Supplementary Table S1. RASopathy Genes on NGS Panel

Gene	Transcript
BRAF	NM_004333.4
CBL	NM_005188.3
HRAS	NM_005343.2
KRAS	NM_004985.3
MAP2K1	NM_002755.3
MAP2K2	NM_030662.3
NF1	NM_001042492.2
NRAS	NM_002524.4
PTPN11	NM_002834.4
RAF1	NM_002880.3
RIT1	NM_001256821.1
SPRED1	NM_152594.2
SOS1	NM_005633.3
*SHOC2**	NM_007373.3

***Tested for the only known pathogenic (c.4A>G (p.Ser2Gly)) variant in exon**

Supplementary Table S2. Variants of Unknown Significance (VUSs) in *NF1* and *SPRED1* Identified on RASopathy Panel

Gene	cDNA	Protein	Variant classification (ACMG/AMP Criteria)	Probands
NF1	c.2410-12T>C	p.(?)	VUS (PM2, PP3)	1
NF1	c.3883A>G	p.(Thr1295Ala)	VUS - favor benign (BP4, PM2, BS2)	1 †
NF1	c.4624C>G	p.(Leu1542Val)	VUS (PM2)	1
NF1	c.4835G>T	p.(Arg1612Met)	VUS (PP3, PM2)	1
NF1	c.5481C>G	p.(Ile1827Met)	VUS (PM2)	1
NF1	c.5509G>A	p.(Asp1837Asn)	VUS (PM2_P)	1
NF1	c.6161T>A	p.(Met2054Lys)	VUS (PM2, PP3)	1 ‡
NF1	c.6172A>G	p.(Ile2058Val)	VUS (BS1_P)	1
NF1	c.6617C>T	p.(Thr2206Ile)	VUS - favor benign (PM2, PP3, BS2)	1†
NF1	c.7439A>G	p.(His2480Arg)	VUS (PP3)	1
NF1	c.7988C>T	p.(Ser2663Phe)	VUS - favor benign (PM2, PP3, BS2)	1†
NF1	c.8162A>G	p.(Gln2721Arg)	VUS (PM2)	1§
SPRED1	c.-12G>T	p.(?)	VUS (PP3, BS1_P)	1
SPRED1	c.424-5A>G	p.(?)	VUS (BP4)	1
SPRED1	c.587C>T	p.(Thr196Ile)	VUS - favor benign (BP4, BS1_P)	1

†Also identified in unaffected parent
‡In homozygous state in proband with a RASopathy and affected sibling
§Also identified in parent, phenotype unknown