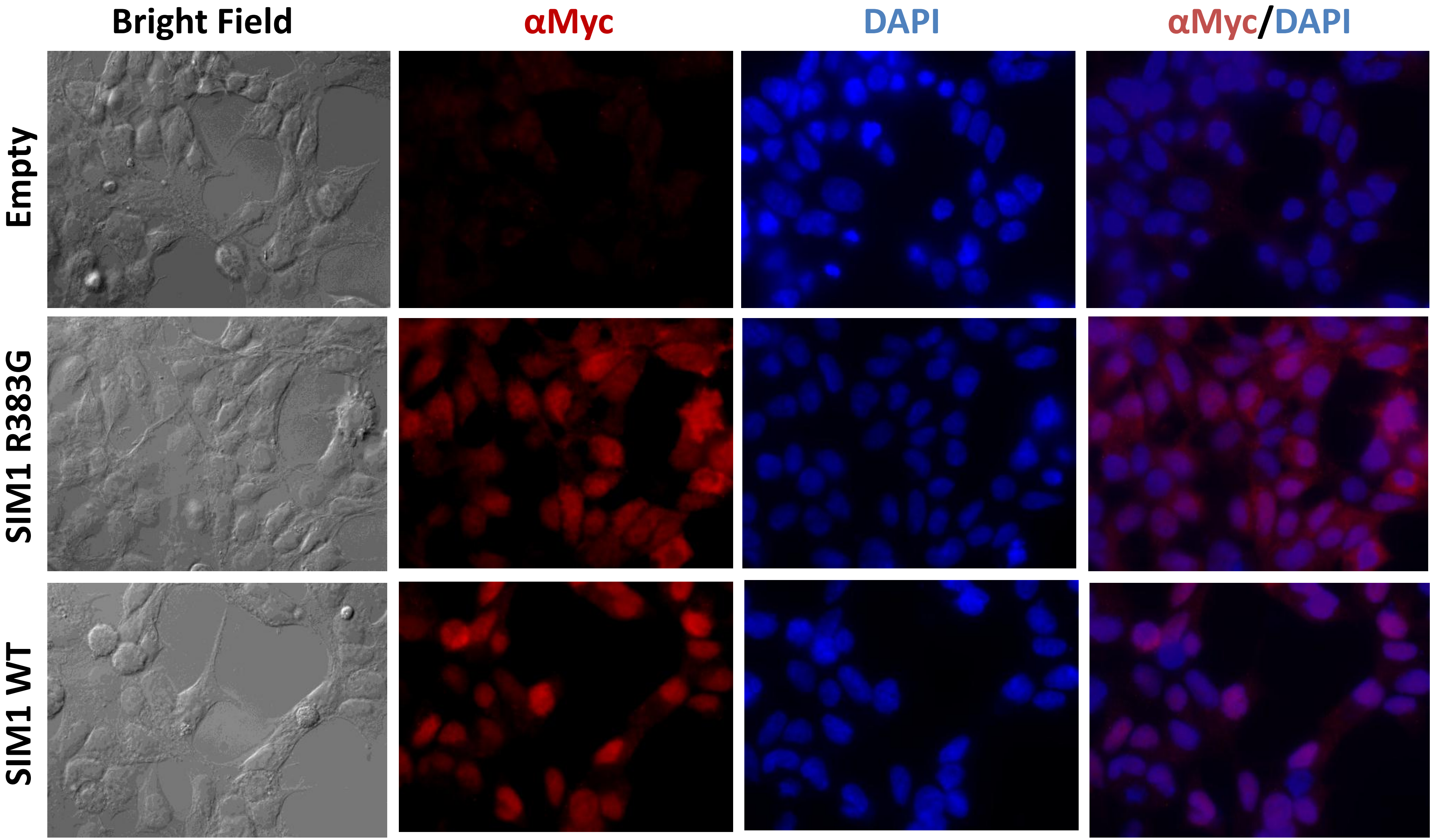
Supplementary Figure 1



The R383G variant of SIM1 has reduced nuclear translocation. Parent 293TRex cells (empty) and cell lines harbouring stable integration of wild type SIM1myc or 383G SIM1myc were grown on coverslips and treated with Doxycycline (1 ug/ml, 16hr) prior to fixing and immunostaining with anti-myc Abs and Alexafluor 594 secondary Abs. Nuclei stained with DAPI (blue).

