SUPPLEMENTAL APPENDIX

Genetic landscape of a large cohort of Primary Ovarian Insufficiency. New genes/pathways and implication for personalized medicine

Supplemental Materials and Methods:

1. **Molecular genetics studies**

a) Whole exome sequencing

Whole exome sequencing studies (WES) were performed on genomic DNA extracted from the peripheral blood of the propositae and available affected and unaffected sisters and mothers. Library preparation, exome capture, sequencing, and data processing were performed by IntegraGen SA (Evry, France) according to their in-house procedures. Data analysis was performed as described in our previous studies [1–4]. In brief, exon enrichment was performed on 600 ng of DNA, using the Agilent SureSelect Human All Exons kit version CRE (Agilent Technologies, Santa Clara, USA). Exon-enriched libraries were subjected to 75 bp paired-end sequencing on a HiSeq2500, according to the manufacturer's protocol. Read alignment to the human reference genome (GRCh38) and variant calling were performed using the Illumina pipeline (CASAVA 1.8.2). Variant annotation was performed using Ensembl's Variant Effect Predictor. The variants were filtered using SIRIUS, an IntegraGen in-house pipeline platform.

Filtration according to the mode of inheritance is a powerful method. Therefore, the exomes of affected patients were compared to the exomes of selected and available affected and non-affected members of the family. The exome analysis was performed as follows: In the presence of known or suspected consanguinity, we focused on all rare homozygous variants identified in the patient's exome. In fact, each exome contained approximately 10–20 rare homozygous variants. When parents' exomes were available, we confirmed the presence of the variant in the heterozygous state in one or both parents. The causal variant was identified using a combination

of *in silico* bioinformatic predictors and bibliographic research (regarding gene function, expression, animal model described, etc.). In the absence of inbreeding, we tested the hypothesis of a recessive mode of transmission but with two compound heterozygous pathogenic variants; these variants occur in the same gene, each of which is transmitted by one of the two parents. We therefore performed a comparative study of the patient's exome with that of the parents or her available relatives. Furthermore, we tested the dominant mode of transmission of a paternal gene variant—which had no effect on male fertility—transmitted to the proposita and affected sisters and absent in the unaffected sisters. Finally, and although rarely described in POI, we tested the *de novo* hypothesis (variant present only in the proposita and absent from WES of both parents when the latter were available).

b) Targeted next generation sequencing

A custom-made targeted NGS study, including all known genes involved in POI [5], was performed in proposita and available relatives. Libraries were prepared using an NEB Next DNA Library Prep Master Mix Set for Illumina (NEB Inc). Enrichment was performed on 500 ng of DNA using a Sure Select XT Reagent Kit (Agilent). Libraries were subjected to 75 bp paired-end sequencing on a MiSeq2500 according to the manufacturer's protocol. Data analysis was performed using an automated bioinformatics pipeline implemented with a local Galaxy instance at Bicêtre Hospital, France. In brief, alignment to the human reference genome 19 (GRCh37) was performed using BWA–MEM 0.7.10. Variant calling was performed using GATK 3.4-46, and single nucleotide variants were annotated using both Annovar 2015-06-17 and Snpeff 4.0. Variants detected were processed using the following bioinformatic filters: (i) variants with a read coverage under 5× and a Q score <20 were filtered out, and (ii) variations against ExAC databases were filtered using a minor allelic frequency (MAF) of 0.02. The short list of variants with an MAF <0.02 according to the ExAC database was then manually annotated using dbNSFP, an integrated database including a wide range of *in silico* predictors and all human polymorphism databases, notably gnomAD [6]. Variant classification according

to the ACMG-AMP 2015 guideline was performed using InterVar [7] (https://wintervar.wglab.org/) and Varsome [8] (https://varsome.com/).

c) NGS Studies in familial POI: In our cohort, 70 proposita belonging to 70 different families have been included. For 24 non-consanguineous patients, mainly of European origin (16 Europeans, 5 North Africans, 2 Africans and 1 Asian), no family member (parents, sisters, cousins) was available for exome studies. A targeted –NGS (T-NGS) was performed. For 46 other families either consanguineous or with available relatives, 13 were studied in our laboratory in 2017 before the implementation of our efficient in-house targeted NGS. We used WES first to study those families. The other 33 patients had T-NGS first after its development, followed by WES in the case T-NGS was negative.

c) Sanger Genomic Sequencing

Direct genomic Sanger sequencing was performed in the proposita and the available relatives to confirm the relevant pathogenic variant and to specify the inheritance.

