The American Journal of Human Genetics, Volume *101*

Supplemental Data

Female Infertility Caused by Mutations in the Oocyte-Specific Translational Repressor *PATL2*

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Supplemental Note

Case #1 (Family 1_IV:19):

23 years old lady with primary infertility for 7 years. Married to a 29 years old gentleman.

Gynecological history:
Normal menarche, regular cycles, no hirsutism, no acne or galactorrhea no dysmenorrhea, no history of PID, endometriosis, or pelvic surgeries. Not on any hormonal treatment or contraception.

Family history:
She gave history of similar infertility concerns in one of her younger sisters (see Case #2 below).

Previous fertility assessment diagnosis & treatment:

- Hormonal profile: hyperprolactinemia on bromocriptine 1.25mg PO OD, last prolactin level 49. FSH = 5.3. LH = 12.4. TSH 5.99
- Underwent 6 ovulation induction cycles via clomiphene citrate. Then 5 ovulation inductions by gonadotropins with timed intercourse.

Partner history:
29 years old gentleman who is medically & surgically free. Not using any medication. Doesn't have any allergies. Non-smoker.
Semen analysis: 6.3 ml, 25 mil/ml, 38% motile, 96% abnormal forms, TMC = 58.950000, acrosome deficiencies 59%

Workup:

- Weight = 44 Kg, Height = 146 cm, BMI = 20.6
- Blood group A+
- Hb = 116 g/L
- FSH = 6.6 IU/L
- LH = 5.5 IU/L
- Estradiol level = 150 pmol/L
- TSH = 2.8
- Prolactin level = 14.5

- Rubella Immune
- AFC 10 +6
- HSG films reviewed: Right tubal block with normal left tube & cavity

Infertility diagnosis: <u>Unexplained Infertility</u>

<u>Infertility treatment offered & outcome:</u>

A. Super ovulation: had 2 cycle of super ovulation IUI as follows:

Cycle #1: → **<u>Super ovulation – IUI</u>** HMG <u>150 IU</u> for 6 days then increased to 187.5 IU for 5 days + 200mcg Buserlin. Had 2 follicles recruited 1 was 18 mm & the other was 15 mm. Endometrium started 2 mm became 12 mm at trigger day. Triggered oocyte maturation by 10,000 IU HCG. IUI was performed smoothly with no complications or difficulties. For luteal phase support progesterone pessary prescribed 200 mg vaginally BID for 14 days. Pregnancy test negative.

Cycle #2: → **<u>Super ovulation – IUI</u>** HMG 187.5 IU for 11 days + 200mcg Buserlin. Had 2 follicles recruited 1 was 18 mm & the other was 16 mm. endometrium started 2 mm became 13 mm at trigger day. Triggered oocyte maturation by 10,000 IU HCG. IUI was performed smoothly with no complications or difficulties. For luteal phase support progesterone pessary prescribed 200 mg vaginally BID for 14 days. Pregnancy test negative.

B. <u>IVF Treatment: had total of 7 cycles as follows:</u>
<u>Summary of cycles:</u>

Cycle #1: → **<u>Long protocol</u>** with leuprolide 3.75 IM once at follicular phase at cycle day → HMG Menogon 225 IU for 13 days then 75 IU for 1 days → triggered 10,000 IU HCG (Endometrial thickness 16mm) → 11 oocytes collected → all were GV

Cycle #2: → **<u>Short protocol</u>** → started at cycled day 4 → HMG Menogon 150 IU for 9 days then 225 IU for 5 days + Buserlin 400 mcg SC daily → triggered 10,000 IU HCG (Endometrial thickness 13mm) → 4 oocytes collected (only right ovary, left ovary not aspirated due to bladder accessibility) → all were GV

Cycle #3: → **Long protocol** (we wanted to try GnRH flexible Antagonist protocol but we didn't have antagonist in the hospital & patient couldn't afford it from outside) had leuprolide 3.75 IM once at follicular phase at cycle day → HMG Menogon 225 IU for 9 days then 300 IU for 5 days → triggered 10,000 IU HCG (Endometrial thickness 16mm) → 21 oocytes collected → all were GV