Supplementary Table 1. SIM1 variants detected in GOOS patients and controls.

								MAF Seattle NHLBI exomes						
SIM1 variant	**Genomic location**	**Nucleotide**	**Patients**	**Controls**	**MAF(obesity)**	**MAF (controls)**	**dbSNP (137)**	**European American Exomes**	**African American Exomes**	**Conservation**	**SIFT**	**Significant reduction in activity**	**BMI sds of proband(s) on recruitment**	**Neurobehavioural phenotype where known**
S71R*	chr6:100901683	c.213 C>G	1	0	0.047619048	0	-	-	-	conserved (to Xenopus)	tolerated (0.75)	yes	4.0	yes
T87S	chr6:100898231	c.260 C>G	0	1	0	0.059171598	-	-	-	conserved (to Zebrafish)	tolerated (0.18)	-		
I128T	chr6:100897541	c.383 T>C	7	5	0.333333333	0.295857988	rs138546433	0.058% (5 / 8600)	0.045% (2 / 4406)	conserved (to Zebrafish)	deleterious(0.00)	no	5.4, 4.1, 3.3,3.5, 5.5, 4.5, BMI>50	no
V151G	chr6:100897472	c.451 T>G	0	1	0	0.059171598	-	0.000% (0 / 8600)	0.023% (1 / 4406)	conserved (to Zebrafish)	tolerated (0.41)	-		
Q152E**	chr6:100897470	c.454 C>G	2	1	0.095238095	0.059171598	rs140908824	0.012% (1 / 8600)	0.000% (0 / 4406)	conserved (to Xenopus)	deleterious(0.04)	no	4.8, BMI>45	yes (one of two probands)
R171H*	chr6:100897270	c.512 G>A	1	0	0.047619048	0	-	-	-	conserved (to Zebrafish)	deleterious(0.00)	yes	4.4	yes
L238R*	chr6:100896385	c.713 T>G	1	0	0.047619048	0	-	0.012% (1 / 8600)	0.000% (0 / 4406)	conserved (to Zebrafish)	deleterious(0.00)	yes	4.0	yes
L242V	chr6:100896374	c.724 C>G	0	1	0	0.059171598	-			conserved (to Zebrafish)	deleterious (0.03)	-		
R383G	chr6:100868686	c.1147 A>G	1	0	0.047619048	0	rs188821440	-	-	conserved (to Zebrafish)	deleterious(0.01)	no	3.8	not known
P497R	chr6:100841443	c.1490 C>G	1	0	0.047619048	0	-	-	-	conserved (to Zebrafish)	tolerated (0.14)	yes	2.9	not known
S541L	chr6:100838916	c.1622 C>T	1	0	0.047619048	0	-	-	-	conserved (to Zebrafish)	deleterious(0.01)	no	4.0	not known
R550H***	chr6:100838889	c.1649 G>A	3	0	0.142857143	0	rs137870558	0.023% (2 / 8600)	0.000% (0 / 4406)	conserved (to Zebrafish)	tolerated (0.40)	yes	4.2, 4.2, 3.6	yes (two of three probands)
R665H	chr6:100838544	c.1994 G>A	0	1	0	0.059171598	rs146866401	0.000% (0 / 8600)	0.023% (1 / 4406)	conserved (to Zebrafish)	tolerated (0.09)	-		
P692L	chr6:100838463	c.2075 C>T	1	0	0.047619048	0	-	-	-	conserved (to Zebrafish)	deleterious(0.00)	no	4.4	not known
R703Q	chr6:100838430	c.2108 G>A	1	0	0.047619048	0	-	0.012% (1 / 8600)	0.000% (0 / 4406)	conserved (to Xenopus)	tolerated (0.40)	no	3.0	not known
D707H****	chr6:100838419	c.2119 G>C	7	4	0.333333333	0.236686391	rs74726213	0.093% (8 / 8600)	0.023% (1 / 4406)	conserved (to Zebrafish)	deleterious(0.02)	yes	4.2, 4.5, 4.7, 3.4, 4.6, 3.5, 2.7	yes (all four probands)
T712I*	chr6:100838403	c.2135 C>T	1	0	0.047619048	0	-	-	-	conserved (to Xenopus)	deleterious(0.01)	yes	4.1	yes