Supplemental References

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6. Liu X, Wu C, Li C, Boerwinkle E. dbNSFP v3.0: A One-Stop Database of Functional Predictions and Annotations for Human Nonsynonymous and Splice-Site SNVs. Hum Mutat. 2016;37:235–41.

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8. Kopanos C, Tsiolkas V, Kouris A, Chapple CE, Albarca Aguilera M, Meyer R, et al. VarSome: the human genomic variant search engine. Bioinformatics. 2019;35:1978–80.

Supplemental Figures

Fig.S1: Clinical characteristics of the patients in the cohort of POI. A. Sporadic or familial cases. **B**. Menses; PA: Primary Amenorrhea, SA: Secondary Amenorrhea, SP: Spaniomenorrhea. **C.** Initial clinical presentation: isolated/non-syndromic (dark blue); syndromic with other extra-ovarian features (light blue). **D.** Ethnicity of the patients.

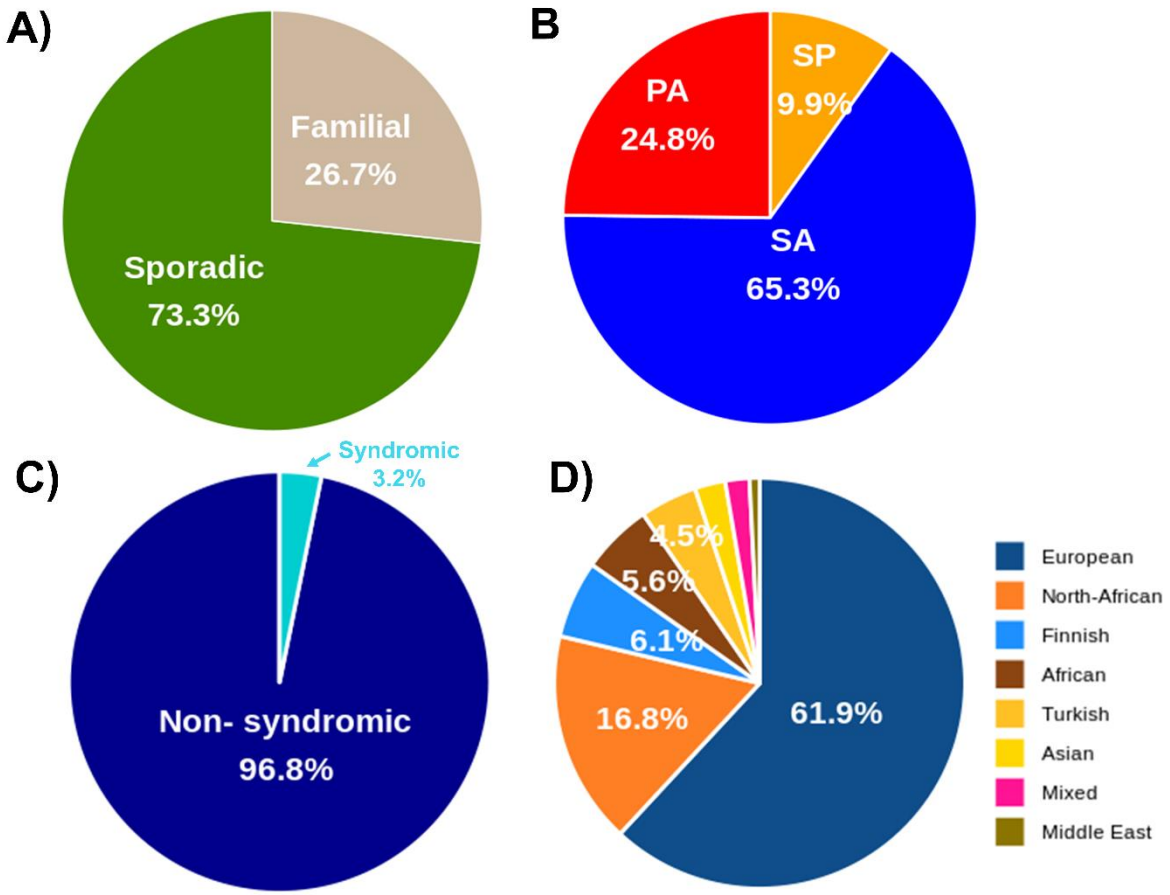
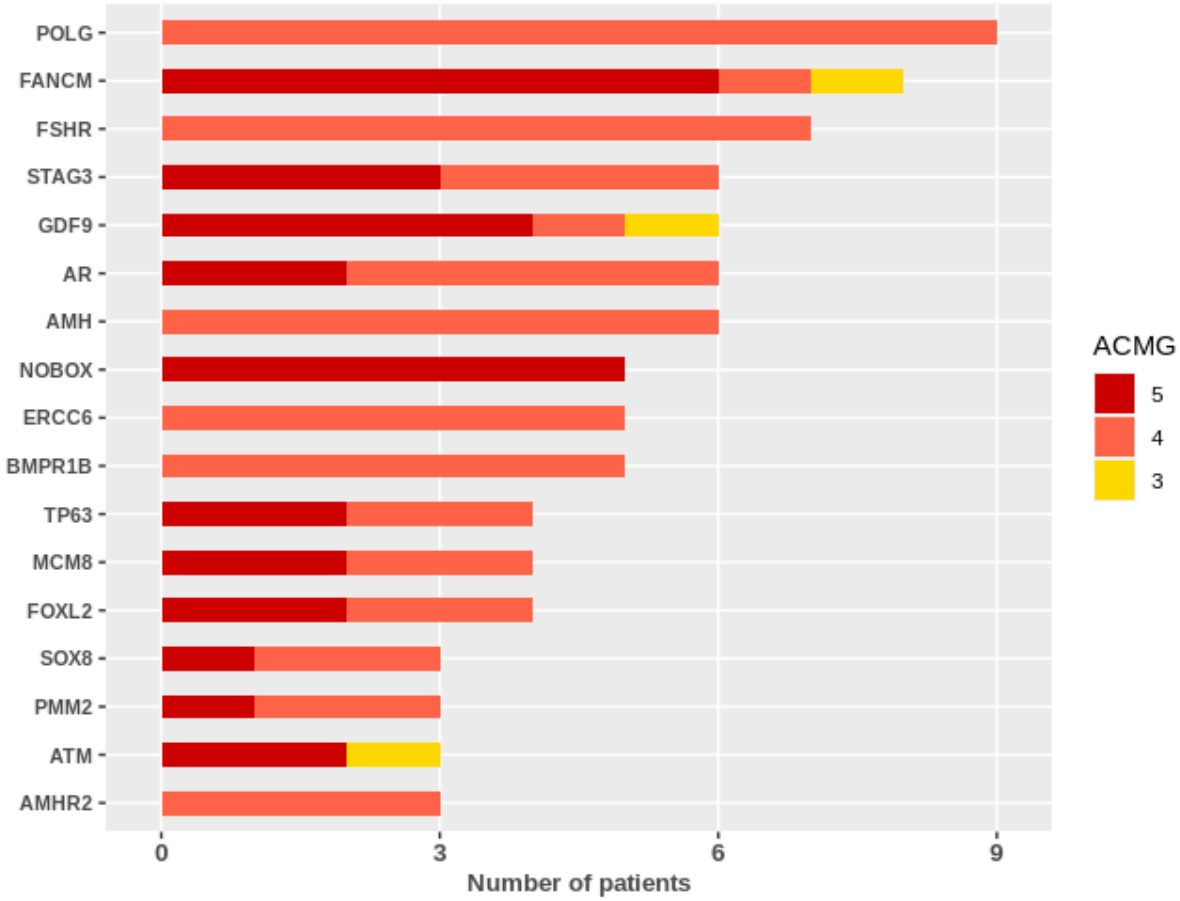


