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Exome sequencing in premature ovarian failure

More precise and personalised guidance for patients and couples

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Premature ovarian failure

Infertility is a major public health problem, affecting 15% of couples of childbearing age worldwide.

Premature (or primary) ovarian failure (POF) is one of the main causes of infertility in women, after endometriosis and polycystic ovary syndrome.

This condition affects nearly 4% of women. It typically manifests as amenorrhoea lasting more than four months and is associated with follicle-stimulating hormone (FSH) levels above 25 IU/l[1-2].

Infertility is not the only symptom of POF; premature cessation of ovarian function is also associated with steroid deficiency, as well as osteoporosis, cardiovascular disease and degenerative neurological disease.

Despite extensive aetiological investigations, around 60-70% of cases of POF remain undiagnosed.

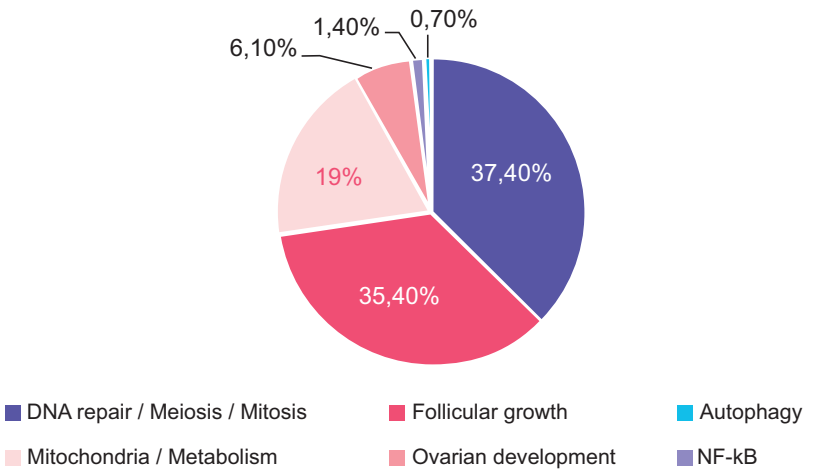
Yet a correct diagnosis is vital to enable personalised care for patients and couples as part of reproductive medical assistance.

The genetic causes of POF

To date, more than 80 genes of interest have been identified in relation to POF, with a high degree of genetic heterogeneity[1]. These genes are involved in different molecular pathways and have an impact at several levels:

- Impact on the establishment of ovarian reserve during foetal life: genes involved in meiosis and DNA repair, the possible alterations of which affect ovarian reserve. It should be noted that these genes are also genes for susceptibility to certain cancers.
- Impact on folicular growth, maturation and atresia.

Gene pathways involved in POF[1]



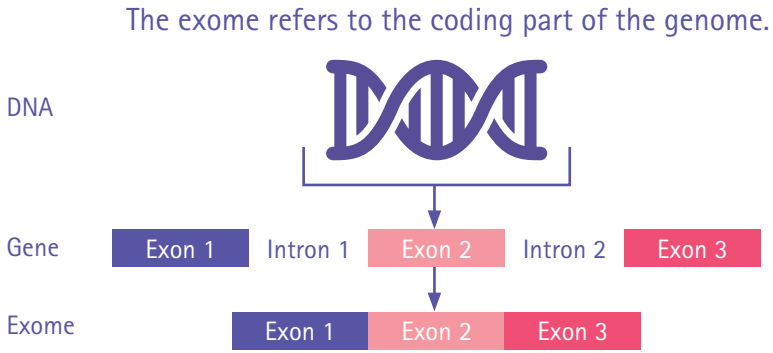
Furthermore, genetic studies have shown that POF may in fact be a symptom of a complex disease that may affect other organs in around 10% of cases[1].

However, despite the advent of high-throughput sequencing (NGS) studies, etiological genetic diagnosis of POF in current practice generally only includes karyotyping and *FMR1* premutation testing, with diagnostic yields of around 7-10% and 3-5% respectively.

By virtue of its exhaustive nature, exome sequencing could significantly improve these yields and enable earlier diagnosis of any comorbidities.

Exome sequencing

Exome sequencing is an effective tool for studying diseases of genetic origin. Exonic regions, representing less than 2% of the genome, can contain up to 85% of the pathogenic variants identified.



This type of exhaustive analysis enables us to study all the known and validated genes involved in POF, as well as rarer variants and even the identification of new genes.

This strategy makes it possible to re-read the data remotely without the need to «re-sequence». The development of knowledge (new genes of interest or pathogenicity of variants) and updating of databases will enable the data to be reinterpreted.

