

ESM Table 1. List of PCR primers and other oligonucleotides employed in the study.

Gene (Protein)	Forward	Reverse
<i>ATF4</i>	GTTCTCCAGCGACAAGGCTA	ATCCTGCTTGCTGTTGTTGG
<i>HSPA5</i> (BiP)	TGTTCAACCAATTATCAGCAAACCTC	TTCTGCTGTATCCTCTTCACCAGT
<i>DDIT3</i> (CHOP)	AGAACCAGGAAACGGAAACAGA	TCTCCTTCATGCGCTGCTTT
<i>GAPDH</i>	GTCTCCTCTGACTTCAACAGCG	ACCACCCTGTTGCTGTAGCCAA
<i>SMG7</i>	TTTCAGGAGGCAGTGGTGGATG	CAAACCTCCTCTGGAAGTGGTGTC
<i>XBP-1</i>	CTGCCAGAGATCGAAAGAAGGC	CTCCTGGTTCTCAACTACAAGGC
<i>UPF1</i>	AACGAGCACCAAGGCATTGGCT	GGCTGCTTTGATAGTGCCTTCG
<i>c.316del</i>	CGACATTCTCCAGCAGCTC	CGACATTCTCCAGCAGCTC
<i>c.316_460del</i>	CCCAAGGCACAGACTGAGGC	CGACATTCTCCAGCAGCTC
<i>c.316_356del</i>	CTGGCCCTGGTGTTAGAGAC	TCGGACGTGATGCCTCTCTC
<i>c.271_513del</i>	AGCAGGAGAGGAGCGAAAG	CGCACGGCCCTCTCCAGGAC
<i>WFS1_ex3</i>	GGGCCTACAAAGGGAGACAT	-
<i>WFS1_ex4</i>	GGCGACACGGATTGAAGAACT	AGTTCTTCATCCGTGTCGCC
<i>WFS1_ex5</i>	-	CCAGTACATGACCAGGGCTG
<i>WFS1_gRNA</i>	TAATACGACTCACTATAGGAGTTCT TCATCCGTG	TTCTAGCTCTAAAACGCGACACGGAT GAAGAAC
<i>WFS1_hr</i>	CTTCCTCCTCACCCAGCCTG	GGGTCTTGGTCACTCACCTT
<i>WFS1_ssODN</i>	GAAAGGAGGTGGGCTGGCAGGGAGCATGGGGTGGGAGAGGGTCGGAGAAT CTGGAGGCTGACTGGTGTCTGGCTTGCAGGTGGGGAAGCACTACCTGCAGT TGGCTGGAGATACAGATGAAGAGCTCAACAGCTGCACCGCTGTGGACTGGC TGGTCCTCGCCGCGAAGCAGGGCCGTCGCGAGGCTGTGAAGCTGCTTC	

ESM Table 2. List of TaqMan assays employed in the study.

Gene ID	Company	Catalog Number
OCT4 (Hs00742896_s1)	Thermo Fisher Scientific	Cat#4331182
NANOG (Hs04399610_g1)	Thermo Fisher Scientific	Cat#4331182
SOX17 (Hs00751752_s1)	Thermo Fisher Scientific	Cat#4331182
FOXA2 (Hs00232764_m1)	Thermo Fisher Scientific	Cat#4331182
HNF1B (Hs00172123_m1)	Thermo Fisher Scientific	Cat#4331182
PDX1 (Hs00236830_m1)	Thermo Fisher Scientific	Cat#4331182
NGN3 (Hs01875204_s1)	Thermo Fisher Scientific	Cat#4331182
NKX2.2 (Hs00159616_m1)	Thermo Fisher Scientific	Cat#4331182
NKX6.1 (Hs00232355_m1)	Thermo Fisher Scientific	Cat#4331182
GCG (Hs01031536_m1)	Thermo Fisher Scientific	Cat#4331182
INS (Hs02741908_m1)	Thermo Fisher Scientific	Cat#4331182
GAPDH (Hs99999905_m1)	Thermo Fisher Scientific	Cat#4331182

ESM Table 3. List of antibodies employed in the study and respective mode of use.

Antibody	Species	Supplier	Code	Use	Dilution
Anti-GAPDH [6C5]	Mouse	Abcam	ab8245	WB	1:5000
Alexa Fluor® 647 anti-Insulin [T56-706]	Mouse	BD	565689	FACS	2µl x 10 ⁶ cells
Anti-Nanog	Rabbit	R&D	AF1997	IF	1:100
PE anti-Nkx6.1 [R11-560]	Mouse	BD	563023	FACS	5µl x 10 ⁶ cells
Anti-OCT4 [486]	Mouse	Novus	NBP2-15052	IF	1:100
Alexa Fluor® 647 Anti-OCT3/4 [40]	Mouse	BD	560329	FACS	4µl x 10 ⁶ cells
PE Anti-CXCR4 [12G5]	Mouse	BD	557145	FACS	6µl x 10 ⁶ cells
Alexa Fluor® 488 anti-PDX1 [658A5]	Mouse	BD	562274	FACS	5µl x 10 ⁶ cells
Anti-SSEA4 [MC813-70]	Mouse	Abcam	ab16287	IF	1:500
Anti-Sox2 [245610]	Mouse	R&D	MAB2018	IF	1:100
Anti-WFS1 C-terminal	Sheep	R&D	AF7417	WB	1:200
Anti-WFS1 N-terminal	Rabbit	Cell Signalling	8749	WB	1:1000
Anti-ATF4 [EPR18111]	Rabbit	Abcam	ab184909	WB	1:1500
Anti-ATF6 [1-7]	Mouse	Abcam	ab122897	WB	1:500
Anti-BiP [C50B12]	Rabbit	Cell Signalling	#3177	WB	1:2000
Anti-Calnexin [C5C9]	Rabbit	Cell Signalling	#2679	WB	1:1000

Anti-phospho eIF2a [119A11]	Rabbit	Cell Signalling	#3597	WB	1:1000
Anti-eIF2a	Mouse	Abcam	ab5369	WB	1:500
Anti-ERO1 α	Rabbit	Cell Signalling	#3264	WB	1:1000
Anti-phospho IRE1a	Rabbit	Abcam	ab124945	WB	1:2000
Anti-IRE1a [14C10]	Rabbit	Cell Signalling	#3294	WB	1:1000
HRP-conjugated anti-mouse	Goat	R&D	HAF007	WB	1:1000
HRP-conjugated anti-rabbit	Goat	R&D	HAF008	WB	1:1000
HRP-conjugated anti-sheep	Donkey	R&D	HAF016	WB	1:1000
Alexa Fluor™ Plus 488 anti-mouse	Goat	Thermo Fisher	A32723	IF	1:500
Alexa Fluor™ Plus 488 anti-rabbit	Goat	Thermo Fisher	A32731	IF	1:500
Alexa Fluor™ Plus 488 anti-goat	Donkey	Thermo Fisher	A32814	IF	1:500
Alexa Fluor™ 546 anti-mouse	Goat	Thermo Fisher	A11030	IF	1:500
Alexa Fluor™ 546 anti-goat	Rabbit	Thermo Fisher	A21085	IF	1:500

ESM Table 4. List of natural and cryptic donor and acceptor splicing sites, ESE/ESS signals and branch points along *WFS1* exon 4 and its 150bp-long flanking regions, as performed by using the Human Splice Finder Pro.

