

Supplemental Figure 1. Validation of the *TP63* mutations in POI patients. (A) Sequence chromatograms showing nine heterozygous variants in POI patients that were not present in the controls. NM_003722.5 was used as the reference sequence. (B and C) Sanger sequencing confirmed the presence of the c.1928G>A variant in POI patient 6 and her father, but not in her mother.

Human	FSSPSHLLRTPSSASTVSVGSSETRGERVIDAV	RFTLRQTISFPPF	DEWNDFNFDMDARRNKQQRIKEEGE		
Chimpanzee	FSSPSHLLRTPSSASTVSVGSSETRGERVIDAV	RFTLRQTISFPPF	DEWNDFNFDMDARRNKQQRIKEEGE		
Macaque	FSSPSHLLRTPSSASTVSVGSSETRGERVIDAV	RFTLRQTISFPPF	DEWNDFNFDMDARRNKQQRIKEEGE		
Elephant	FSSPPHLLRTPSGASTVSVGSSETRGERVIDAV	RFTLRQTISFPPF	DEWNDFNFDMDARRNKQQRIKEEGE		
Mouse	FSSPPHLLRTPSGASTVSVGSSETRGERVIDAV	RFTLRQTISFPPF	DEWNDFNFDMDSRRNKQQRIKEEGE		
Rat	FSSPPHLLRTPSGASTVSVGSSETRGERVIDAV	RFTLRQTISFPPF	DEWNDFNFDMDSRRNKQQRIKEEGE		
Dog	FSSPPHLLRTPSGASTVSVGSSETRGERVIDAV	RFTLRQTISFPPF	DEWNDFNFDMDARRNKQQRIKEEGE		
Xenopus	FTSPPHLLRTTSSASTVSVGSNEPRGERVIDAV	RFTLRQTISFPPF	DDWNDFNFDLDTRRNKQQRIKEEGE		
Zebrafish	FSPPPHILRTSSGTSTVSVGSTEARGERVIDAV	RFTLRQTISFPPF	DDWTDFSFDLAPDSRRNKQQRIKEEGE		
		A AA A			
p.R643Q p.R655Q					
p.L646P					
p.R647C					

Supplemental Figure 2. Conservation analysis of amino acids in the TID among various species. The yellow frame indicates the core sequence of the TID. The positions of the four novel point mutations in the core sequence are shown.



Supplemental Figure 3. Epidermis characterization of $p63^{+/\Delta TID}$ mice. (A) HE staining of dorsal skin sections of P1 WT and $p63^{+/\Delta TID}$ mice. Scale bar: 50 μ M. (B and C) IF staining of K10 (red), K14 (green), and Ki67 (red) on dorsal skin sections of P1 WT and $p63^{+/\Delta TID}$ mice. Cell nuclei were counterstained with DAPI (blue). Scale bar: 50 μ M. (D) Quantitative analysis of Ki67-positive cells in the epidermis. Data are shown as the mean \pm SD, n = 6 for each genotype. Unpaired two-tailed Student's *t*-test was used for the comparison of the two groups. ns, not significant.



Supplemental Figure 4. Expression of *p63* and functional analysis of the hypothalamus and pituitary in *p63^{+/ATID}* mice. (A) Serum follicle-stimulating hormone (FSH) and Estradiol (E₂) levels were measured in 2M WT and *p63^{+/ATID}* mice (n = 6 for each genotype). (B) C-terminal structure of the *p63* gene. The primers F1, F2, F3, R1, and R2 are indicted by horizontal black arrows. The stop codons of *p63a*, *p63β*, and *p63*^{γ} are indicted by vertical black arrows, and the introduced stop codon in *p63a* is indicated by the red arrow. (C) Semi-quantitative RT-PCR analysis of *p63* isoform expression in the P1 epidermis, P1 ovary, 2M hypothalamus, and 2M pituitary of WT and *p63^{+/ATID}* mice. The three isoforms amplified by the primers are indicated in parentheses. The *p63β* isoform with a predicted band size of 446 bp was not detected. (D) Sanger sequencing of the PCR products of F1+R1 primers obtained by amplifying the cDNA from P1 WT and *p63^{+/ATID}* ovaries. The red arrow indicates the site of GA insertion. (E and F) Quantitative RT-PCR analyses of the *Gnrh* gene in

the hypothalamus and the *Cga*, *Fshb*, and *Lhb* genes in the pituitary of 2M WT and $p63^{+/\Delta TID}$ mice. *Gapdh* was used as the internal control. n = 5 for each phenotype. In panel A, E, and F, data are presented as the mean \pm SD, and differences between the groups were analyzed for statistical significance by the unpaired two-tailed Student's *t*-test. **P < 0.01, ***P < 0.001, ns, not significant.



