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SHORT REPORT

Shifting the landscape: Dominant C-terminal rare missense *FOXL2* variants in non-syndromic primary ovarian failure etiology

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Abstract

Pathogenic germline variants in the *FOXL2* gene are associated with Blepharophimosis, Ptosis, and Epicanthus Inversus syndrome (BPES) in humans, an autosomal dominant condition. Two forms of BPES have emerged: (i) type I (BPES-I), characterized by ocular signs and primary ovarian failure (POI), and (ii) type II (BPES-II) with no systemic associations. This study aimed to compare the distribution of *FOXL2* variants in idiopathic POI/DOR (diminished ovarian reserve) and both types of BPES, and to determine the involvement of FOXL2 in non-syndromic forms of POI/DOR. We studied the whole coding region of the *FOXL2* gene using next-generation sequencing in 1282 patients with non-syndromic POI/DOR. Each identified *FOXL2* variant was compared to its frequency in the general population, considering ethnicity. Screening of the entire coding region of the *FOXL2* gene allowed us to identify 10 different

Pénélope Jordan and Camille Verebi contributed equally to this work.

variants, including nine missense variants. Of the patients with POI/DOR, 14 (1%) carried a *FOXL2* variant. Significantly, six out of nine missense variants (67%) were overrepresented in our POI/DOR cohort compared to the general or specific ethnic subgroups. Our findings strongly suggest that five rare missense variants, mainly located in the C-terminal region of FOXL2 are high-risk factors for non-syndromic POI/DOR, though *FOXL2* gene implication accounts for approximately 0.54% of non-syndromic POI/DOR cases. These results support the implementation of routine genetic screening for patients with POI/DOR in clinical settings.

KEYWORDS

FOXL2, missense variants, premature ovarian insufficiency

1 | INTRODUCTION

FOXL2 encodes a transcription factor comprising 376 amino acids, belonging to the forkhead/winged helix family of transcription factors. This transcription factor is involved in ovarian function and maintenance.[1] In 2001, pathogenic germline *FOXL2* variants were involved in an autosomal dominant disorder responsible with blepharophimosis, ptosis, and epicanthus inversus syndrome (BPES, MIM #110100).[2,3] Two forms of BPES have been described: (i) type I (BPES-I), featuring eyelid and craniofacial malformations, associated with primary ovarian failure (POI), and (ii) type II (BPES-II) with isolated craniofacial phenotype. This *FOXL2* gene has also been implicated in adult granulosa cell tumors, with the p.Cys134Trp variant present in over 90% of cases of this tumor type.[4] The FOXL2 protein includes a poly-glycine region, a DNA binding protein or forkhead region, two conserved poly-alanine (poly-Ala) regions, and a poly-proline. Genotype–phenotype correlation studies have suggested that *FOXL2* variants resulting in a truncated protein, either lacking or containing the forkhead domain or before the poly-alanine tract, lead to BPES-I.[5] In contrast, no clear-cut predictions can be made for variants resulting in truncated or extended protein that contains an intact forkhead and poly-Ala tract, even within the same family, although variants leading to an expanded poly-Ala region are mostly associated with BPES-II.[5] Following the identification of several ovarian FOXL2 targets in the adult ovary, the role of *FOXL2* variants in idiopathic non-syndromic POI has been questioned. Eight studies have reported *FOXL2* variants in non-syndromic POI (Table S1).[6–13] Interestingly, all these variants are located outside of the DNA binding domain, with only a few demonstrating functional effects in vitro.[10,11,13]

In this study, we screened the *FOXL2* gene in a large cohort of 1282 patients with non-syndromic POI/DOR, identifying 14 variants of *FOXL2*, including two novel ones. The aim of the study was to compare the distribution of *FOXL2* variants in idiopathic POI/DOR and the two types of BPES, and to ascertain the involvement of *FOXL2* in non-syndromic forms of POI. These novel insights may contribute in improving diagnostics, genetic counseling, as well as fertility guidance in clinical settings.

2 | MATERIALS AND METHODS

2.1 | Patients

Between January 2020 and July 2023, 1282 women under 40 years of age with idiopathic, sporadic, or familial POI/DOR were recruited. Each participant signed an informed consent form approved by the local ethics committee, and the study was conducted in accordance with the ethical standards of the Declaration of Helsinki. POI/DOR patients were diagnosed based on the diagnosis criteria defined in Data S1.

2.2 | Next generation sequencing, in silico analysis and mutation validation

The detailed methods of next-generation sequencing, Sanger sequencing, and bioinformatics analyses for detected variants in *FOXL2* are described in Data S1.