HSF_Signals			
Type	Position	Motif	Value
Donor splice site	6288849	CTGGTGTGA	81.53
Donor splice site	6288851	GGTGTGACC	66.49
Donor splice site	6288886	TGGGTGACA	76.86
Acceptor splice site	6288886	TGGGTGACAAAGGG	69.99
Donor splice site	6288895	AAGGGAAGT	72.72
Donor splice site	6288899	GAAGTGGGT	78.76
Acceptor splice site	6288901	AGTGGGTGAAAGGA	68.74
Donor splice site	6288903	TGGGTGAAA	77.31
Donor splice site	6288913	GAGGTGGGC	85.92
Acceptor splice site	6288916	GTGGGCTGGCAGGG	77.91
Acceptor splice site	6288933	ATGGGGTGGGAGAG	66.2
Donor splice site	6288935	GGGGTGGGA	80.07
Donor splice site	6288945	AGGGTCGGA	77.67
Acceptor splice site	6288952	GAGAATCTGGAGGC	69.92
Donor splice site	6288969	CTGGTGTCT	74.19
Donor splice site	6288971	GGTGTCTGG	66.26
(WT) Acceptor splice site	6288975	TCTGGCTTGCAGGT	88.95
Donor splice site	6288984	CAGGTGGGG	87.37
Acceptor splice site	6288996	CACTACCTGCAGTT	81.29
Donor splice site	6289004	GCAGTTGGC	66.32
Acceptor splice site	6289018	ACACGGATGAAGAA	66.66
Acceptor splice site	6289028	AGAACTCAACAGCT	72.98
Donor splice site	6289059	CTGGTCCTC	67.66
Acceptor splice site	6289065	CTCGCCGCGAAGCA	71.7
Acceptor splice site	6289068	GCCGCGAAGCAGGG	72.8
Acceptor splice site	6289080	GGCCGTCGCGAGGC	68.89
Acceptor splice site	6289089	GAGGCTGTGAAGCT	68.12
Donor splice site	6289092	GCTGTGAAG	67.2
Donor splice site	6289109	CCGGTGCTT	73.55
Acceptor splice site	6289115	CTTGCGGACAGAA	78.06
(WT) Donor splice site	6289129	GAGGTGGGT	88.85
Donor splice site	6289133	TGGGTCTGT	78.98
Acceptor splice site	6289135	GGTCTGTGTGAGGC	72.8
Donor splice site	6289137	TCTGTGTGA	69.1
Donor splice site	6289139	TGTGTGAGG	76.44
Acceptor splice site	6289141	TGTGAGGCTTAGAA	72.09
Acceptor splice site	6289146	GGCTTAGAACAGCC	73.12
Acceptor splice site	6289155	CAGCCTCTGGAGGG	75.12
Acceptor splice site	6289162	TGAGGGTTGAGCA	66.07

Donor splice site	6289165	AGGGTTGAG	68.21
Acceptor splice site	6289165	AGGGTTGAGCAGCT	71.81
Donor splice site	6289177	CTTGTAATG	71.43
Donor splice site	6289228	CTGGTGATG	79.1
Donor splice site	6289236	GCTGTTGGG	66.22
Acceptor splice site	6289242	GGGAAATTCAGTT	74.65
Acceptor splice site	6289256	TCTGTTTTGCTGGT	65.33
Donor splice site	6289265	CTGGTGGCC	71.26
MaxEnt_Signals			
Type	Position	Motif	Value
Donor splice site	6288913	GAGGTGGGC	6.32
(WT) Acceptor splice site	6288967	GACTGGTGTCTGGCTTGCAGGTG	8.62
Donor splice site	6288984	CAGGTGGGG	6.92
(WT) Donor splice site	6289129	GAGGTGGGT	7.07
BP_Signals			
Type	Position	Motif	Value
Branch point	6288857	ACCCCAT	82.59
(WT) Branch point	6288948	GTCGGAG	72.02
Branch point	6288963	GGCTGAC	88.62
Branch point	6289019	CACGGAT	68.98
Branch point	6289030	AACTCAA	82.03
Branch point	6289063	TCCTCGC	68.61
Branch point	6289070	CGCGAAG	65.54
Branch point	6289118	GGCGGAC	73.53
Branch point	6289146	GGCTTAG	79.00
Branch point	6289157	GCCTCTG	65.78
Branch point	6289191	TGCTAAC	81.83
Branch point	6289195	AACTGAA	77.09
Branch point	6289203	AACTAAA	70.20
Branch point	6289210	ATCTTAC	80.32
Branch point	6289215	ACCAAAC	68.60
Branch point	6289220	ACCTAAC	83.69
Branch point	6289247	ATTTCAG	65.58
Branch point	6289274	TTCTCAT	90.98
ESE_Signals			
Name	Position	Motif	CV
ESE_9G8 (ESE Site)	6288839	GTGGAC	77.79
ESE_SRp40 (ESE Site)	6288846	TGCCTGG	79.13
ESE_9G8 (ESE Site)	6288853	TGTGAC	60.94
ESE_SC35 (ESE Site)	6288856	GACCCCAT	77.21
ESE_SC35 (ESE Site)	6288861	CATTTCTG	75.30
ESE_SRp40 (ESE Site)	6288863	TTTCTGC	85.17
ESE_SRp40 (ESE Site)	6288877	TTCCTGG	82.18
ESE_SC35 (ESE Site)	6288882	GGCCTGGG	75.06
ESE_9G8 (ESE Site)	6288888	GGTGAC	82.69
ESE_9G8 (ESE Site)	6288891	GACAAA	66.58

ESE_SRp40 (ESE Site)	6288892	ACAAAGG	84.22
ESE_ASF (ESE Site)	6288893	CAAAGGG	79.12
ESE_ASFB (ESE Site)	6288893	CAAAGGG	79.15
ESE_9G8 (ESE Site)	6288899	GAAGTG	65.31
ESE_9G8 (ESE Site)	6288905	GGTGAA	70.61
ESE_SRp40 (ESE Site)	6288907	TGAAAGG	85.59
ESE_ASF (ESE Site)	6288908	GAAAGGA	74.17
ESE_ASF (ESE Site)	6288911	AGGAGGT	76.09
ESE_9G8 (ESE Site)	6288913	GAGGTG	60.47
ESE_9G8 (ESE Site)	6288916	GTGGGC	61.82
ESE_SC35 (ESE Site)	6288919	GGCTGGCA	80.41
ESE_9G8 (ESE Site)	6288920	GCTGGC	62.42
ESE_SRp40 (ESE Site)	6288922	TGGCAGG	79.37
ESE_ASFB (ESE Site)	6288923	GGCAGGG	72.61
ESE_ASF (ESE Site)	6288923	GGCAGGG	80.75
ESE_9G8 (ESE Site)	6288929	GAGCAT	60.14
ESE_9G8 (ESE Site)	6288941	GGAGAG	71.82
ESE_ASF (ESE Site)	6288942	GAGAGGG	81.92
ESE_9G8 (ESE Site)	6288944	GAGGGT	65.91
ESE_SC35 (ESE Site)	6288947	GGTCGGAG	78.75
ESE_ASF (ESE Site)	6288950	CGGAGAA	77.78
ESE_ASFB (ESE Site)	6288950	CGGAGAA	81.61
ESE_9G8 (ESE Site)	6288951	GGAGAA	74.84
ESE_9G8 (ESE Site)	6288952	GAGAAT	61.35
ESE_9G8 (ESE Site)	6288960	GGAGGC	70.94
ESE_9G8 (ESE Site)	6288961	GAGGCT	62.49
ESE_9G8 (ESE Site)	6288964	GCTGAC	78.39
ESE_ASF (ESE Site)	6288965	CTGACTG	75.80
ESE_ASFB (ESE Site)	6288965	CTGACTG	76.15
ESE_SRp40 (ESE Site)	6288966	TGACTGG	93.50
ESE_SC35 (ESE Site)	6288967	GACTGGTG	84.89
ESE_9G8 (ESE Site)	6288971	GGTGTC	63.29
ESE_SRp40 (ESE Site)	6288973	TGTCTGG	87.21
ESE_SC35 (ESE Site)	6288978	GGCTTGCA	81.20
ESE_SRp40 (ESE Site)	6288981	TTGCAGG	82.42
ESE_ASFB (ESE Site)	6288982	TGCAGGT	72.61
ESE_ASF (ESE Site)	6288982	TGCAGGT	74.99
ESE_SRp55 (ESE Site)	6288982	TGCAGG	75.89
ESE_9G8 (ESE Site)	6288989	GGGGAA	70.00
ESE_9G8 (ESE Site)	6288992	GAAGCA	68.33
ESE_9G8 (ESE Site)	6288996	CACTAC	59.33
ESE_ASFB (ESE Site)	6289002	CTGCAGT	71.77
ESE_9G8 (ESE Site)	6289007	GTTGGC	62.42
ESE_SC35 (ESE Site)	6289010	GGCCGGCG	84.59
ESE_9G8 (ESE Site)	6289011	GCCGGC	66.04
ESE_ASFB (ESE Site)	6289012	CCGGCGA	76.23

