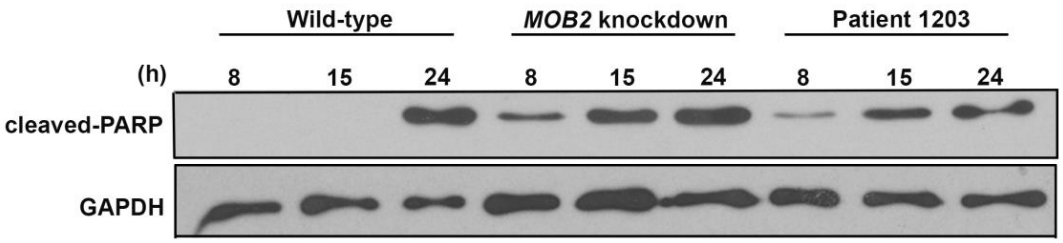
Supplementary materials:

Tables S1

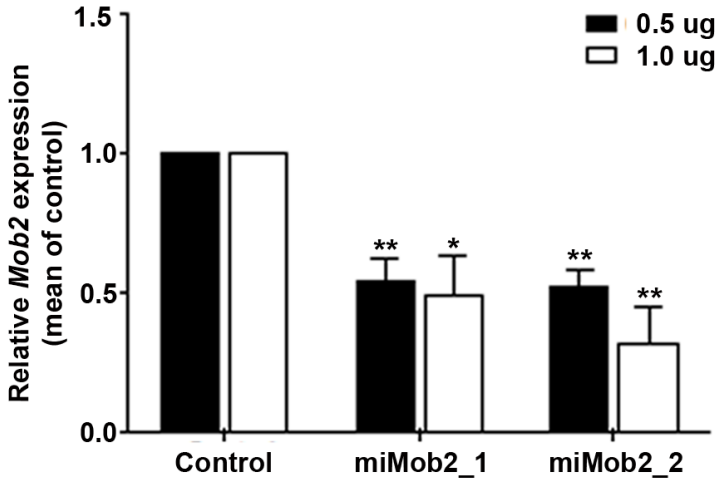
Figures S1-S3

Supplementary Table 1: List of loci with candidate loss-of-function biallelic variants identified in 65 PH trios

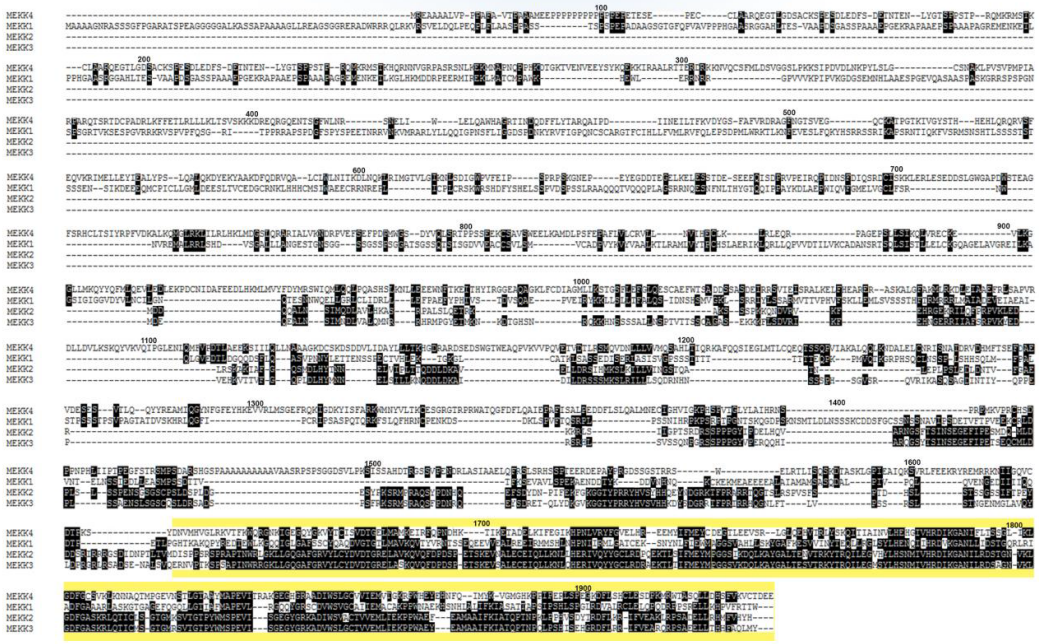
Individual	Candidate gene(s)	Chr	Position	Nucleotide	Protein	*In silico* predictions			
						PolyPhen-2	Grantham	RVIS	pLI
1203	*MOB2*	11	1502019	c.207delC	p.Phe69Phefs*127	1.00 (Probably damaging)	na	24.00	0.64
	MOB2	11	1491530	c.679C>T	p.Glu227Lys	1.00 (Probably damaging)	56	24.00	
2758	*PLEKHG6*	12	6422338	c.28delG	p.Glu10Argfs*40	1.00 (Probably damaging)	54	12.63	0.00
2859	*HKDC1*	10	70987024	c.125G>A	p.Arg42Gln	0.926 (Possibly damaging)	43	70.88	0.00
	HKDC1	10	71000508	IVS6-1G>A	Splice defect	1.00 (Probably damaging)	na	70.88	
3096	*ARHGAP39*	8	145773344	c.24_26delTCG	p.Gln376del	1.000 (Probably damaging)	na	4.305	0.00
3495	*CABP1*	12	121093653	c.43_44delGC	p.Ala15fs	1.000 (Probably damaging)	na	na	0.74
	CABP1	12	121093759	c.146G>A	p.Arg49His	Unknown	29	na	



Supplementary Figure 1: Patient 1203 fibroblasts exhibit increased susceptibility to apoptosis. Age-matched control fibroblasts subjected to scrambled siRNA (control) or *MOB2* siRNA (*MOB2* knockdown) for 24 hours and patient 1203 fibroblasts were induced to undergo apoptosis via the addition of 200 uM camptothecin. Total cell lysates were prepared at 0, 8, 15 and 24 h post camptothecin treatment and processed for immunoblotting using the indicated antibodies.



Supplementary Figure 2: Validation of *Mob2* targeting microRNAs. Mean (± s.e.m) *Mob2* expression in C2C12 cells 24 hours post transfection (0.5 µg or 1.0 µg) with one of two miRNA targeting *Mob2* (miMob2_1 and miMob2_2) relative to control treated sample (empty vector) expression using the delta-delta Ct method, as determined by real-time PCR. Expression was normalised against Gapdh and Dimt1 housekeeping genes in the same sample using the relative standard curve method.Mann Whitney U test; * $P < 0.05$, ** $P < 0.005$.



Supplementary Figure 3: Carboxy-termini conservation among MEKK family proteins. Peptide sequence conservation among MEKK family proteins, MEKK1-4. Detailed residue alignments with sites of at least 50% conservation among the four proteins highlighted in black. The C-terminal peptide sequence containing NDR1/2 binding domain identified in common between MEKK1 and MEKK2, as defined by Enomoto *et al*., (*1*) is flanked by yellow.

Reference:

1. A. Enomoto *et al.*, Negative regulation of MEKK1/2 signaling by serine-threonine kinase 38 (STK38). *Oncogene* **27**, 1930-1938 (2008).