Cycle #4: → **Short protocol** → started at cycled day 4 → HMG Menogon 300 IU for 12 days → after 10 days of stimulation a leading follicle reached 15m, (LH measured on same day 5.9 iu/L, next day 3.3 iu/L the day after 3 iu/L) → triggered Buserelin 500 mcg SC (Endometrial thickness 14mm) → 5 oocytes collected → all were GV

Cycle #5: → **Short protocol** → started at cycled day 3 → HMG Menogon 300 IU for 6 days then 375 IU for 4 days then increased to 450 IU 2 days + Buserlin 400 mcg SC daily → triggered 10,000 IU HCG (Endometrial thickness 14mm) → 2 oocytes collected → all were GV

Cycle #6: → **Flexible antagonist protocol** →started at cycled day 4 → FSH Gonal-F 300 IU for 9 days then antagonist started 0.5 Orgalotran both continued 3 days (developed 2 right hemorrhagic cyst at CD 10) → triggered by Superfact 0.4 ml SC (Endometrial thickness 18mm) → 13 oocytes collected → all were GV

Cycle #7: → **Flexible antagonist protocol →** started at cycled day 3 → FSH Gonal-F 300 IU for 10 days then antagonist started 0.5 Orgalotran both continued 3 days→ triggered by Superfact 0.4 ml SC & HCG 10,000 IU SC (Endometrial thickness 18mm) → had 22 follicles recruited 23 oocytes collected → 14 eggs were GV's & 7 eggs degenerated.

Case #2 (Family 2_IV:18):

25 years old lady with primary infertility for 6 years, married to a 31 years old gentleman.

Gynecological history:
Menarche at age of 12, cycles range 28 – 35 days with flow 5-6 days, no acne or galactorrhea, mild dysmenorrhea & no history of PID, endometriosis, pelvic surgeries. Not on any hormonal treatment or contraception.

Past medical history: free
Past surgical history: free
Medications: None
Allergies: None

Partner history:
He's known to be diabetic controlled on oral hypoglycemic agents. Surgically free. Doesn't have any allergies. Nonsmoker.

Workup:

- Weight = 59.7 Kg, Height = 158 cm, BMI = 23.9
- Blood group A+
- Hb = 123 g/L
- FSH = 5.6 IU/L
- LH = 14.7 IU/L
- Estradiol level = 189 pmol/L
- TSH = 2.29
- Prolactin level = 14.79
- Rubella Immune
- AFC 15+20
- Semen analysis: 1 ml, 162 mil/ml, 72% motile, 1% normal forms, TMC = 116.640000, acrosome deficiencies 77%
- HSG films reviewed: normal cavity & patent tubes

Infertility diagnosis: <u>Unexplained Infertility</u>

<u>Infertility treatment offered & outcome:</u>

1. **<u>Short protocol</u>** → started at cycled day 3 → HMG Menogon 150 IU for 6 days then 75 IU for 5 days then increased to 150 IU for 2 days + Buserlin 400 mcg SC daily → triggered 10,000 IU HCG (Endometrial thickness 8mm) → 4 oocytes collected → all were GV