ESE_9G8 (ESE Site)	6289014	GGCGAC	86.31
ESE_SRp40 (ESE Site)	6289016	CGACACG	90.98
ESE_ASFB (ESE Site)	6289017	GACACGG	72.00
ESE_ASF (ESE Site)	6289017	GACACGG	86.93
ESE_SRp55 (ESE Site)	6289019	CACGGA	79.54
ESE_ASF (ESE Site)	6289021	CGGATGA	81.63
ESE_ASFB (ESE Site)	6289021	CGGATGA	83.00
ESE_9G8 (ESE Site)	6289023	GATGAA	83.49
PESE (ESE Site)	6289025	TGAAGAAC	62.05
ESE_9G8 (ESE Site)	6289026	GAAGAA	87.72
ESE_Tra2 (ESE Site)	6289027	AAGAA	100.34
ESE_SC35 (ESE Site)	6289029	GAACTCAA	77.46
ESE_SRp40 (ESE Site)	6289031	ACTCAAC	78.83
ESE_SRp40 (ESE Site)	6289034	CAACAGC	79.13
ESE_Tra2 (ESE Site)	6289035	AACAG	83.54
ESE_SRp55 (ESE Site)	6289041	TGCACC	75.76
ESE_ASF (ESE Site)	6289043	CACCGCT	74.06
ESE_ASFB (ESE Site)	6289043	CACCGCT	78.38
ESE_SC35 (ESE Site)	6289043	CACCGCTG	79.42
ESE_ASF (ESE Site)	6289048	CTGTGGA	74.58
ESE_ASFB (ESE Site)	6289048	CTGTGGA	77.00
ESE_SRp55 (ESE Site)	6289049	TGTGGA	78.83
ESE_9G8 (ESE Site)	6289050	GTGGAC	77.79
ESE_SRp40 (ESE Site)	6289052	GGACTGG	78.53
ESE_SC35 (ESE Site)	6289061	GGTCCTCG	81.57
ESE_ASFB (ESE Site)	6289067	CGCCGCG	79.08
ESE_ASFB (ESE Site)	6289069	CCGCGAA	71.00
ESE_ASFB (ESE Site)	6289072	CGAAGCA	72.00
ESE_9G8 (ESE Site)	6289073	GAAGCA	68.33
ESE_ASF (ESE Site)	6289075	AGCAGGG	75.34
ESE_9G8 (ESE Site)	6289077	CAGGGC	59.67
ESE_ASF (ESE Site)	6289079	GGGCCGT	79.30
ESE_SC35 (ESE Site)	6289080	GGCCGTCG	79.61
ESE_9G8 (ESE Site)	6289081	GCCGTC	62.62
ESE_9G8 (ESE Site)	6289089	GAGGCT	62.49
ESE_9G8 (ESE Site)	6289097	GAAGCT	67.32
ESE_SRp55 (ESE Site)	6289102	TGCTTC	81.58
ESE_SC35 (ESE Site)	6289107	CGCCGGTG	76.04
ESE_ASF (ESE Site)	6289107	CGCCGGT	86.40
ESE_ASFB (ESE Site)	6289107	CGCCGGT	93.31
ESE_9G8 (ESE Site)	6289119	GCGGAC	77.79
ESE_ASF (ESE Site)	6289120	CGGACAG	77.08
ESE_ASFB (ESE Site)	6289120	CGGACAG	79.92
ESE_SC35 (ESE Site)	6289121	GGACAGAA	75.86
ESE_SRp40 (ESE Site)	6289123	ACAGAAG	79.90
ESE_ASFB (ESE Site)	6289124	CAGAAGA	80.00

ESE_ASF (ESE Site)	6289124	CAGAAGA	84.25
ESE_9G8 (ESE Site)	6289126	GAAGAG	84.70
ESE_ASF (ESE Site)	6289127	AAGAGGT	78.72
ESE_Tra2 (ESE Site)	6289127	AAGAG	89.41
ESE_9G8 (ESE Site)	6289129	GAGGTG	60.47
ESE_SRp55 (ESE Site)	6289133	TGGGTC	76.72
ESE_SC35 (ESE Site)	6289135	GGTCTGTG	85.81
ESE_SRp55 (ESE Site)	6289139	TGTGTG	75.05
ESE_SRp40 (ESE Site)	6289141	TGTGAGG	78.41
ESE_SRp55 (ESE Site)	6289143	TGAGGC	77.42
ESE_9G8 (ESE Site)	6289144	GAGGCT	62.49
ESE_SRp40 (ESE Site)	6289149	TTAGAAC	79.25
ESE_9G8 (ESE Site)	6289152	GAACAG	62.96
ESE_Tra2 (ESE Site)	6289153	AACAG	83.54
ESE_SC35 (ESE Site)	6289156	AGCCTCTG	84.15
ESE_SRp40 (ESE Site)	6289158	CCTCTGG	89.96
ESE_ASF (ESE Site)	6289159	CTCTGGA	76.04
ESE_ASFB (ESE Site)	6289159	CTCTGGA	79.92
ESE_9G8 (ESE Site)	6289164	GAGGGT	65.91
ESE_9G8 (ESE Site)	6289168	GTTGAG	63.29
ESE_SRp55 (ESE Site)	6289172	AGCAGC	75.18
ESE_SRp55 (ESE Site)	6289184	TGCTGC	76.40
ESE_9G8 (ESE Site)	6289199	GAACAA	65.98
ESE_Tra2 (ESE Site)	6289200	AACAA	94.47
ESE_Tra2 (ESE Site)	6289207	AAAAT	81.36
ESE_SRp40 (ESE Site)	6289216	CCAAACC	81.40
ESE_SRp40 (ESE Site)	6289221	CCTAACG	80.20
ESE_ASF (ESE Site)	6289226	CGCTGGT	77.90
ESE_ASFB (ESE Site)	6289226	CGCTGGT	83.69
ESE_9G8 (ESE Site)	6289230	GGTGAT	69.60
ESE_9G8 (ESE Site)	6289233	GATGCT	63.09
ESE_SC35 (ESE Site)	6289252	AGTTTCTG	79.24
ESE_SRp40 (ESE Site)	6289262	TTGCTGG	80.92
ESE_9G8 (ESE Site)	6289267	GGTGGC	66.72
ESS_Signals			
Name	Position	Motif	CV
ESS_hnRNPA1 (ESS Site)	6288837	TAGTGG	82.27
Sironi_motif2 (ESS Site)	6288838	AGTGAC	66.73
Sironi_motif2 (ESS Site)	6288850	TGGTGTG	63.08
Sironi_motif2 (ESS Site)	6288851	GGTGTGA	69.67
Sironi_motif3 (ESS Site)	6288855	TGACCCCA	64.15
Sironi_motif3 (ESS Site)	6288856	GACCCCAT	61.86
Sironi_motif3 (ESS Site)	6288865	TCTGCCCC	73.33
Sironi_motif3 (ESS Site)	6288871	CCTTCCTT	65.62
Sironi_motif3 (ESS Site)	6288875	CCTTCCTG	68.80
Sironi_motif2 (ESS Site)	6288883	GCCTGGG	60.01