Fig.S2: Most recurrent genes in the cohort. Genes with variants in three patients or more are represented. Variants are classified according to ACMG criteria. Only Pathogenic and Likely pathogenic variants are considered for the genetic diagnosis as recommended by the ACMG.



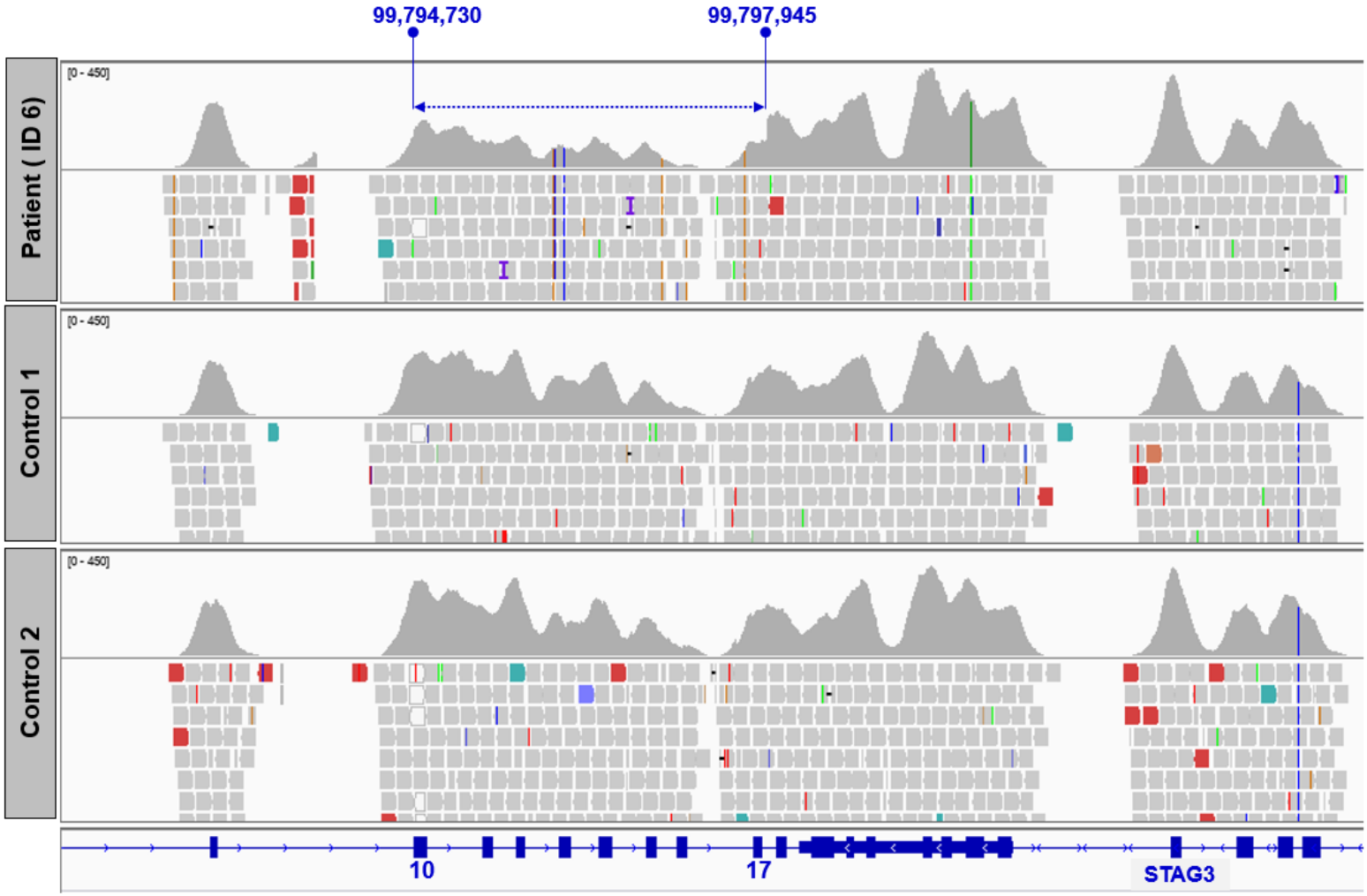


Figure S3: **intragenic deletion of *STAG3*.** Targeted-NGS data is visualized with IGV (*integrative genomics viewer*) centered on *STAG3*.
The patient (ID 6) has an intragenic deletion of *STAG3* detected by an in-house pipeline based on coverage, to detect Copy Number Variation (CNV). The deletion has a size of 3215 pb (3,2Kbp) (Coordinates according to hg 19: 99,794,730-99,797,945) and extends from exon 10 to exon 17 of STAG3

Supplemental Tables

(Tables S1, S6 and S7 are larger tables added as separate Excel files)

Table S2: Clinical characteristics of the cohort of patients with POI

Age at diagnosis (Years)	**N**	**%**
Mean age	*25,54[12-40]*	
Ethnicity		
European	232	61,9 %
North- African	63	16,8 %
Finnish	23	6,1 %
African	21	5,6 %
Asian	9	2,4 %
Turkish	17	4,5 %
Middle East	3	0,8 %
Mixed	7	1,9 %
Initial clinical presentation		
Isolated POI	363	96,8%
Syndromic POI	12	3,2%
Menses		
Primary Amenorrhea (PA)	*93*	24,8%
Secondary Amenorrhea (SA)	*245*	65,3%
Spaniomenorrhea (SP)	*37*	9,9%
Pregnancy before POI (SA or SP)		
Yes spontaneously	**81**	**21,6%**
1 pregnancy	*46*	12,3%
2 pregnancies	*28*	7,5%
3 pregnancies	*5*	1,3%
4 pregnancies	*2*	0,5%
Yes with IVF	**5**	**1,3%**
1 pregnancy	*4*	1,1%
2 pregnancies	*1*	0,2%
No	**279**	**74,4%**
Unkown	10	2,7%
Hormonal Assays		
FSH (IU/l)	76,5[25-244]	
LH (IU/l)	37,34 [4,6-143]	
Estradiol (IU/l)	48,24[0- 430]	
AMH (ng/l)	0,31[0-8,3]	