Supplemental Figure 5. Metabolic phenotypes of WT and $p63^{+/4TTD}$ mice. (A) Gross morphology of 12M WT and $p63^{+/4TTD}$ females. (B) No significant differences were observed in body weight between 12M WT and $p63^{+/4TTD}$ mice. n = 6 per group. (C) HE staining of liver sections of 12M WT and $p63^{+/4TTD}$ mice. Scale bar: 50 μ M. (D and E) Fasting blood glucose levels and results of the glucose tolerance test performed in 2M WT and $p63^{+/4TTD}$ mice fasted for 16 h. Each point on the graph indicates the level of glucose in the blood. Blood glucose levels were detected at 15 min, 30 min, and 60 min in the glucose tolerance test. n = 6 per group. (F) Areas under the curves (AUC) calculated from mice in the glucose tolerance test. n = 6 for each genotype. (G and H) Serum total cholesterol and triglyceride levels in 2M WT and $p63^{+/4TTD}$ mice. n = 6 for each genotype. In panel B, D, and F-H, data are presented as the mean \pm SD, and differences between the groups were analyzed for statistical significance by the unpaired two-tailed Student's *t*-test. n, not significant.

Patient	Phenotype	Menarche	Amenorrhea	Age at	FSH	E ₂	Left ovary	Right ovary
ID		age (yr)	age (yr)	diagnosis (yr)	(IU/l)	(pg/ml)	(cm*cm)	(cm*cm)
1	SA	13	16	28	88.88	20	Invisible	Invisible
2	SA	15	29	38	88.27	<5	1.5*0.7	1.6*1
3	SA	13	19	28	67.3	<5	1.4*0.7	1.4*1
4	PA	-	-	32	34.51	11.5	Invisible	1.3*0.5
5	PA	-	-	27	48.73	<5	Invisible	Invisible
6	PA	-	-	24	54.6	<5	1.1*0.5	1.4*0.7
7	PA	-	-	23	70.91	<5	Invisible	Invisible
					55.77;	<5;	1.5*0.8;	1.4*0.6;
8, 9, 10	SA	13; 19; 16	25; 19; 16	27; 28; 30	78.32;	20;	Invisible;	Invisible;
					26.45	<5	1.4*1.1	1.7*0.8
11	SA	13	13	28	67.16	<5	1.7*0.7	1.7*0.6

Supplemental Table 1. Clinical characteristics of POI patients with mutations in TP63.

E₂, estradiol; FSH, follicle-stimulating hormone; POI, premature ovarian insufficiency; PA, primary amenorrhea; SA, secondary amenorrhea; yr, years; -, not available.

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HMPMAGDMNGLSPTQALPPPLSMPSTSHCTPPPPYPTDCSIV <u>RIWQV</u> * Nat Commun, 2021 Cα' VRGRETYEMLLKIKESLELMQYLPQHTIETYRQQQQQQHQHLLQKQTSMQSQ Suzuki D, et al. SSYGNSSPPLNKMNSMNKLPSVSQLINPQQRNALTPTTIPDGMGANI <u>S</u> * Development, 2015 VRGRETYEMLLKIKESLELMQYLPQHTIETYRQQQQQQHQHLLQKQTSMQSQ Lena AM, et al.	Сβ	SSYGNSSPPLNKMNSMNKLPSVSQLINPQQRNALTPTTMPEGMGANIPMMGT	+	Lena AM, et al.
Cα' VRGRETYEMLLKIKESLELMQYLPQHTIETYRQQQQQQHQHLLQKQTSMQSQ Suzuki D, et al. SSYGNSSPPLNKMNSMNKLPSVSQLINPQQRNALTPTTIPDGMGANI <u>S</u> * Development, 2015 VRGRETYEMLLKIKESLELMQYLPQHTIETYRQQQQQQHQHLLQKQTSMQSQ Lena AM, et al.		HMPMAGDMNGLSPTQALPPPLSMPSTSHCTPPPPYPTDCSIV <u>RIWQV</u> *		Nat Commun, 2021
Cα' VRGRETYEMLLKIKESLELMQYLPQHTIETYRQQQQQQHQHLLQKQTSMQSQ Suzuki D, et al. SSYGNSSPPLNKMNSMNKLPSVSQLINPQQRNALTPTTIPDGMGANIS* Development, 2015 VRGRETYEMLLKIKESLELMQYLPQHTIETYRQQQQQQHQHLLQKHLLSACE Lepa AM, et al.				
SSYGNSSPPLNKMNSMNKLPSVSQLINPQQRNALTPTTIPDGMGANI <u>S</u> * Development, 2015	C α'	VRGRETYEMLLKIKESLELMQYLPQHTIETYRQQQQQQHQHLLQKQTSMQSQ	-	Suzuki D, et al.
VRGRETVEMI I KIKESI EI MOVI POHTIETVROOOOOHOHI I OKHI I SACE Lena AM et al		SSYGNSSPPLNKMNSMNKLPSVSQLINPQQRNALTPTTIPDGMGANI <u>S</u> *		Development, 2015
	Сү	VRGRETYEMLLKIKESLELMOYLPOHTIETYROOOOOOHOHLLOKHLLSACF		Lena AM, et al
Cγ RNELVEPRGEAPTQSDVFFRHSNPPNHSVYP* - Nat Commun, 2021		RNELVEPRGEAPTQSDVFFRHSNPPNHSVYP*	-	Nat Commun, 2021