Sironi_motif2 (ESS Site)	6288884	CCTGGGT	61.65
Sironi_motif2 (ESS Site)	6288886	TGGGTGA	60.21
Sironi_motif1 (ESS Site)	6288892	ACAAAGGG	64.83
Sironi_motif2 (ESS Site)	6288894	AAAGGGA	62.87
ESS_hnRNPA1 (ESS Site)	6288894	AAAGGG	65.13
ESS_hnRNPA1 (ESS Site)	6288895	AAGGGA	85.13
Sironi_motif2 (ESS Site)	6288898	GGAAGTG	62.31
Sironi_motif2 (ESS Site)	6288899	GAAGTGG	60.55
Sironi_motif1 (ESS Site)	6288899	GAAGTGGG	65.72
ESS_hnRNPA1 (ESS Site)	6288900	AAGTGG	67.03
Sironi_motif2 (ESS Site)	6288901	AGTGGGT	81.60
Sironi_motif2 (ESS Site)	6288903	TGGGTGA	60.21
Sironi_motif1 (ESS Site)	6288907	TGAAAGGA	62.38
Sironi_motif2 (ESS Site)	6288907	TGAAAGG	65.39
ESS_hnRNPA1 (ESS Site)	6288909	AAAGGA	67.98
ESS_hnRNPA1 (ESS Site)	6288910	AAGGAG	73.94
Sironi_motif1 (ESS Site)	6288910	AAGGAGGT	76.76
Sironi_motif2 (ESS Site)	6288912	GGAGGTG	77.46
ESS_hnRNPA1 (ESS Site)	6288913	GAGGTG	74.41
Sironi_motif2 (ESS Site)	6288914	AGGTGGG	73.16
Sironi_motif2 (ESS Site)	6288915	GGTGGGC	87.38
Sironi_motif2 (ESS Site)	6288919	GGCTGGC	66.88
Sironi_motif2 (ESS Site)	6288923	GGCAGGG	69.72
Sironi_motif2 (ESS Site)	6288924	GCAGGGA	66.62
ESS_hnRNPA1 (ESS Site)	6288925	CAGGGA	85.13
Sironi_motif2 (ESS Site)	6288931	GCATGGG	69.50
Sironi_motif1 (ESS Site)	6288932	CATGGGGT	67.99
Sironi_motif2 (ESS Site)	6288932	CATGGGG	73.71
Sironi_motif2 (ESS Site)	6288934	TGGGGTG	71.04
Sironi_motif2 (ESS Site)	6288935	GGGGTGG	67.96
Sironi_motif2 (ESS Site)	6288936	GGGTGGG	76.91
Sironi_motif2 (ESS Site)	6288937	GGTGGGA	86.58
Sironi_motif2 (ESS Site)	6288939	TGGGAGA	60.21
Sironi_motif2 (ESS Site)	6288941	GGAGAGG	77.46
Sironi_motif1 (ESS Site)	6288941	GGAGAGGG	79.52
ESS_hnRNPA1 (ESS Site)	6288942	GAGAGG	74.65
Sironi_motif2 (ESS Site)	6288943	AGAGGGT	78.55
ESS_hnRNPA1 (ESS Site)	6288944	GAGGGT	87.98
Sironi_motif2 (ESS Site)	6288946	GGGTCGG	60.01
Sironi_motif2 (ESS Site)	6288947	GGTCGGA	71.43
ESS_hnRNPA1 (ESS Site)	6288952	GAGAAT	68.22
Sironi_motif2 (ESS Site)	6288957	TCTGGAG	66.68
Sironi_motif1 (ESS Site)	6288958	CTGGAGGC	78.22
Sironi_motif2 (ESS Site)	6288959	TGGAGGC	62.77
Sironi_motif2 (ESS Site)	6288960	GGAGGCT	65.40
ESS_hnRNPA1 (ESS Site)	6288961	GAGGCT	77.98

Sironi_motif2 (ESS Site)	6288966	TGACTGG	65.39
Sironi_motif2 (ESS Site)	6288973	TGTCTGG	68.44
Sironi_motif2 (ESS Site)	6288982	TGCAGGT	60.74
Sironi_motif2 (ESS Site)	6288983	GCAGGTG	60.55
ESS_hnRNPA1 (ESS Site)	6288984	CAGGTG	70.60
Sironi_motif2 (ESS Site)	6288985	AGGTGGG	73.16
Sironi_motif2 (ESS Site)	6288986	GGTGGGG	97.41
Sironi_motif2 (ESS Site)	6288988	TGGGGAA	60.21
Sironi_motif3 (ESS Site)	6288997	ACTACCTG	65.95
Sironi_motif2 (ESS Site)	6289006	AGTTGGC	75.67
ESS_hnRNPA1 (ESS Site)	6289019	CACGGA	65.84
Sironi_motif1 (ESS Site)	6289026	GAAGAACT	63.88
Sironi_motif1 (ESS Site)	6289034	CAACAGCT	73.34
Sironi_motif2 (ESS Site)	6289047	GCTGTGG	63.60
Sironi_motif2 (ESS Site)	6289049	TGTGGAC	73.56
Sironi_motif2 (ESS Site)	6289052	GGA CTGG	62.31
Sironi_motif2 (ESS Site)	6289057	GGCTGGT	64.85
Sironi_motif3 (ESS Site)	6289064	CCTCGCCG	67.10
Sironi_motif2 (ESS Site)	6289075	AGCAGGG	65.97
Sironi_motif2 (ESS Site)	6289076	GCAGGGC	67.43
ESS_hnRNPA1 (ESS Site)	6289077	CAGGGC	83.22
Sironi_motif2 (ESS Site)	6289086	CGCGAGG	61.17
Sironi_motif1 (ESS Site)	6289086	CGCGAGGC	75.30
ESS_hnRNPA1 (ESS Site)	6289089	GAGGCT	77.98
Sironi_motif2 (ESS Site)	6289091	GGCTGTG	60.01
Sironi_motif2 (ESS Site)	6289094	TGTGAAG	66.68
Sironi_motif2 (ESS Site)	6289113	TGCTTGG	63.08
Sironi_motif2 (ESS Site)	6289114	GCTTGGC	62.52
Sironi_motif2 (ESS Site)	6289117	TGGCGGA	61.96
Sironi_motif1 (ESS Site)	6289123	ACAGAAGA	64.77
Sironi_motif2 (ESS Site)	6289126	GAAGAGG	60.55
Sironi_motif1 (ESS Site)	6289126	GAAGAGGT	89.73
ESS_hnRNPA1 (ESS Site)	6289127	AAGAGG	70.84
Sironi_motif2 (ESS Site)	6289128	AGAGGTG	73.70
ESS_hnRNPA1 (ESS Site)	6289129	GAGGTG	74.41
Sironi_motif2 (ESS Site)	6289130	AGGTGGG	73.16
Sironi_motif2 (ESS Site)	6289131	GGTGGGT	85.35
Sironi_motif2 (ESS Site)	6289139	TGTGTGA	72.75
Sironi_motif1 (ESS Site)	6289141	TGTGAGGC	65.65
Sironi_motif2 (ESS Site)	6289141	TGTGAGG	83.58
Sironi_motif2 (ESS Site)	6289143	TGAGGCT	68.47
ESS_hnRNPA1 (ESS Site)	6289144	GAGGCT	77.98
ESS_hnRNPA1 (ESS Site)	6289150	TAGAAC	78.70
Sironi_motif2 (ESS Site)	6289160	TCTGGAG	66.68
Sironi_motif1 (ESS Site)	6289161	CTGGAGGG	76.30
Sironi_motif2 (ESS Site)	6289162	TGGAGGG	72.80