Figure S1

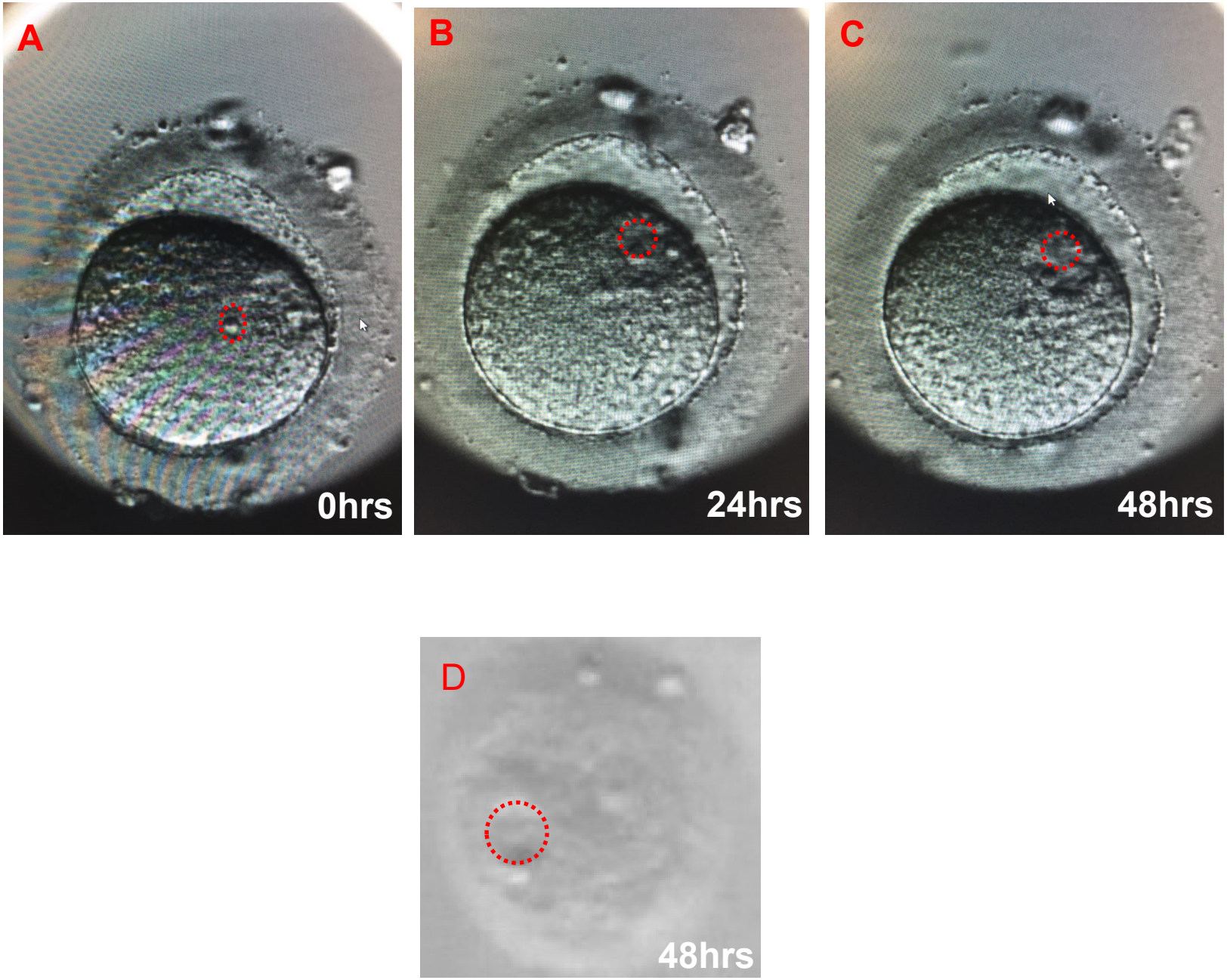
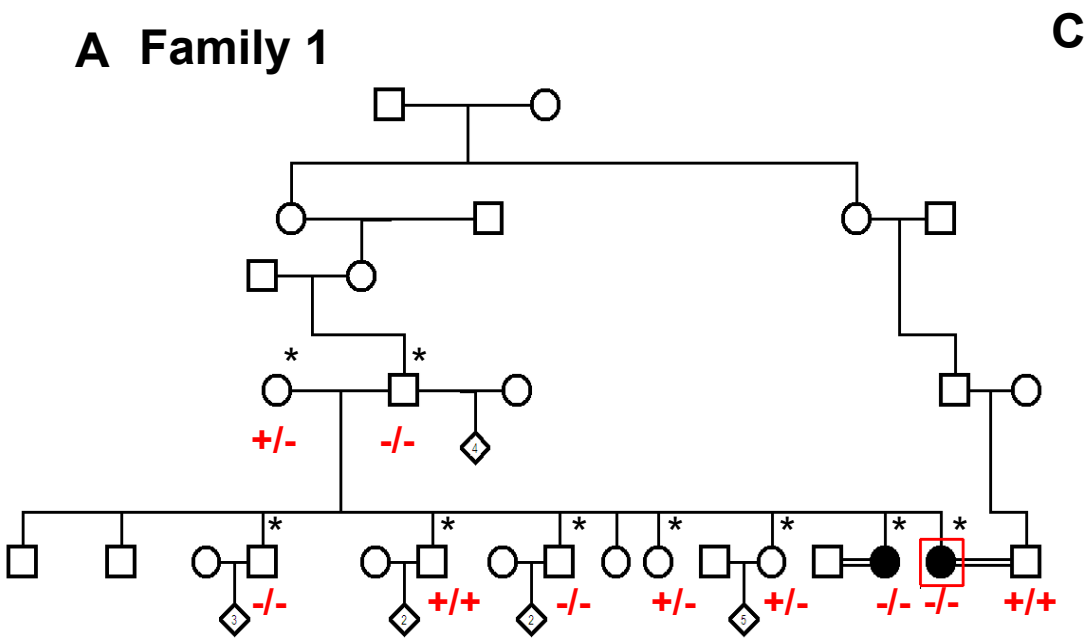