2.3 | Statistical analysis

The specific process is outlined in Supplementary Method S1.

3 | RESULTS

Screening of the entire coding region of the *FOXL2* gene allowed us to identify 10 different variants in 14 patients with POI/DOR. Except for one, all were missense variants (Figure 1; Table 1). These missense variants were predominantly distributed in two hot spots from the end of the forkhead region to the C-terminal region: (i) the intermediate region between the forkhead region and the poly-Ala tract, and (ii) the C-terminal part of the protein (Table 1). The variant p.(Ala234-del) was located in the poly-Ala region. Among these variants, two variants have not been previously reported. None of the variants were

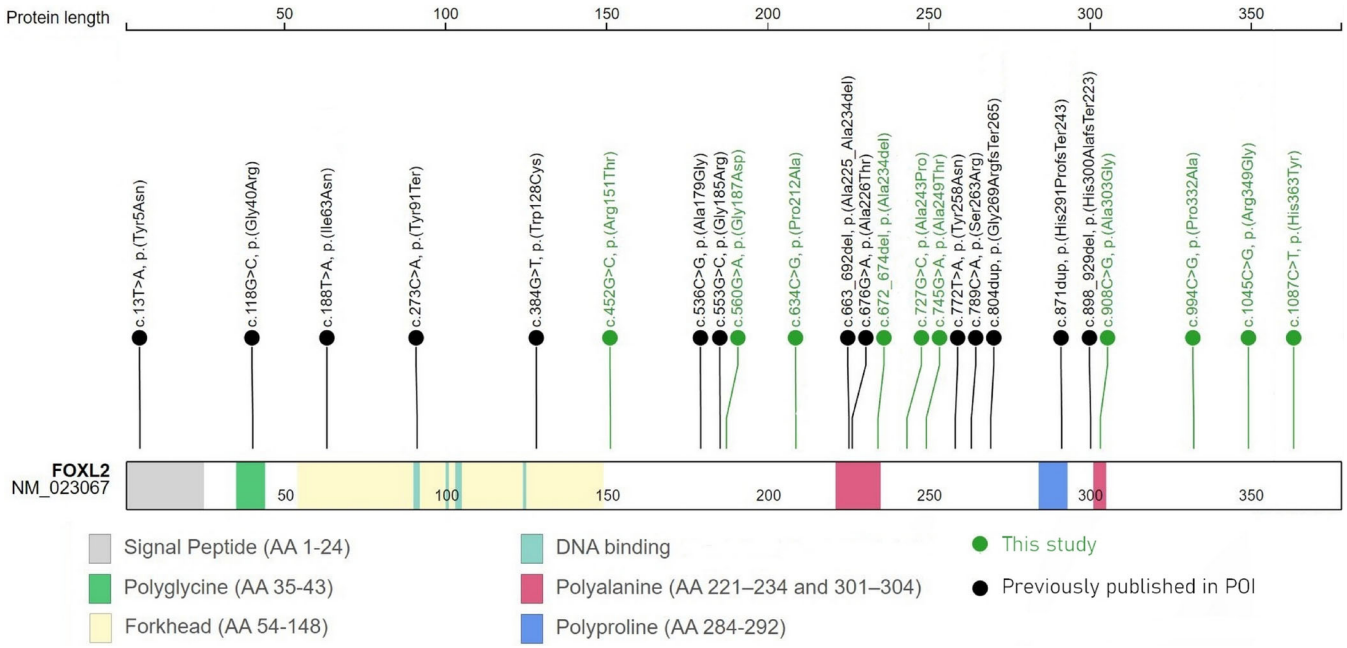

FIGURE 1 Location of the different *FOXL2* variants previously reported in POI and identified in the cohort of women with POI in this study. Variants discussed in this study are shown in green. The Figure was generated using St. Jude PeCan Data Portal. [Colour figure can be viewed at wileyonlinelibrary.com]

found in the poly-glycine, the DNA binding forkhead domain, or the poly-proline region. Bioinformatics predictions using tools such as SIFT, Polyphen-2, CADD, and REVEL suggested a pathogenic effect for five missense variants (Table 1). Overall, 1.09% of patients with non-syndromic POI/DOR in our study carried a rare *FOXL2* variant.

We compared the frequency of *FOXL2* variants (with MAF <0.03) between our cohort of patients with POI/DOR and the general population (Table 1). Significant differences were observed for seven rare variants, with Odds ratio (OR) ranging from 8.65 to an infinite value (Figure S1).