Sironi_motif2 (ESS Site)	6289163	GGAGGGT	82.30
ESS_hnRNPA1 (ESS Site)	6289164	GAGGGT	87.98
Sironi_motif2 (ESS Site)	6289167	GGTTGAG	72.55
Sironi_motif2 (ESS Site)	6289170	TGAGCAG	63.63
ESS_hnRNPA1 (ESS Site)	6289181	TAATGC	66.08
Sironi_motif3 (ESS Site)	6289212	CTTACCAA	69.36
ESS_hnRNPA1 (ESS Site)	6289223	TAACGC	66.08
Sironi_motif2 (ESS Site)	6289227	GCTGGTG	63.60
Sironi_motif2 (ESS Site)	6289230	GGTGATG	63.60
Sironi_motif2 (ESS Site)	6289232	TGATGCT	60.51
Sironi_motif2 (ESS Site)	6289238	TGTTGGG	92.53
Sironi_motif2 (ESS Site)	6289239	GTTGGGA	69.67
Sironi_motif2 (ESS Site)	6289263	TGCTGGT	67.93
Sironi_motif2 (ESS Site)	6289264	GCTGGTG	63.60
Sironi_motif1 (ESS Site)	6289265	CTGGTGGC	62.62
Sironi_motif2 (ESS Site)	6289266	TGGTGGC	69.96
Sironi_motif2 (ESS Site)	6289267	GGTGGCC	70.48
Sironi_motif3 (ESS Site)	6289273	CTTCTCAT	62.47

ESM Table 5. Consensus sequences starting from the ATG of the four alternative splicing variants deriving from the c.316-1G>A-carrying allele. Lowercase letters highlighted in cyan refer to the skipped sequence in the wild type isoform.

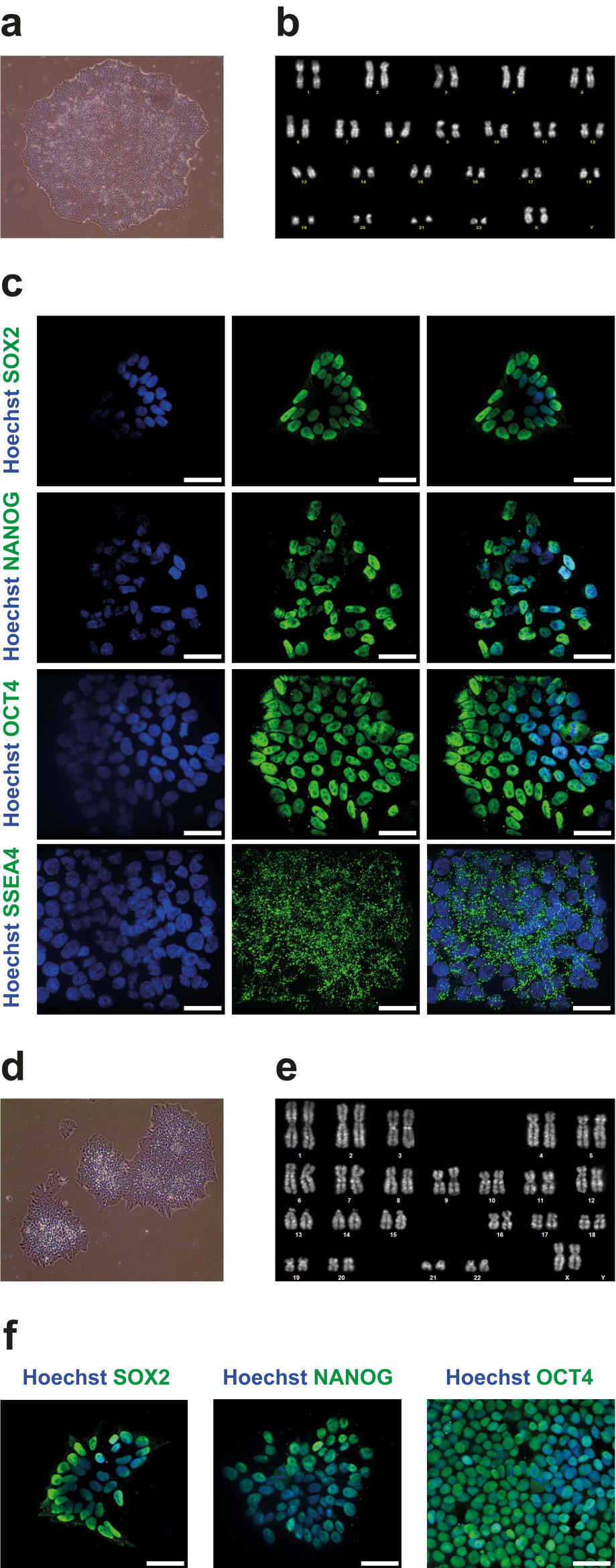
WFS1 splice variant	Consensus sequence
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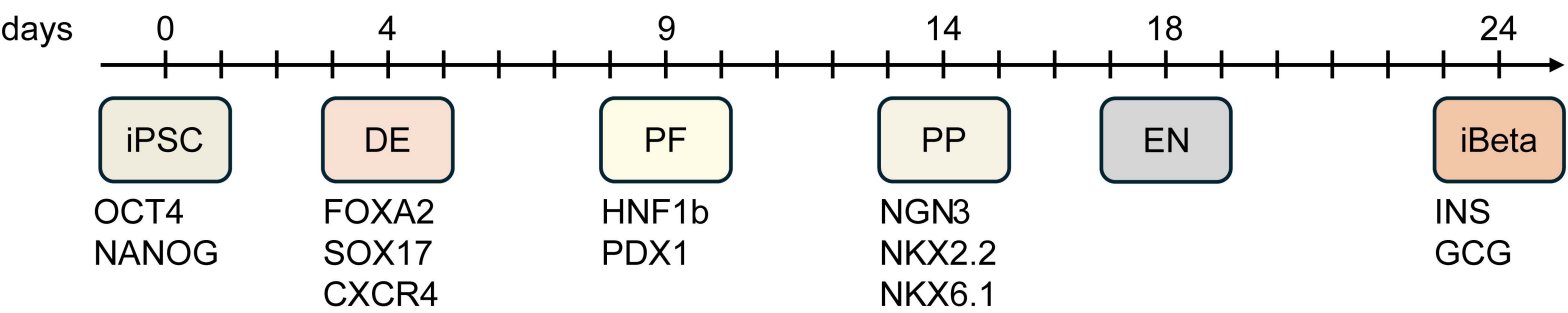
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EMS Fig. 1