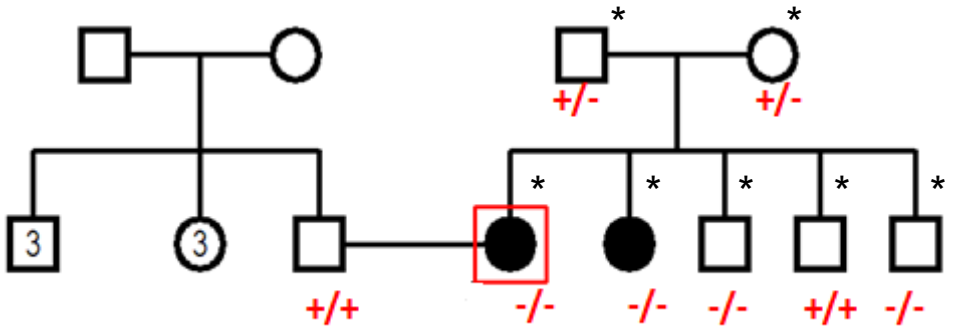
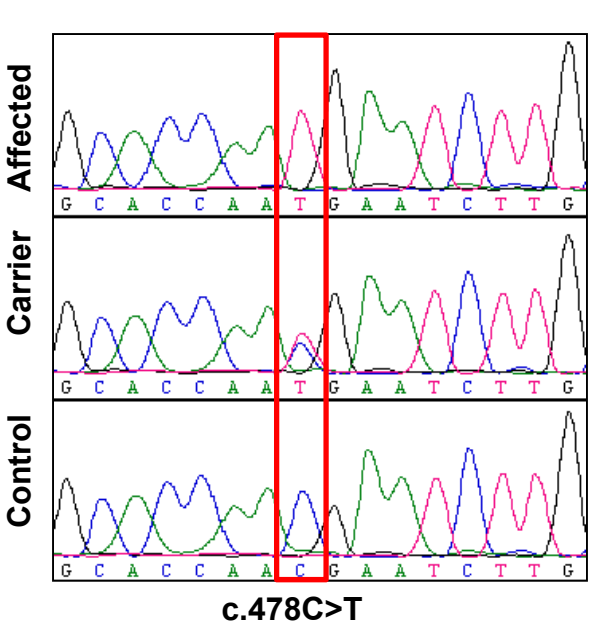