Note:

Genomic location (NCBI build 37.1)

MAF (minor allele frequency)

Conservation (Amino acid conservation)

SIFT 'Sorting Intolerant From Tolerant' software [Ng PC, Henikoff S. Nucleic Acids Res. 2003 Jul 1;31(13):3812-4.]

Reduced activity (Functional consequence measured by transcriptional activity assay in complex with ARNT/ARNT2)

For each SIM1 variant, the inclusion of family members of a single (*), two (**), three (***) or four (****) unrelated probands carrying the variant, in detailed phenotypic studies is indicated.

BMI sds of probands recruited in childhood; where probands were recruited as adults, BMI is shown (for some accurate weights were not obtained as too heavy for local scales)

Supplementary Table 2

Primers for SIM1 variant cloning	seq 5'-3'
hSIM1 S71R-F	CAAGTCGGACCAGGCCCCTGGACAAC
hSIM1 S71R-R	GTTGTCCAGGGGCCTGGTCCGACTTG
hSIM1 I128T-F	GAATACACTCACCCG
hSIM1 I128T-R	CGGGTGAGTGTATTC
hSIM1 Q152E-F	TTCGTGGAGGAGTAT
hSIM1 Q152E-R	GATCTCATACTCCTCCACGAAGTGAGA
hSIM1 R171H-F	GCCAAGCATAACGCC
hSIM1 R171H-R	GGCGTTATGCTTGGC
hSIM1 L238R-F	GTTCCGCGCCAGCCGGGACATGAAGCTCATC
hSIM1 L238R-R	GATGAGCTTCATGTCCCGGCTGGCGCGGAAC
hSIM1 R383G-F	CAAAGTCAAAATCCGGGACTTCCCCATAC
hSIM1 R383G-R	GTATGGGGAAGTCCCGGATTTTGACTTTG
hSIM1 P497R-F	GCCTTGCGCCTGACA
hSIM1 P497R-R	GGAGGCCTTTGTCAGGCGCAAGGCTGCGCGAGAG
hSIM1 S541L-F	CCTGGGTTGGCCAGT
hSIM1 S541L-R	ACTGGCCAACCCAGG
hSIM1 R550H-F	CGATATCATACTGAGCAG
hSIM1 R550H-R	CTGCTCAGTATGATATCG
hSIM1 P692L-F	GCAGGAGACCACCTTACTGTCTCTCC
hSIM1 P692L-R	GGAGAGACAGTAAGGTGGTCTCCTGC
hSIM1 R703Q-F	GCTTTGGCTCTCACCAGCAGTATTTTGAC
hSIM1 R703Q-R	GTCAAAATACTGCTGGTGAGAGCCAAAGC
hSIM1 D707H-F	CGGCAGTATTTTCACAAGCATGCTTAC
hSIM1 D707H-R	GTAAGCATGCTTGTGAAAATACTGCCG
hSIM1 T712I-F	CAAGCATGCTTACATATTAACTGGATATGC
hSIM1 T712I-R	GCATATCCAGTTAATATGTAAGCATGCTTG