**

PCR amplification of regions spanning DUOX2Y1203H, rs965513, BRAFV600, KRASQ61, HRASQ61, and NRASQ61 was performed using the specific primers outlined in Supplemental Table 1. PCR was performed using the following conditions: 98˚C for 30 sec; 25 cycles of 98˚C for 5 sec, annealing for 30 sec, 72˚C for 30 sec; final extension at 72˚C for 5 minutes, and a 4˚C hold (Supplemental Table 2). PCR products were visualized on 1% Agarose Gels using SYBR Safe DNA Stain (ThermoFisher, MA) and extracted using a QIAquick gel extraction kit (Qiagen, CA).

**References**

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