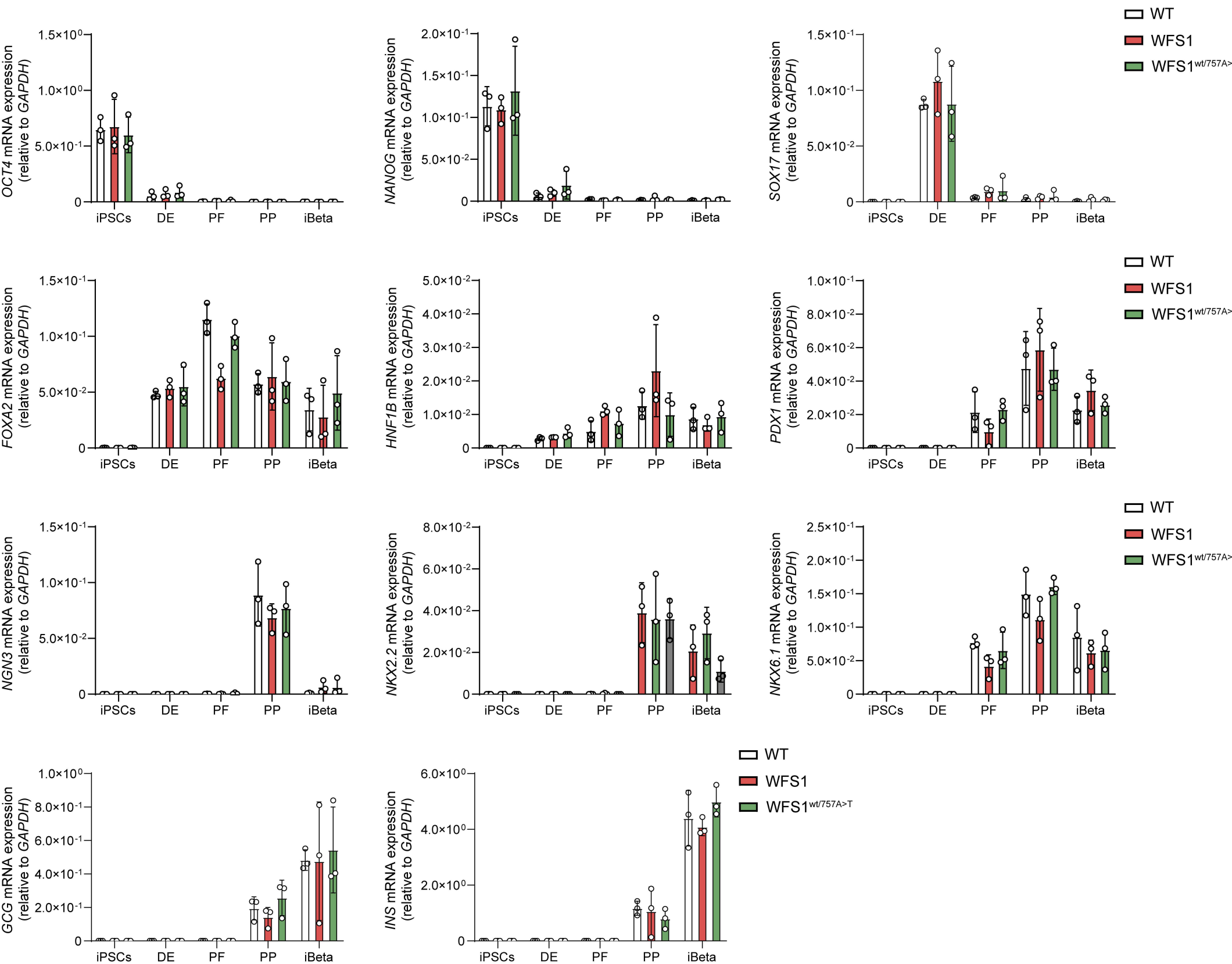


(a) Representative image at 10x magnification of WFS1 iPSC colony. **(b)** Representative karyotype of stabilized WFS1 iPSC clones. **(c)** Immunofluorescence analysis of pluripotency markers (SOX2, NANOG, OCT4 and SSEA4) in WFS1 iPSCs. Nuclei were counterstained with Hoechst. Scale bar 40µm. **(d)** Representative image at 10x magnification of WFS1^{wt/757A>T} iPSC colony. **(e)** Representative karyotypes of stabilized WFS1^{wt/757A>T} iPSC clones. **(f)** Immunofluorescence analysis of pluripotency markers (SOX2, NANOG and OCT4) in the WFS1^{wt/757A>T} iPSCs. Nuclei were counterstained with Hoechst. Scale bar 40µm.