However, the distribution of these *FOXL2* variants showed geographic and ethnic disparities. For instance, variants p.(Arg349Gly) was more common in East Asia subjects, while variants p.(Pro212Ala), p.(Ala234del), and p.(Ala303Gly) were more frequently observed in European subjects (Table 1). Considering these distributional differences, we performed an analysis of *FOXL2* variants with ethnic subgrouping. Within these subgroups, no significant differences were observed for four variants, showing a higher proportion of these variants in the ethnic general population than in the POI cohort. However, significant difference remains with the c.634C > G (p.Pro212Ala) variant ($p = 0.025$) (Figure S2).

4 | DISCUSSION

Haploinsufficiency of the *FOXL2* gene causes BPES.[3] To date, over 500 patients have been reported with *FOXL2*-related BPES. The most prevalent *FOXL2* variants in patients with BPES impact the poly-Ala region, typically small duplications, and the poly-proline region, often through frameshift variants. Variants leading to an expanded poly-Ala region are frequently associated with BPES-II, which does not include POI. Despite some interfamilial variability, the majority of non-sense or frameshift variants are reported to be associated with BPES-I, often resulting in a truncated protein lacking the forkhead domain and poly-Ala tract or a shorter protein missing the N-terminal region due to translation re-initiation.[5,14] The impact of missense variants depends on their location, with the gene being highly conserved and certain regions functionally crucial.[3] Up to now, 46 missense variants have been identified in patients with BPES: 37 in the DNA binding and forkhead domain, one in the N-terminal region, and seven in the C-terminal region (Table S2). Previous report showed that mutant FOXL2 exerts a dominant-negative effect on wild-type FOXL2's activity as a transcriptional repressor of key genes in ovarian follicle differentiation.[14]

In our cohort of 1282 patients with idiopathic non-syndromic POI/DOR, we identified one in-frame deletion and 13 missense variants, including two recurrent ones (p.(Pro212Ala) and p.(Arg349Gly)). None of these variants were previously reported in patients with BPES. However, two variants, (p.(Gly187Asp) and p.(Arg349Gly)) have been previously identified in patients with non-syndromic POI.[10,13] To date, all missense variants located in the *FOXL2* gene's forkhead domain have been implicated in BPES. However, no clear-cut predictions are possible for missense variants located in the N-terminal and C-terminal region of the protein. In our cohort, we did not identify any missense variants in the N-terminal region, but two different variants previously identified in this region, were associated with one patient with BPES and one patient with non-syndromic POI.[11] We identified 13 variants in the C-terminal region, with seven of these

TABLE 1 *FOXL2* variants identified in our cohort of 1282 patients with POI. *FOXL2* variants identified in our cohort of 1282 patients with non-syndromic POI.

Patient ID	Variant NM_023067.4	Aminoacid substitution	ACMG criteria	ACMG classification	GnomAD v3	GnomAD v3 (women)	CADD	SIFT	Polyphen-2	Revel
2122ME000291_F	c.452G > C	p.(Arg151Thr)	PS4, PM2, PP2, PP3	Likely pathogenic	Nd	Nd	24.80		Probably damaging	Damaging
19ME000170F	c.560G > A	p.(Gly187Asn)	PS4, PP2, PP3, PP5	Likely pathogenic	2/151714	0/77632	25.70	Damaging	Probably damaging	Damaging
2119ME000604	c.634C > G	p.(Pro212Ala)	PS4, PP2, PP3	Likely pathogenic	40/151770 (31/67867 European)	22/77648	25.20	Damaging	Probably damaging	Uncertain
2120ME000143	c.634C > G	p.(Pro212Ala)	PS4, PP2, PP3	Likely pathogenic	40/151770 (31/67876 European)	22/77648	25.20	Damaging	Probably damaging	Uncertain
2120ME000377	c.634C > G	p.(Pro212Ala)	PS4, PP2, PP3	Likely pathogenic	40/151770 (31/67876 European)	22/77648	25.20	Damaging	Probably damaging	Uncertain
2121ME000296	c.672_674delAGC	p.(Ala234del)	PM4, PM1, BS2, BP3, BP4	Variant of unknown significance	115/151498 (84/67792, European)	58/77504	17.16			
2121ME000114	c.727G > C	p.(Ala243Pro)	PS4, PM2, PP2	Likely pathogenic	Nd	Nd	17.30	Damaging	Possibly damaging	Uncertain
2120ME00090	c.745G > A	p.(Ala249Pro)	PS4, PM2, PP2	Likely pathogenic	2/151458	0/77460	21	Tolerated	Benign	Benign
2122ME000047	c.908C > G	p.(Ala303Gly)	PM1, PP2, BS2, BP2	Variant of unknown significance	54/148752 (47/66694 European)	32/76262	21	Damaging	Possibly damaging	Uncertain
2123ME000040_F	c.994C > G	p.(Pro332Ala)	PM2, PP2, BP2	Variant of unknown significance	21/150086	13/76864	19.20	Tolerated	Benign	Uncertain
2122ME000257_F	c.1045C > G	p.(Arg349Gly)	PS4, PP2, PP3, PP5, BS2	Variant of unknown significance	32/151792 (24/5178, East Asian)	14/77654	28.10	Damaging	Probably damaging	Damaging
2122ME000132_F	c.1045C > G	p.(Arg349Gly)	PS4, PP2, PP3, PP5, BS2, BP2	Variant of unknown significance	32/151792 (24/5178, East Asian)	14/77654	28.10	Damaging	Probably damaging	Damaging
2120ME000235	c.1045C > G	p.(Arg349Gly)	PS4, PP2, PP3, PP5, BS2	Variant of unknown significance	32/151792, (24/5178, East Asian)	14/77654	28.10	Damaging	Probably damaging	Damaging
2121ME00050	c.1087C > T	p.(His363Tyr)	PS4, PM2, PP2, PP3	Likely pathogenic	1/152134	0/77840	29	Damaging	Probably damaging	Damaging