Clinical benefits

A positive exome result is obtained in over 29% of cases[1].

It is essential to identify the cause of the POF, as this allows:

- For the patient or couple:
  - Establish a precise aetiological diagnosis, leading to greater acceptance of the condition and pathology and adherence to treatment,
  - Predict the quality of ovarian reserve according to the molecular anomaly identified, and thus estimate the prognosis for fertility,
  - Guide the woman or couple towards the most appropriate management strategy in their medically assisted procreation programme (e.g. referral for ocyte donation),
  - Diagnose and manage any co-morbidities.
- For first-degree relatives:
  - Offer appropriate genetic counselling,
  - Implement early fertility preservation within the family.

Benefits of first-line exome:

- Better diagnostic yield compared with conventional approaches
- A reliable and accurate tool for making therapeutic decisions
- Generation of data that can be used in other clinical settings
- Identification of new therapeutic targets for POF
- Reduce healthcare costs by avoiding unnecessary treatments

In practice

Test	Exome sequencing and CNV analysis in premature ovarian failure
Test code	EXOME
Level of interpretation	Detailed report
Turnaround time	**4 weeks**, excluding any additional tests
Sample	Whole blood EDTA or extracted DNA
Storage & transport	Room temperature
Required document	Test request form **B34-INTGB**, available on www.eurofins-biomnis.com > Test guide > test code EXOME
Price	Please contact us
Related test	Study of relatives using targeted research techniques (Sanger or qPCR)
Related documents	• Brochure "Exome sequencing" (Ref. **DS34-INTGB**) • Brochure «Genetic characterisation of male infertility by exome sequencing» (Ref. **DS66-INTGB**), available on www.eurofins-biomnis.com > Section Expertises > Genetics

Key points

- **Exhaustive analysis** of known and validated genes involved in premature ovarian failure and of candidate genes, including the identification of new genes.
- **Re-interpretation** of data remotely, as knowledge evolves or in another clinical context.
- Reliable tool enabling couples to make informed **decisions about their treatment plan and their family future.**

Relying on experts

With its multi-disciplinary expertise (clinical, genetic, scientific and bioinformatics), Eurofins Biomnis offers the following after sequencing the patient's genetic material:

- Availability of raw data (fastQ, VCF, BAM and quality report) via a secure interface within two weeks.
- Analysis of more than 10,000 variants according to the rules of the American College of Medical Genetics (ACMG) and of the French NGS diag network.
- Classification of the selected variations in consultation with the clinician.
- Issuing a detailed results report within four weeks.

Why Eurofins Biomnis?

- Specialised clinical pathology laboratory
- ISO 15189 accreditation
- Authorisation to carry out constitutional genetic tests
- Certified clinical pathologists
- Mastery of sequencing techniques in diagnostic practice
- Ongoing bio-pathological support

Performance

- Whole exome coverage: ~22,000 genes and a target of 37.5 Megabases
- ~ 98 % of bases covered beyond 30X[2]
- > 99 % sensitivity[3]

References

[1] Huhtaniemi I, Hovatta O, La Marca A, et al. Advances in the Molecular Pathophysiology, Genetics, and Treatment of Primary Ovarian Insufficiency. Trends Endocrinol Metab. 2018;29(6):400-419. doi:10.1016/j.tem.2018.03.010

[2] Golezar S, Ramezani Tehrani F, Khazaei S, Ebadi A, Keshavarz Z. The global prevalence of primary ovarian insufficiency and early menopause: a meta-analysis. Climacteric. 2019;22(4):403-411. doi:10.1080/13697137.2019.1574738

[3] Ke H, Tang S, Guo T, et al. Landscape of pathogenic mutations in premature ovarian insufficiency. Nat Med. 2023;29(2):483-492. doi:10.1038/s41591-022-02194-3

[4] Cible Refseq CDS +/- 2 paires de base

[5] Données calculées à partir des SNV des échantillons du NIST002, pour 40 millions de paires de reads générées.

Gorsi B, Hernandez E, Moore MB, et al. Causal and Candidate Gene Variants in a Large Cohort of Women With Primary Ovarian Insufficiency. J Clin Endocrinol Metab. 2022;107(3):685-714. Doi:10.1210/clinem/ dgab775

Luo W, Ke H, Tang S, et al. Next-generation sequencing of 500 POI patients identified novel responsible monogenic and oligogenic variants. J Ovarian Res. 2023;16(1):39. Published 2023 Feb 15. doi:10.1186/s13048-023-01104-6

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