Green, SAM domain; Red, TID domain; Blue, essential for activation in oocytes (EAO) domain; *, stop codon; Underline, sequences of Cβ and Cγ different from C α ; +/-, auto-activation/inactivation in oocyte.

Supplemental Table 3. Primers used in this study.

Primer	mer Sequence (5'-3')			
Genotyping <i>p63+/ATID</i> mice				
Forward	CATTTAAGCCAAAACACCAGAGAGT	387bp		
Reverse	ATTCTCCTTCCTCTTTGATACGCT			
Genotyping <i>p63^{+/R647C}</i> mice				
rward TGAGGCCAGTGGAGAACAAG		590ha		
Reverse	GCCTCCTAATTCTCCGTCCC			
qPCR				
Noxa-Forward	Noxa-Forward GTTCGCAGCTCAACTCAGGA			
Noxa-Reverse	ACCACAGTTATGTCCGGTGC	/20p		
Puma-Forward	CAGCACTTAGAGTCGCCCG	10(1)		
Puma-Reverse	everse GTGAGGGTCGGTGTCGATG			
Gapdh-Forward	apdh-Forward AGGTCGGTGTGAACGGATTTG			
Gapdh-Reverse	TGTAGACCATGTAGTTGAGGTCA			
Gnrh-Forward	-Forward GGGAAAGAGAAACACTGAACA			
Cnrh-Reverse	GGACAGTACATTCGAAGTGCT	980p		
Cga-Forward	orward CTGTTGCTTCTCCAGGGCATA			
Cga-Reverse	TTCTTTGGAACCAGCATTGTCTT	- 660p		
Fshb -Forward	<i>b</i> -Forward GGAGAGCAATCTGCTGCCATA			
Fshb-Reverse	GCAGAAACGGCACTCTTCCT	//bp		
Lhb -Forward	TGGCCGCAGAGAATGAGTTC	0.41		
hb-Reverse CTCGGACCATGCTAGGACAGTAG		846p		
Semi-quantitative RT-PCR				
F1-Forward	GACTCAGCCCTACCCAAGCTCTC	F1+R1 (α/β):		
R1-Reverse	TGTAGGGGCTGGGAGGTGGAAG	541bp/446bp		
F2-Forward	GACCACCATCTATCAGATTGAGC	F2+R1 (α):		
R1-Reverse	TGTAGGGGCTGGGAGGTGGAAG	384bp		
F3-Forward	GTGAGAGGTCGTGAGACGTAC	F3+R2 (γ):		

R2-Reverse	CTATGGGTACACGGAGTGGTT	252bp			
β-Actin-Forward	TGTCCCTGTATGCCTCTGGTCG	347bp			
β-Actin-Reverse	GAACCGCTCGTTGCCAATAGTG				
Human mutations					
Forward (c.854) TTTTGCCACCAACATCCTGT		297ha			
Reverse (c.854)	CTGAAGGGAAAGCATGTGGAG	38/0p			
Forward (c.1612)	TGTAGGCTGTTTGAAGGGGT	653bp			
Reverse (c.1612)	GAGTAAGTGAAGGCGAGGGA				
Forward (c.1700, 1703)	TGTCACCAGTAATCTCCAGACC	543bp			
Reverse (c.1700, 1703)	CTCCTCTTTCCCACCTTGAGA				
Forward (c.1780, 1928, 1937, 1939, 1964)	GTTCTACACAGGCAGGAAAGAC				
Reverse (c.1780, 1928, 1937, 1939, 1964)	GCCAGAATCAGAATTAGATGCCA	do/op			