Note: Results of prediction of pathogenicity using different software (CADD, SIFT, Polyphen-2, Revel) are indicated for each variant. Results of frequency in the gnomad database are indicated. Location of each variant in the sub-units of the preproprotein are indicated: the peptide signal (amino acids (aa)1-24); the pro-domain (aa 25-319); the mature region (aa 320-454).

TABLE 2 Clinical characteristics of patients carrying potential *FOXL2* pathogenic variants.

Patient ID	2122ME000291	19ME000170	2119ME000604	2120ME000143	2120ME000377	2121ME000296	2121ME000114
Current age (years)	30	38	26	29	38	45	15
Mutation	c.452G > C	c.560G > A	c.634C > G	c.634C > G	c.634C > G	c.672_674delAGC	c.727G > C
Aminoacid substitution	p.(Arg151Thr)	p.(Gly187Asn)	p.(Pro212Ala)	p.(Pro212Ala)	p.(Pro212Ala)	p.(Ala234del)	p.(Ala243Pro)
Ethnic Origin	African (Guinea)	North African (Tunisia)	Caucasian (France)	Caucasian (France)	Caucasian	Caucasian (France)	Nd
POI/DOR	POI	POI	POI	POI	POI	POI	POI
Age of First Menstruation (years)	11	Nd	17	11	15	11	Nd
Amenorrhea (P/S)	S	P	S	S	S	S	Nd
Age of amennorhea (years)	Nd	Nd	24	28	33	40	13
N° of pregnancies (G/P)	G0P0	G0P0	G0P0	G2P1	G0P0	G0P0	G0P0
BMI	22.7	34.6	19	19.9	22	36.5	18
Height (cm)	150	163	175	Nd	178	156	Nd
Smoking	No	No	No	No	No	No	No
FSH (IU/L)	25	76.2	69	149.7	65	63	125
LH (IU/L)	25.2	42.5	24	44	38	49	69
Estradiol (pg/ml)	20	28	<10	20	15	<20	0
AMH (ng/ml)	0.09	<0.01	<1	Nd	Nd	<0.01	<0.02
Syndromic features	None	Pendred syndrome (deafness)	None; Autoimmunity anti-GAD 29 UI/mL, anti-IA2 14 UI/ml	None	None	Dilated cardiomyopathy	None
Antral follicle count (AFC)	2 + 1	0 + 0	0 + 0	0 + 0	1 + 0	0 + 0	1 + 0

Patient ID	2120ME00090	2122ME000047	2123ME000040	2122ME000257	2122ME000132	2120ME000235	2121ME00050
Current age (years)	31	29	37	33	31	30	22
Mutation	c.745G > A	c.908C > G	c.994C > G	c.1045C > G	c.1045C > G	c.1045C > G	c.1087C > T
Aminoacid substitution	p.(Ala249Pro)	p.(Ala303Gly)	p.(Pro332Ala)	p.(Arg349Gly)	p.(Arg349Gly)	p.(Arg349Gly)	p.(His363Tyr)
Ethnic Origin	African (Senegal)	Caucasian (France)	Caucasian (France)	Asian (Tibet)	Asian (China)	Asian (India)	Nd
POI/DOR	POI	DOR	POI	POI	POI	POI	POI
Age of First Menstruation (years)	14	Nd	14	13	13	15	13
Amenorrhea (P/S)	S	S	S	S	S	S	S
Age of amennorhea (years)	30	Nd	Nd	13	17	29	Nd
N° of pregnancies (G/P)	G0P0	G0P0	G1P1	G0P0	G0P0	G0P0	G0P0
BMI	23.9	25.1	22.3	28.4	18.7	19	28.6
Height (cm)	165	Nd	172	170	155	170	163