Table S3: Associated clinical features in patients with syndromic POI

ID	Ethnicity	Age	Menses	Phenotype	Gene	Variant(s)	Status	Known syndrome
92	European	27	SP	Blepharophimosis, epicanthus inversus, and ptosis	**FOXL2**	NM_023067.4:c.655C>T : p.Gln219Ter	Het	**BPES**
242	European	34	SA	Blepharophimosis, epicanthus inversus, and ptosis	**FOXL2**	NM_023067.4:c.196G>A : p.Ala66Thr	Het	**BPES**
324	European	28	SP	Blepharophimosis, epicanthus inversus, and ptosis	**FOXL2**	NM_023067.4:c.576del : p.Lys193SerfsTer78	Het	**BPES**
175	European	27	SA	Hypoparathyroidism	**AIRE**	NM_000383.4:c.769C>T : p.Arg257Ter & c.967_979del : p.Leu323SerfsTer51	Comp Het	**APECED**
272	European	13	PA	Mild Intellectual disability, Sensorineural hearing loss, hyperthroidism	**RCBTB1**	NM_018191.4:c.1271T>G :p.Phe424Cys & c.962C>T : p.Pro321Leu	Comp Het	**Syndromic retinal dystrophy**
182	African	27	SA	Marinesco-Sjogren syndrome	**SIL1**	NM_022464.5 :c.1249C>T : p.Gln417Ter	Hom	**Marinesco-Sjogren syndrome**
315	Turkish	14	PA	Intra uterine growth retardation (IUGR), Hypothyroidism, pilomatricomas	**MCM8**	NM_032485.6 : c.925C>T:p.Arg309Ter	Hom	**IUGR, Hypothyroidism, pilomatricomas**
104	European	16	PA	Single kidney, Haschimoto's thyroiditis, Ptosis, Scoliosis	**NI**	-	-	**-**
115	European	13	PA	Horseshoe kidney epilepsy	**NI**	-	-	**-**
139	European	18	PA	Keratoconus	**NI**	-	-	**-**
235	European	12	PA	Marfanoid habitus , scoliosis, hyperlaxity	**NI**	-	-	**-**

PA: Primary Amenorrhea; SA: Secondary Amenorrhea; SP: Spaniomenorrhea. Age: age at diagnosis. NI: Not identified. BPES**:** Blepharophimosis, epicanthus inversus, and ptosis syndrome; APECED: Autoimmune PolyEndocrinopathy Candidiasis Ectodermal Dystrophy

Table S4: Diagnostic performance according to patient's ethnicity

	Positive	Carrier	VUS	Negative	Total
European	61 (26,3%)	15 (6,5%)	44(19%)	112 (48.2%)	**232**
North African	16	3	21	23	**63**
Finnish	11	1	1	10	**23**
African	6	3	4	8	**21**
Asian	4	1	3	1	**9**
Turkish	8	1	5	3	**17**
Midle East	2	0	0	1	**3**
Mixed	2	1	2	2	**7**
Total	**110 (29,3%)**	**25 (6,7%)**	**80 (21,3%)**	**160 (41,7%)**	**375**

Vus: variant of unknown significance

Table S5: Classification of the variants detected in the cohort of patients with POI

	N	%
ACMG Classification		
Pathogenic	51	23,6%
Likely Pathogenic	60	27,8%
Unkown significance	105	48,6%
Haplotype		
Heterozygous	144	66,7%
Homozygous	27	12,5%
Compound Heterozygous	24	11,1%
Presumed compound heterozygous	21	9,7%
Type of variant		
Missense	159	73,6%
Frameshift	23	10,7%
Stopgain	24	11,1%
Inframe deletion	6	2,8%
Splice	3	1,4%
Start lost	1	0,4%
Total	**216**	**100%**

Table S8: Quantification of chromosomal breaks in patients with POI and molecular defects in novel DNA repair -genes