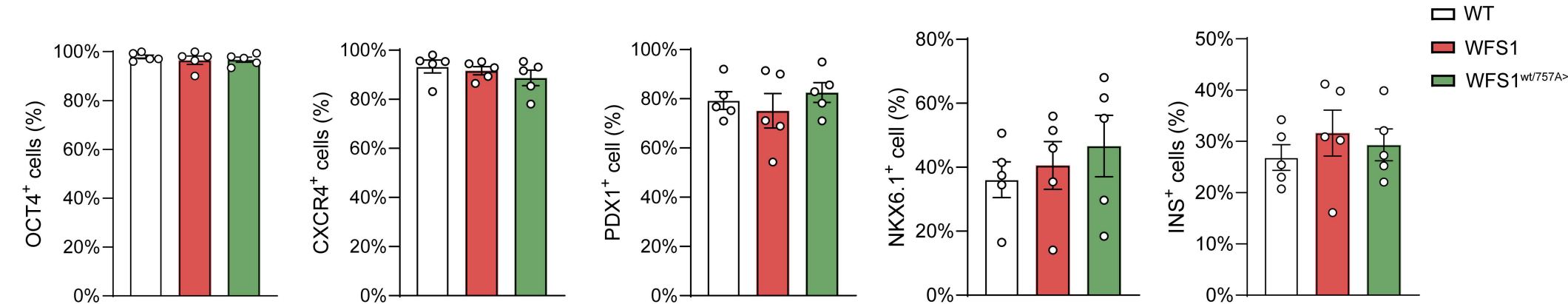
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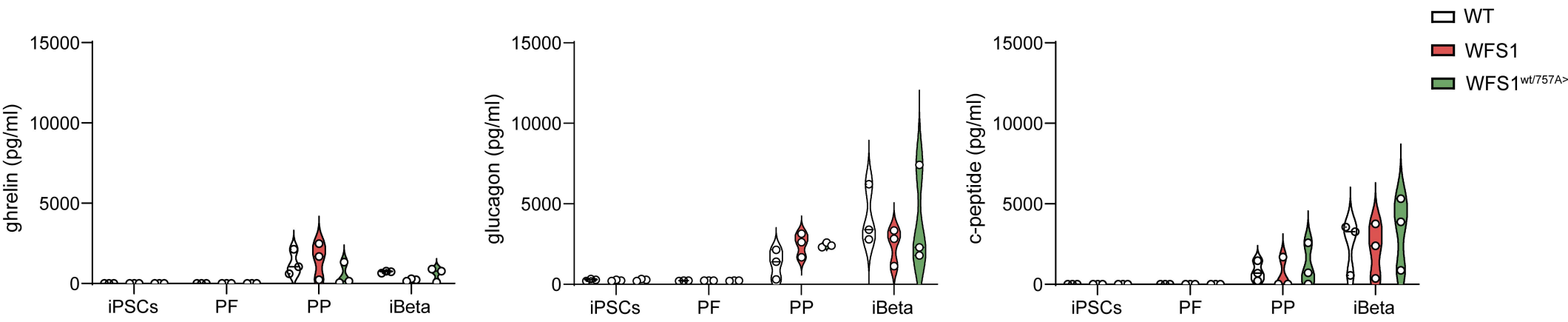
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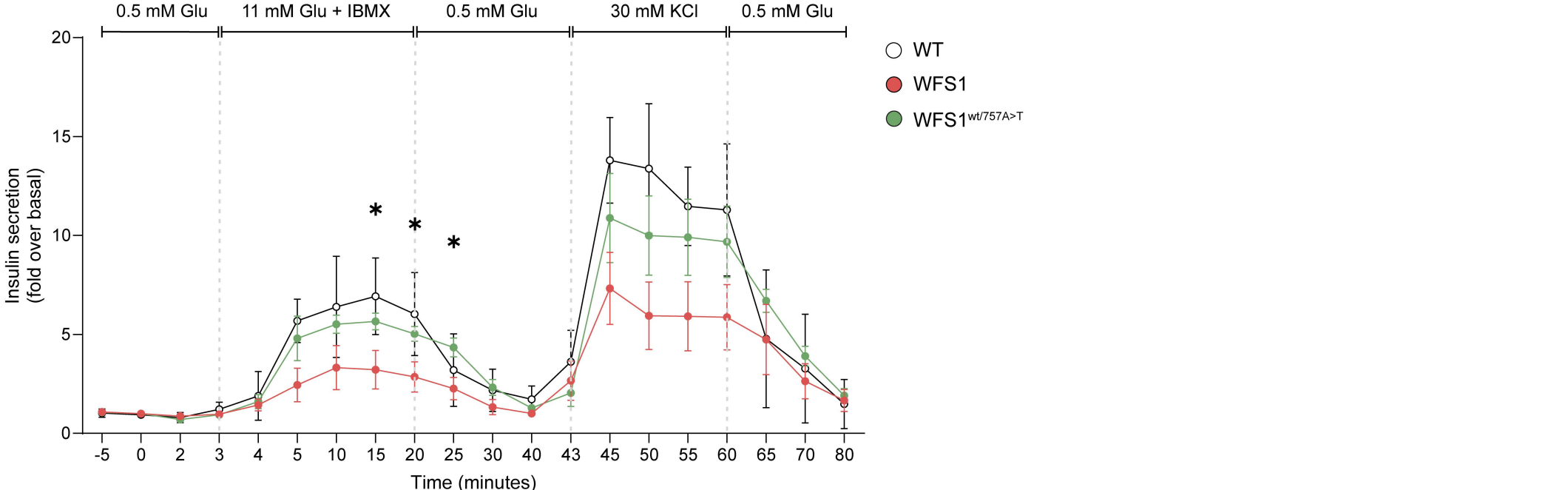
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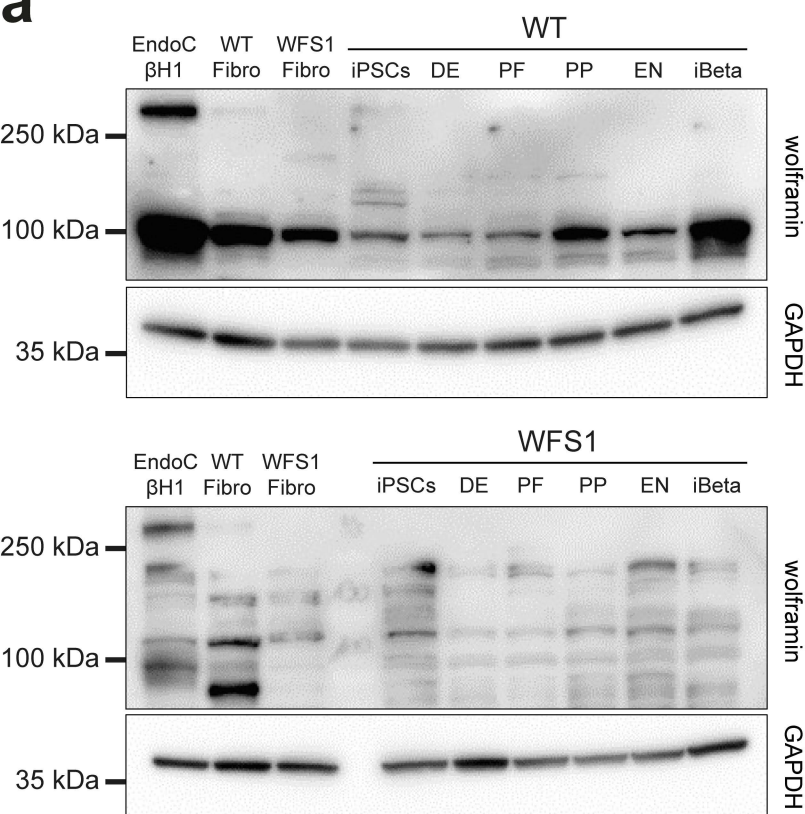
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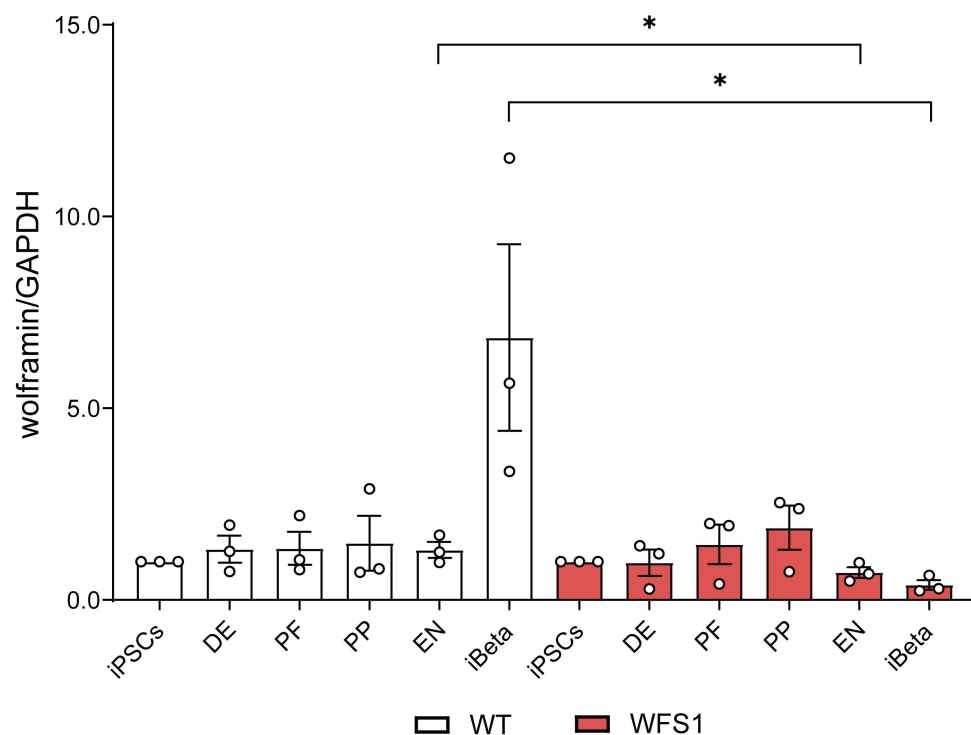
(a) Schematic representation of iPSC differentiation process into pancreatic β cells (iBeta), indicating the key markers of each step. DE=Definitive Endoderm; PF=Posterior Foregut; PP=Pancreatic Progenitors; EN=Endocrine Cells. **(b)** Gene expression analysis by TaqMan of markers of pluripotency (OCT4 and NANOG), DE (SOX17 and FOXA2), PF (HNF1B and PDX1), PP (NGN3, NKX2.2 and NKX6.1) and EN/iBeta (GCG and INS) stages of WT, WFS1 and WFS1^{wt/757A>T} iPSCs. Data are plotted as mean±SD. N=3 independent in vitro differentiations. **(c)** FACS analysis of OCT4 in iPSCs, CXCR4 at DE stage, PDX1 at PF stage, NKX6.1 at PP stage, and INS in iBeta expressed as percentage (%) of positive cells. Data are plotted as mean±SD. N=5 independent in vitro differentiations. **(d)** Secretory capacity of iPSC-derived insulin-producing cells. Unstimulated levels of ghrelin, glucagon and C-peptide in the supernatant of WT, WFS1 and WFS1^{wt/757A>T} in iPSCs and at different stages of differentiation (PF, PP and iBeta) were measured by Luminex and expressed as pg/mL. Data are plotted as mean±SD. N=5 independent in vitro differentiations. **(e)** Dynamic perfusion to assess insulin secretion following stimulation with high glucose (11 mM) + IBMX, and 30 mM of KCl. Data are plotted as fold from the baseline, mean±SEM. N=3 (WT) and 5 (WFS1 and WFS1^{wt/757A>T}) independent in vitro differentiations. The data were analyzed using two-way ANOVA with Dunn-Šidák correction (*p<0.05).

