Supplemental Digital Content 3. Methods.

Cloning approach

DNA sequences were synthesized and inserted into pGL4.26 (Genewiz, Frederick, MD). For rs7996030 and rs9582036, a 2142 bp *FLT1* fragment (chr13:28,883,317-28,885,458) was cloned using KpnI and XhoI sites. A 2537 bp *KRAS* fragment (chr12:25,392,343-25,394,879), encompassing rs10505980 and rs12813551, and a 660 bp *KRAS* fragment (chr12:25384371-25385030), encompassing rs10842513, were cloned using NheI and XhoI sites. Mutagenesis was carried out according to the method of the QuikChange II Site-Directed Mutagenesis kit (Agilent, Santa Clara, CA) to introduce allelic variants.

Cell culture conditions

HEK-293 cells were obtained from American Type Culture Collection (ATCC, Manassas, VA) and authenticated by genetic profiling using short tandem repeat (STR) loci in May 2014. SVEC4-10 and HEK-293 cells were cultured in DMEM and EMEM (ATCC), respectively, with fetal bovine serum (Thermo Fisher Scientific, Waltham, MA) and penicillin/streptomycin (Mediatech, Manassas, VA).

Nucleic acid isolation and genotyping using TaqMan SNP assays in the validation cohort

Nucleic acid isolation was performed by using TriReagent® (Sigma-Aldrich, St. Louis, MO). DNA was extracted from the organic phase after RNA extraction according to the manufacturer's instructions. DNA was resuspended in Nuclease-Free Water (Qiagen, Valencia, CA) and the quantity was measured using a NanoDrop™ spectrophotometer (Thermo Scientific, Carlsbad, CA). DNA samples were stored at -20ºC. For five SNPs (rs7996030, rs9582036, rs10505980, rs12813551, rs10842513), genotyping was conducted using 20 ng of DNA by real-time PCR using predesigned TaqMan® SNP genotyping assays and genotyping master mix (Applied Biosystems, Carlsbad, CA) in 384-well plates and a 5 µl final volume. The following amplification protocol was used: denaturation at 95°C for 10 min, followed by 40 cycles of denaturation at 95°C for 15 s and annealing and extension at 60°C for 1 min. The PCRs were performed and analyzed on a 7900 HT Fast Real Time PCR System (Applied Biosystems, Carlsbad, CA) using the SDS 2.4 allelic discrimination software.