	Gene	Genotype	Aberrant metaphases			Breaks/ metaphase			Radial figures		
			Untreated	MMC (150 nM)	MMC (300 nM)	Untreated	MMC (150 nM)	MMC (300 nM)	Untreated	MMC (150 nM)	MMC (300 nM)
Control 1	**WT**	WT	0/50 (0%)	1/50 (2%)	1/50 (2%)	0	1/50 (0,02)	7/50 (0,14)	0/50 (0%)	0/50 (0%)	0/50 (0%)
Patient 1*	**BRCA2-R2842C**	Hom	1/50 (2%)	5/50 10%)	9/50 (18%)	1/50 (0,02)	7/50 (0,14)	19/50 (0,38)	0/50 (0%)	2/50 (4%)	2/50 (4%)
Mother*	**BRCA2-R2842C**	Het	0/50 (0%)	3/50 (6%)	2/50 (4%)	0	5/50 (0,1)	10/50 (0,2)	0/50 (0%)	2/50 (4%)	1/50 (2%)
Patient 2	**HELQ**	Hom	3/50 (6%)	23/50 (46%)	41/50 (82%)	4/50 (0,08)	64/50 (1,28)	199/50 (3,98)	1/50 (2%)	8/50 (16%)	26/50 (52%)
Mother	**HELQ**	Het	1/50 (2%)	3/50 (6%)	28/50 (56%)	3/50 (0,06)	8/50 (0,16)	61/50 (1,22)	0/50 (0%)	2/50 (4%)	4/50 (8%)
Patient 3	**HROB**	Hom	5/50 (10%)	43/50 (86%)	19/19 (100%)	6/50 (0,12)	190/50 (3,8)	309/19 (16,26)	0/50 (0%)	numerous	extremely numerous
Patient 4	**SWI5**	Hom	0/50 (0%)	19/50 (38%)	45/50 (90%)	0	40/50 (0,8)	450/50 (9)	0/50	4/50 (8%)	49/50 (98%)
Patient 5	**Fanconi anemia**	Hom	4/50 (8%)	48/50 (96%)	30/30 (100%)	4/50 (0,08)	437/50 (8,74)	>30	0/50 (0%)	numerous	extremely numerous

WT: wild type, Hom: Homozygous, Het : heterozygous.* Previous reported patient and her mother with the hypomorphic variant of BRCA2 (R2842C)[3.] . Note that the patient with homozygous pathogenic variants of HROB have the highest chromosomal breaks (radial figures and breaks /metaphase) closed to what is observed in Fanconi anemia cells.

Table S9: Patients initially presenting as isolated POI with Pathogenic or Likely Pathogenic variants in genes causing syndromic POI

ID	Ethnicity	Menses (ages)	Gene	Variant	Status	ACMG	Pathway	Related syndrome and associated symptoms
24	European	SA (21)	GALT	NM_000155.4 :c.563A>G:p.Gln188Arg	Hom	5	Metabolism	Galactosemia: cataract, mild intellectual disability, feeding difficulties, poor weight gain and growth, lethargy, and jaundice.
9*	European	SA (39)	POLG	NM_001126131.2:c.2528A>G:p.Gln843Arg	Het	4	Mitochondria	Progressive external ophthalmoplegia,Parkinsonism,
152*	European	SP (32)	POLG	NM_001126131.2:c.2528A>G : p.Gln843Arg	Het	4	Mitochondria	Progressive external ophthalmoplegia,Parkinsonism,
85	European	SA (33)	POLG	NM_001126131.2:c.2492A>G : p.Tyr831Cys	Het	4	Mitochondria	Progressive external ophthalmoplegia, autosomal dominant
133	European	SA (38)	POLG	NM_001126131.2:c.2492A>G : p.Tyr831Cys	Het	4	Mitochondria	Progressive external ophthalmoplegia,Parkinsonism,
			PCCB	NM_000532.5:c.911C>T: p.Thr304Ile	Het	4	Metabolism	Propionicacidemia : poor feeding, pancytopenia, dystonia, psychomotor delay,seizures and cardiomyopathy
190	Finnish	SA	POLG	NM_001126131.2:c.2492A>G : p.Tyr831Cys	Het	4	Mitochondria	Progressive external ophthalmoplegia,Parkinsonism,
241	North-African	SA (34)	POLG	NM_001126131.2:c.1550G>T : p.Gly517Val	Het	4	Mitochondria	Progressive external ophthalmoplegia,Parkinsonism,
278	European	SA (34)	POLG	NM_001126131.2:c.1550G>T:p.Gly517Val	Het	4	Mitochondria	Progressive external ophthalmoplegia,Parkinsonism,
52	European	SA (29)	PMM2	NM_000303.3:c.422G>A:p.Arg141His	Comp Htz	5	Metabolism	Congenital disorder of glycosylation, type Ia: Intellectual disability, hypotonia, growth retardation and seizures, and multiple organ failure.
				NM_000303.3: c.91T>C :p.Phe31Leu		4	Metabolism	
300	North-African	SA (16)	PMM2	NM_000303.3:c.95T>G:p.Leu32Arg	Hom	4	Metabolism	
301	North-African	SA (16)	PMM2	NM_000303.3:c.95T>G:p.Leu32Arg	Hom	4	Metabolism	
276	European	SA (28)	**PCCB**	**NM_000532.5:c.911C>T : p.Thr304Ile**	**Pres Comp Htz**	**4**	Metabolism	Propionicacidemia : poor feeding, pancytopenia, dystonia, psychomotor delay,seizures and cardiomyopathy
				NM_000532.5: c.1490C>T : p.Ala497Val		**3**	Metabolism	
186	Finnish	SA	**LMNA**	**NM_170707.4:c.1256G>T : p.Arg419Leu**	**Het**	**4**	Metabolism	Cardiomyopathy, dilated, 1A; Hutchinson-Gilford progeria
43	Turkish	PA	CYP19A1	NM_000103.4:c.568dupC:p.Leu190ProfsTer11	Hom	5	Metabolism	Aromatase deficiency syndrome : pseudohermaphroditism and virilization in women; and tall stature, osteoporosis and obesity in men
44	Turkish	PA	CYP19A1	NM_000103.4:c.568dupC:p.Leu190ProfsTer11	Hom	5	Metabolism	
130	European	SA (20)	TWNK	NM_021830.5:c.904C>T:p.Arg302Trp	Het	4	Mitochondria	Progressive external ophthalmoplegia with mitochondrial DNA deletions, autosomal dominant, Perrault syndrome.