TABLE 2 (Continued)

Patient ID	2120ME00090	2122ME000047	2123ME000040	2122ME000257	2122ME000132	2120ME000235	2121ME00050
Smoking	No	No	No	No	No	No	No
FSH (IU/L)	89.5	Nd	98.1	76	43	93	113
LH (IU/L)	46	Nd	40.9	42	11	45	45.2
Estradiol (pg/ml)	12.3	Nd	<12	5.4	<50	18	25
AMH (ng/ml)	<0.03	Nd	0.01	<0.01	<0.01	<0.01	0.01
Syndromic features	None	Ovarian cystectomy	Chemotherapy for lymphoma	None	Turner syndrome (delXq)	None	None
Antral follicle count (AFC)	1 + 0	NA	0 + 0	2 + 2	0 + 0	0 + 0	0 + 1

Abbreviations: DOR, diminished ovarian reserve; Nd, not determined; P, primary; POI, primary ovarian insufficiency; S, secondary.

previously reported in patients with POI. The pathogenicity of these variants remains questionable. For example, the missense variant, p.(Gly187Asn), which affected in vitro the transactivation capacity of FOXL2 in vitro, was also found in a male individual with BPES but was considered non-pathogenic due to its presence in unaffected family individuals.[10,15] Our epidemiological study, encompassing a large cohort, indicates that five missense variants (p.(Arg151Thr), p.(Pro212Ala), p.(Ala243Pro), p.(Ala249Pro), and p.(His363Tyr)) have a higher frequency in our cohort compared to the general population, as per the gnomAD database, considering gender and specific ethnic backgrounds. These findings strongly suggest the pathogenicity of these variants in non-syndromic POI/DOR. The pathogenicity of p.(Pro212Ala) remains questionable, because in one patient carrying this variant, an autoimmune process was suggested since the identification of anti-GAD and anti-IA2 antibodies (Table 2). Moreover, the rare *FOXL2* variants p.(Ala234del), p.(Ala303Gly), p.(Pro332Ala), and p.(Arg349Gly), which showed no pathogenic effects in predictive software and no over-representation in individuals with POI, could be considered as variants of uncertain significance. These conclusions are reinforced by the fact that the POI patients carrying p.(Ala303Gly), p.(Pro332Ala), and p.(Arg349Gly) variants presented another etiology of POI (Table 2). The effect of these variants may vary depending on genetic background and environmental factors.

However, there are several limitations to our study. First, there is considerable phenotypic heterogeneity among women with fertility disorders (POI/DOR). Second, the gnomAD database, could include women with either known or unknown POI, estimated at around 2% in the 35–40-year age group. Thirdly, we cannot exclude the presence of another pathogenic variant in distinct genes in favor of a polygenic or oligogenic origin for POI.[16] Whole genome sequencing should be considered in the future care of these patients, mainly in familial cases of POI.

Despite these limitations and remaining questions, our analysis robustly supports the view that some rare *FOXL2* variants, particularly those located in the C-terminal region, are relatively high-risk factors for POI/DOR (Figure S3). We found that *FOXL2* contributes to ~0.54% of non-syndromic POI/DOR cases. While these findings advocate for the routine genetic screening of patients with POI/DOR in clinical settings, it is important to note that *FOXL2* does not seem to be a major cause of non-syndromic POI/DOR.

AUTHOR CONTRIBUTIONS

Thierry Bienvenu co-conceptualized and designed the study. Sandrine Perol, Valérie Bernard, Pénélope Jordan, Sophie Jonard-Catteau, Anne Bachelot, Virginie Grouthier, Philippe Touraine, Sophie Christin-Maître, Zeina Chakhtoura, Céline Renard, Stanislas Mulot de la Croix, Aude Brac de la Perrière, and Geneviève Plu-Bureau reviewed medical records and collected patient data. Corinne Fouveaut performed molecular analysis, and provided data analysis, tables and figures. Pénélope Jordan, Thierry Bienvenu, Camille Verebi, Jean Michel Dupont and Bérénice Hervé written content toward the first draft of the manuscript. All authors reviewed and revised the manuscript and approved the final version as submitted and agree to be accountable

for all aspects of the work. All authors are responsible for the accuracy and integrity of the work.

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CONFLICT OF INTEREST STATEMENT

The authors declare no competing interests.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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