EMS Fig. 3

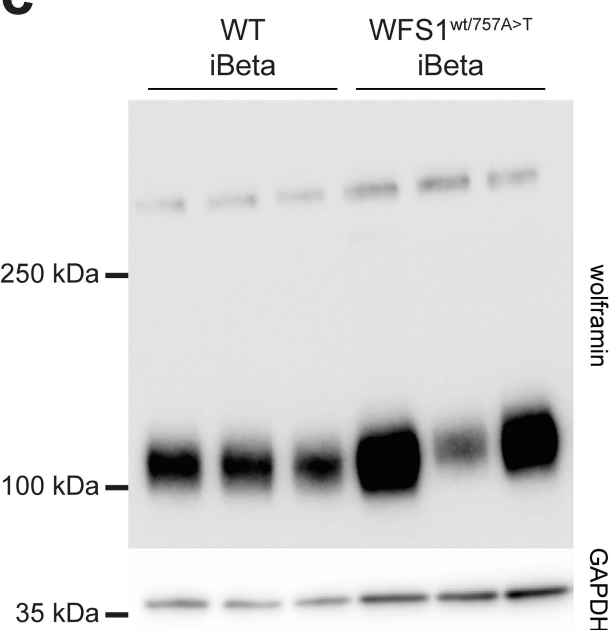
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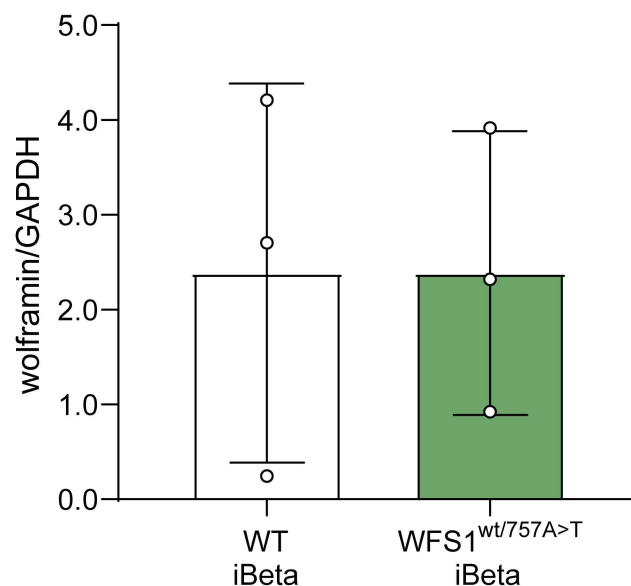
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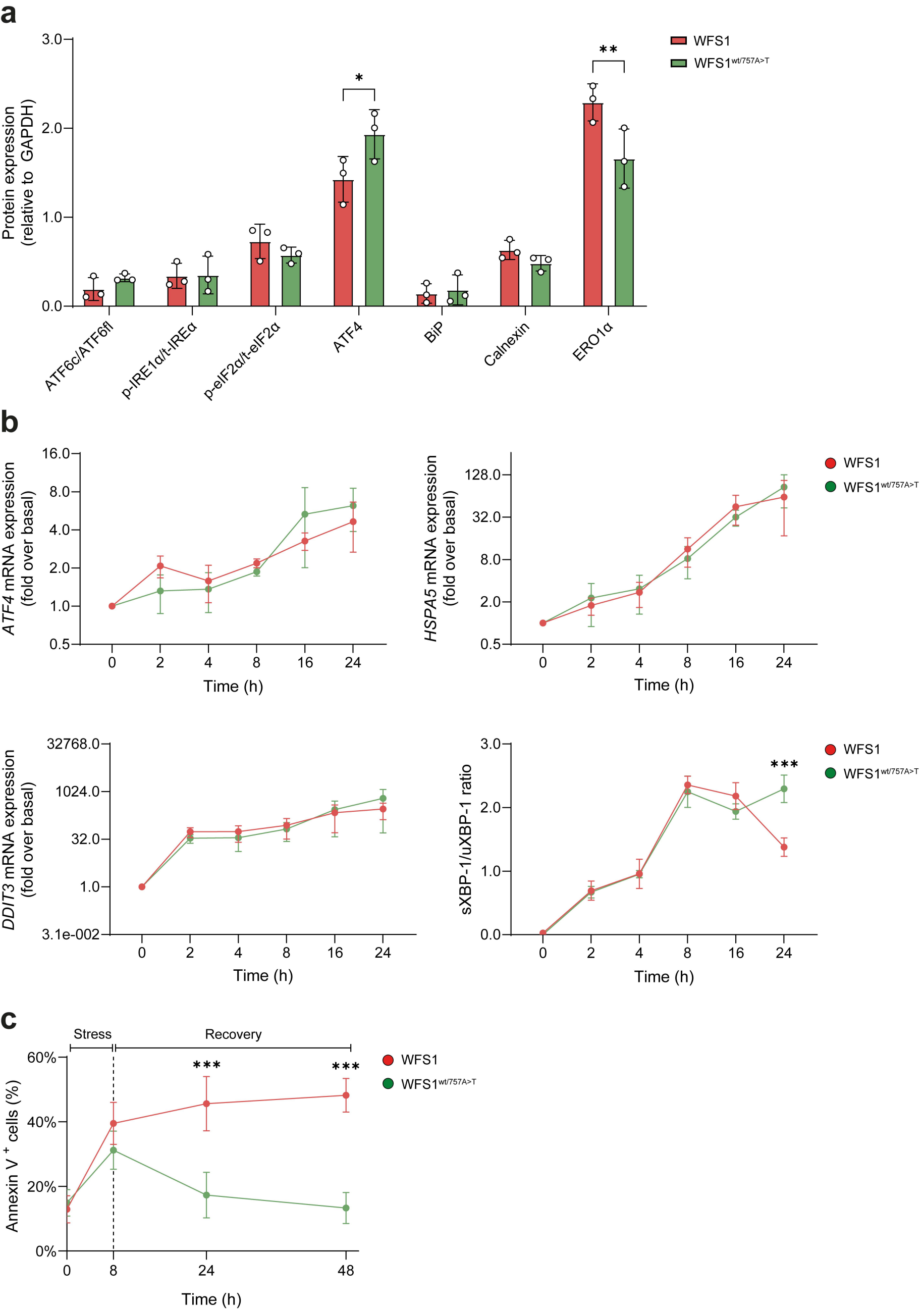


d



(a) Immunoblot analysis of Wolframin expression in WT and WFS1 iPSCs and throughout the differentiation steps (DE, PF, PP, EN, iBeta). EndoC-βH1 cells, WT and WFS1 fibroblasts were used as controls. GAPDH was used as housekeeping gene. **(b)** Relative quantification expressed as Wolframin/GAPDH ratio and expressed as mean±SD. N=3 independent in vitro differentiation. The data were analyzed using the Student's unpaired one-tailed t-test (*p<0.05). **(c)** Immunoblot analysis of Wolframin expression in WT and WFS1^{wt/757A>T} iBeta. GAPDH was used as housekeeping gene. **(d)** Relative quantification expressed as Wolframin/GAPDH ratio and expressed as mean±SD. N=3.

EMS Fig. 4



(a) Protein levels of the UPR markers in WFS1 and WFS1^{wt/757A>T} iPSCs. Mean±SD, N=3. The data were analyzed using the Student's unpaired two-tailed t-test (*p<0.05, **p<0.01). **(b)** Fold increase of ATF4, HSPA5 (BiP), DDIT3 (CHOP) genes and sXBP1/uXBP1 ratio changes in WFS1 and WFS1^{wt/757A>T} iPSCs after 100 nM TG treatment at the indicated times. Data are plotted as mean±SD. N=3-4 independent experiments. **(c)** Annexin V-positive cell percentages in WFS1 and WFS1^{wt/757A>T} iPSCs during treatment with 100 nM TG and in the recovery period with fresh medium w/o TG. Data are plotted as mean±SEM. N=3. The data were analyzed using two-way ANOVA with Dunn-Šídák correction (**p<0.001).