			FANCM	NM_020937.4:c.5791C>T : p.Arg1931Ter	Het	5	DNA repair & Meiosis	Breast-ovarian cancer, familial,Fanconi Anemia
247	North-African	SP (23)	WT1	NM_024426:c.299C>G:p.Ala100Gly	Het	4	Follicular growth	Denys-Drash syndrome,Frasier syndrome: Disorder of Sex developement, Nephrotic syndormic, nephroblastoma.
255	North-African	SA (24)	WT1	NM_024426: c.299C>G:p.Ala100Gly	Het	4	Follicular growth	
140	European	PA	BMPR1A	NM_004329.3:c.1327C>T : p.Arg443Cys	Het	4	Follicular growth	Hereditary mixed polyposis syndrome
112	Turkish	SA (14)	**CAV1**	**NM_001172895.1:c.1A>G: p.Met1Val**	**Het**	**5**	Follicular growth	Pulmonary Arterial hypertension: Lipodystrophy, familial partial
163	European	SA (21)	**BMPR2**	**NM_001204.7:c.1967T>C : p.Leu656Ser**	**Het**	**4**	Follicular growth	Pulmonary Arterial hypertension
275	European	PA	**BMPR2**	**NM_001204.7:c.1790G>A : p.Arg597Gln**	Het	4	Follicular growth	Pulmonary Arterial hypertension
			AMH	NM_000479.5:c.35T>G :p.Val12Gly	Het	4	Follicular growth	
76	Middle East	SA (19)	**FOXL2**	**NM_023067.4:c.1049A>T : p.Gln350Leu**	**Het**	**4**	Follicular growth	BPES: Blepharophimosis, epicanthus inversus, and ptosis ,POI
198	Finnish	PA	**TP63**	**NM_003722.5:c.191+2T>G:p.?**	**Het**	**5**	DNA repair & Meiosis	Ectrodactyly, ectodermal dysplasia, cleft lip or palate syndrome
224	African	PA	TP63	NM_003722.5:c.674T>C:p.Ile225Thr	Het	4	DNA repair & Meiosis	
			BLM	**NM_000057.4:c.772_773delCT:p.Leu258GlufsTer7**	**Het**	**5**	DNA repair & Meiosis	Bloom syndrome : pre- and postnatal growth deficiency, a telangiectatic erythematous rash; predisposition to early onset cancer
262	North-African	SA (27)	TP63	NM_003722:c.1697C>T:p.Thr566Met	Het	4	DNA repair & Meiosis	Ectrodactyly, ectodermal dysplasia, cleft lip or palate
336	European	SA (38)	TP63	NM_003722:c.640A>G :p.Lys214Glu	Het	4	DNA repair & Meiosis	Ectrodactyly, ectodermal dysplasia, cleft lip or palate
318**	Turkish	PA	BRCA2	NM_000059.4:c.8524C>T :p.Arg2842Cys	Hom	4	DNA repair & Meiosis	Breast-ovarian cancer, familial / Fanconi Anemia
280	North-African	PA	BRCA2	NM_000059.4:c.7234_7235insG : p.Thr2412SerfsTer2	Pres Comp Htz	5	DNA repair & Meiosis	Breast-ovarian cancer, familial / Fanconi Anemia
				NM_000059.4: c.9364G>A:p.A3122T		3	DNA repair & Meiosis	Breast-ovarian cancer, familial / Fanconi Anemia
282	European	SA (15)	ATM	NM_000051.4:c.8494C>T : p.Arg2832Cys	Pres Comp Htz	5	DNA repair & Meiosis	Ataxia Telangiectasia syndrome : Progressive cerebellar ataxia, telangiectasia, increased susceptibility to infections and higher risk of cancer
				NM_000051.4: c.6998C>A : p.Thr2333Lys		3	DNA repair & Meiosis	