Figure S1. A-C) Images of immature oocytes from the individual IV:18 in family 1 with maturation arrest phenotype from family 1. Red circles indicate germinal vesicles. D) Images of immature oocytes from individual II:4 in family 2 showing a similar defect despite the much lower quality of the image.

Figure S2


A Family 1
+/-
-/-
-/-
+/+
-/-
+/-
+/-
-/-
-/-
+/+


B Family 2
3
3
+/+
-/-
-/-
-/-
+/-
+/-
+/+
-/-


C
Affected
Carrier
Control
G C A C C A A T G A A T C T T G
G C A C C A A T G A A T C T T G
G C A C C A A C G A A T C T T G
c.478C>T

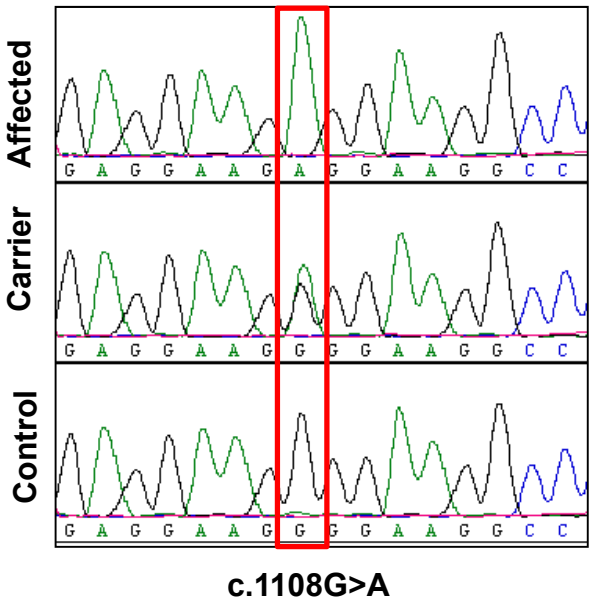

D
Affected
Carrier
Control
G A G G A A G A G G A A G G C C
G A G G A A G G G G A A G G C C
G A G G A A G G G G A A G G C C
c.1108G>A

Figure S2. Pedigrees of family1 (A) and family 2 (B) showing the *PATL2* mutation status. Red box indicates index for whom whole exome sequence (WES) was performed. Segregation was performed for the available family members. -/- denotes homozygous status; +/- denotes carrier status; +/+ denotes wild type; * marks individuals included in the linkage analysis. C) Chromatogram for the mutation c.478C>T:p.(Arg160*) in family 1. D) Chromatogram for the mutation c.1108G>A:p.(Gly370Arg) in family 2.

Figure S3


Yeast LHI---DDSSYDVNPFISMLSFDKGIKIMPRIFNFLDKQQ
C.elegans -----VIINELMGDDLSKLMQMSKGRAVITRTLKVVEPRD
Drosophila --LVNKLKAGLAFDKVIAMMNVRKGKILIRRIMPFIADQS
Zebrafish L---RCTNLD-SGEEFLSCLLVSKGKRLVARLLPFLSHDS
Xenopus LNMAPCHSEDESENEFLQLLQVGKGKKLIARLLPFLTRVQ
Mouse LKTQEQNNLEEAADNLLQVLSVRKGKVLVARLLPFLPPDQ
Cattle LKAQGQNNLEAADDGFLQALSVGKGKALVARLLPILPRDR
Dog LKTQEQKNLEEAADGFLQVLSVRKGKALVARLLPFLPQDQ
Chimpanzee LKTQEQNNLEEAADGFLQVLSVRKGKALVARLLPFLPQDQ
Human LKTQEQNNLEEAADGFLQVLSVRKGKALVARLLPFLPQDQ
Gly370Arg

Figure S3. The glycine 370 residue of PATL2 is highly conserved from human to yeast. Protein sequences were obtained publically available genomic databases: human (NM_001145112.1), chimpanzee (XM_001146504.2), dog (XM_003640026.1), cattle (XM_002691093.2), mouse (NM_026251.2), *Xenopus* (NP_001135679.1), zebrafish (XP_683261.4), *Drosophila* (NP_001287369.1), *C.elegans* (NP_496514.1) and yeast (NP_010002.3). PATL2 protein sequences were aligned by using ClustalW.

Table S1: list of haplotypes from two families with in the shared ROH (chr15:42,254,070-45,702,800).