PA: Primary amenorrhea; SA: secondary amenorrhea; Novel variants are in bold. Hom: homozygous; Het: heterozygous; Comp Het: Compound heterozygous; Pres Comp Het: Presumed compound heterozygous (parents not available); ACMG: Classification of variant according to American College of Medical Genetics and Genomics; P: Pathogenic, LP, Likely pathogenic. *Patients 9 and152 are sisters; Patients 300 and 301 are sisters; patients 247 and 255 are sisters; patients 43 and 44 are sisters. ** previously described [3]

Table S10: Patients with Pathogenic or Likely Pathogenic variants in more than one POI gene

ID	Ethnicity	Menses	Anomalie	ACMG	Status	Pathway
130	European	SA (20)	**TWNK(NM_021830.5) : c.904C>T : p.Arg302Trp**	4	Het	Mitochondria
			FANCM(NM_020937.4) : c.5791C>T : p.Arg1931Ter	5	Het	DNA repair & Meiosis
133	European	SA (38)	**POLG(NM_001126131.2): c.2492A>G: p.Tyr831Cys**	4	Het	Mitochondria
			PCCB (NM_000532.5) : c.911C>T : p.Thr304Ile	4	Het	Metabolism
138	Asian	SA (36)	**HFM1(NM_001017975.6): c.3470G>A: p.Cys1157Tyr**	5	Pres Comp Het*	DNA repair & Meiosis
			HFM1(NM_001017975.6): c.905G>A: p.Cys302Tyr	3		
			PCCA(NM_000282.4) : c.1168C>T : p.Arg390Cys	4	Het	Metabolism
167	European	SA (18)	**FANCM(NM_020937.4) : c.5101C>T :p.Gln1701Ter**	5	Pres Comp Het*	DNA repair & Meiosis
			FANCM(NM_020937.4): c.1528G>A: p.Gly510Ser	3		
			ATM (NM_000051.4): c.6596_6597delCT: p.Ser2199Ter	5	Het	DNA repair & Meiosis
224	African	PA	**TP63(NM_003722.5) : c.674T>C: p.Ile225Thr**	4	Het	DNA repair & Meiosis
			BLM (NM_000057.4) : c.772_773delCT : p.Leu258GlufsTer7	5	Het	DNA repair & Meiosis
232	Mixed	SP (30)	**AR(NM_000044.6) : c.2395C>G : p.Gln799Glu**	4	Het	Follicular growth
			FANCA (NM_000135.4): c.3558dupG: p.Arg1187GlufsTer28	5	Het	DNA repair & Meiosis
268	North-African	SA (35)	**BMPR1B(NM_001256793): c.1165A>G: p.Ser389Gly**	4	Het	Follicular growth
			PCCB (NM_000532): c.646A>G: p.Met216Val	4	Het	Metabolism
275	European	PA	**BMPR2(NM_001204.7):c.1790G>A : p.Arg597Gln**	4	Het	Follicular growth
			AMH(NM_000479.5):c.35T>G :p.Val12Gly	4	Het	Follicular growth

PA: Primary amenorrhea; SA: secondary amenorrhea; Het: heterozygous: Pres Comp Het: Presumed compound heterozygous (Parents not available); ACMG: Classification of variants according to the American College of Medical Genetics and Genomics; * parents not available**.** In bold the gene variant sufficient to cause POI