SNP	Mb distance	Family 1 IV:19	Family 1 IV:18	Family 2 II:4	Family 2 II:5
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RS1618332	42184794	ab	ab	BB	BB
RS1048166	42192040	ab	ab	AA	AA
RS8041458	42196846	ab	ab	BB	BB
RS17686769	42205483	ab	ab	BB	BB
RS4923919	42208041	ab	ab	AA	AA
RS2899033	42212047	BB	BB	BB	BB
RS10518742	42220257	BB	BB	BB	BB
RS1648856	42233912	AA	AA	BB	BB
RS1648855	42237403	AA	AA	BB	BB
RS34899815	42254068	BB	BB	AA	AA
RS1868831	42257929	AA	AA	AA	AA
RS1704345	42270697	ab	ab	AA	AA
RS4924593	42273259	ab	ab	AA	AA
RS1668572	42273526	ab	ab	BB	BB
RS1704352	42281805	BB	BB	BB	BB
RS7175837	42300303	ab	ab	BB	BB
RS1704367	42300475	BB	BB	BB	BB
RS12438854	42300886	ab	ab	AA	AA
RS9919954	42302520	ab	ab	AA	AA
RS7182446	42302751	BB	BB	BB	BB
RS12439430	42305042	ab	ab	BB	BB
RS12909362	42315401	AA	AA	BB	BB
RS2665203	42316527	BB	BB	BB	BB
RS2724943	42319233	ab	ab	AA	AA
RS4924608	42332784	ab	ab	AA	AA
RS1668596	42336250	BB	BB	AA	AA
RS7175879	42336450	BB	BB	BB	BB
RS1712436	42338079	BB	BB	BB	BB
RS1993069	42339158	ab	ab	BB	BB
RS12902878	42343794	ab	ab	BB	BB
RS776688	42345046	ab	ab	AA	AA
RS16972565	42350013	BB	BB	BB	BB
RS776699	42350037	BB	BB	BB	BB
RS1668588	42364362	BB	BB	BB	BB
RS59107494	42366224	AA	AA	BB	BB
RS7166111	42368506	ab	ab	BB	BB
RS2412657	42387203	BB	BB	AA	AA
RS8028204	42392164	AA	AA	BB	BB
RS17748385	42395956	AA	AA	AA	AA
RS12050606	42396187	ab	ab	BB	BB
RS1008979	42399642	AA	AA	BB	BB
RS2122677	42400066	AA	AA	AA	AA
RS675996	42400764	ab	ab	AA	AA
RS28665345	42405470	BB	BB	BB	BB
RS11852412	42409999	ab	ab	BB	BB

RS1712440	42411029	AA	AA	AA	AA
RS4924623	42411189	ab	ab	AA	AA
RS1712439	42411286	AA	AA	AA	AA
RS1712426	42412606	BB	BB	AA	AA
RS2034521	42415270	ab	ab	AA	AA
RS4924626	42423090	ab	ab	AA	AA
RS2899041	42429490	AA	AA	AA	AA
RS650392	42430535	ab	ab	BB	BB
RS3825786	42431142	AA	AA	AA	AA
RS648130	42431683	AA	AA	AA	AA
RS1712442	42502282	BB	BB	BB	BB
RS16972887	42522558	BB	BB	BB	BB
RS16972896	42524104	AA	AA	BB	BB
RS1679012	42528676	ab	ab	AA	AA
RS17694281	42528739	AA	AA	AA	AA
RS8036187	42533879	AA	AA	AA	AA
RS8024732	42570718	BB	BB	BB	BB
RS16972989	42572231	AA	AA	AA	AA
RS34373997	42583801	BB	BB	BB	BB
RS16973015	42585099	AA	AA	AA	AA
RS12914737	42589317	AA	AA	AA	AA
RS2412697	42605791	AA	AA	AA	AA
RS12903690	42615305	AA	AA	AA	AA
RS1659215	42619508	AA	AA	AA	AA
RS16973119	42636303	BB	BB	BB	BB
RS7181742	42643529	AA	AA	AA	AA
RS7180279	42643538	AA	AA	AA	AA
RS3743006	42645768	BB	BB	BB	BB
RS28364384	42666499	BB	BB	BB	BB
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RS28364405	42679414	AA	AA	AA	AA
RS28364409	42679857	AA	AA	AA	AA
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RS2617237	42765624	BB	BB	AA	AA
RS17709596	42767981	AA	AA	BB	BB
RS6493048	42787459	BB	BB	BB	BB
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RS34359922	42836056	AA	AA	AA	AA
RS876992	42878456	BB	BB	BB	BB
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RS6493054	42886504	AA	AA	AA	AA
RS1667493	42889170	BB	BB	AA	AA
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RS17767439	42927182	AA	AA	AA	AA
RS12594951	42934631	BB	BB	BB	BB
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RS7048	43620073	AA	AA	AA	AA
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RS2453274	44774202	BB	BB	BB	BB
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RS883943	44788705	BB	BB	BB	BB
RS4611428	44815160	BB	BB	BB	BB
RS2556560	44821843	AA	AA	AA	AA
RS10518980	44822774	AA	AA	AA	AA
RS28409610	44827024	BB	BB	BB	BB
RS17586936	44847394	AA	AA	AA	AA
RS2303578	44849698	BB	BB	BB	BB
RS17586985	44851244	BB	BB	BB	BB
RS12594905	44881964	AA	AA	AA	AA
RS17515394	44898870	AA	AA	AA	--
RS36014111	44900675	BB	BB	BB	BB
RS12594578	44934061	BB	BB	BB	BB
RS3759871	44943757	AA	AA	AA	AA

RS3759875	44943958	AA	AA	AA	AA
RS7165146	44951174	AA	AA	AA	AA
RS12594463	44984631	AA	AA	AA	AA
RS4099	44988610	AA	AA	AA	AA
RS1901530	45005146	BB	BB	BB	BB
RS11553037	45007770	BB	BB	BB	BB
RS2290330	45021227	BB	BB	AA	AA
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RS3759878	45028587	AA	AA	AA	AA
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RS2444006	45043972	BB	BB	BB	BB
RS7182597	45045260	AA	AA	AA	AA
RS2470911	45047134	BB	BB	AA	AA
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RS3759883	45048841	BB	BB	AA	AA
RS7182022	45069742	AA	AA	BB	BB
RS8023560	45072082	BB	BB	AA	AA
RS2462043	45074519	BB	BB	BB	BB
RS1720726	45076085	AA	AA	AA	AA
RS35922426	45078790	BB	BB	BB	BB
RS2049333	45085225	AA	AA	BB	BB
RS1295359	45089019	AA	AA	BB	BB
RS1288092	45090821	AA	AA	AA	AA
RS11856785	45094155	BB	BB	BB	BB
RS2443978	45094624	BB	BB	BB	BB
RS7172822	45094869	BB	BB	BB	BB
RS10152725	45095196	BB	BB	BB	BB
RS17518970	45095902	AA	AA	BB	BB
RS2924123	45096023	BB	BB	AA	AA
RS16974812	45096283	BB	BB	BB	BB
RS16952664	45096539	AA	AA	AA	AA
RS16952671	45097181	AA	AA	BB	BB
RS17592201	45135017	AA	AA	BB	BB
RS956093	45202972	BB	BB	BB	BB
RS13379531	45225352	BB	BB	BB	BB
RS12902975	45267670	AA	AA	AA	AA
RS11635836	45299916	BB	BB	BB	BB
RS199335	45306556	AA	AA	AA	AA
RS7183046	45379702	AA	AA	AA	AA
RS10851420	45385916	BB	BB	BB	BB

Table S1: list of haplotypes from two families with in the shared ROH (chr15:42,254,070-45,702,800).

Table S2

Family	Affected *(n)*	Mutation	ExAC Frequency	*In silico* analysis of pathogenicity
1	2	PATL2 NM_001145112.1:c.478C>T:p.(Arg160*)	0.00003362	Truncation of 383 amino acids
2	2	PATL2 NM_001145112.1:c.1108G>A:p.(Gly370Arg)	0	PolyPhen: possibly_damaging (0.915) SIFT: deleterious (0.03) CADD: 33

Table S2: Variants identified in *PATL2* in two families.