

Fibroblast growth factors in female reproductive disorders: A systematic review

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ABSTRACT

Background: Fibroblast Growth Factors (FGFs) are a family of signaling proteins that play key roles in various biological processes, including cell proliferation, differentiation, and tissue repair. In recent years, there has been growing interest in the role of FGFs in reproductive biology, particularly in the context of female fertility and assisted reproductive technologies (ART).

Objective: This systematic review aimed to evaluate the role of Fibroblast Growth Factors (FGFs) in female reproductive disorders with a focus on repeated implantation failure (RIF), diminished ovarian reserve (DOR), polycystic ovary syndrome (PCOS), and premature ovarian insufficiency (POI).

Materials and methods: A comprehensive literature search was conducted across PubMed, Web of Science, and Scopus databases for studies published between January 2014 and December 2024, yielding 8 eligible studies.

Results: The review found: reduced FGF-2 levels in PCOS patients' serum and follicular fluid, contrasting with earlier research; lower serum FGF-1 levels and specific genetic variants in RIF patients; elevated FGF-13 levels associated with increased androgen levels and ovarian volume in PCOS; altered FGF-5 expression in DOR cases; and unexpectedly elevated FGF-2 levels in biochemical POI.

Conclusion: FGF isoforms may be a contributor to the pathophysiology of female reproductive disorders. However, these findings while important, the review identified important limitations including small sample sizes and the tendency to focus on individual FGF isoforms. For future studies, there's a need for larger and more comprehensive studies examining the entire FGF family and their connections in reproductive dysfunction.

Introduction

Fibroblast Growth Factors (FGFs) are a family of signaling proteins that play key roles in various biological processes, including cell proliferation, differentiation, and tissue repair.¹ In recent years, there has been growing interest in the role of FGFs in reproductive biology, particularly in the context of female fertility and assisted reproductive technologies (ART). The FGF family consists of 22 members in humans, classified into seven subfamilies based on their sequence homology and functional properties.² Among, these several FGF isoforms have been implicated in ovarian function, folliculogenesis, and embryo development. FGF-2 (basic FGF) and FGF-1 (acidic FGF) are perhaps the most studied in this context, with roles in promoting angiogenesis and regulating granulosa cell function.^{1,3,4} Other isoforms, such as FGF-5, FGF-13, and FGF-21, have also appeared to contribute to reproductive processes.⁵⁻⁷

The complex relationship between FGFs and

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reproductive function has been increasingly reported in many female reproductive disorders. These include repeated implantation failure (RIF), defined as the failure to achieve clinical pregnancy after transfer of at least four good-quality embryos in a minimum of three fresh or frozen cycles,⁸⁻¹⁰ diminished ovarian reserve (DOR), characterized by reduced quantity and quality of oocytes,^{5,11} biochemical Premature Ovarian Insufficiency (bPOI), a condition of ovarian dysfunction before age 40 characterized by irregular menses and elevated follicle-stimulating hormone levels,¹²⁻¹⁴ and polycystic ovary syndrome (PCOS), an endocrine disorder marked by irregular menstruation, elevated androgens, and polycystic ovaries.^{15,16} Despite the growing body of research, the role of FGFs in female reproductive disorders remains a subject of large debate, particularly when some reports show controversial findings. Thus, this review aims to systematically evaluate the current evidence on the role of FGFs in female reproductive disorders, with a focus on RIF, DOR, PCOS, and POI.

Materials and methods

Literature search

A systematic literature search was conducted to find studies on the relationship between Fibroblast Growth Factor (FGF) and female reproductive disorders, with a focus on *in vitro* fertilization (IVF) outcomes. Four electronic databases, including PubMed, Web of Science, Scopus, and Embase, were used for relevant articles published between January 2014 and December 2024 (10-year period). The search strategy combined terms related to FGF (e.g., "Fibroblast Growth Factor" and "FGF") with terms associated with female reproductive disorders and IVF (e.g., "in vitro fertilization", "IVF", "ICSI", "embryo transfer", "repeated implantation failure", "RIF", "diminished ovarian reserve", "DOR", "polycystic ovary syndrome", "PCOS", "premature ovarian insufficiency", "POI"). In addition, the reference lists of included studies and relevant review articles were manually searched

to identify any potentially missed studies. The search was limited to English-language publications on human subjects.

Eligibility criteria

Studies were considered eligible if they were observational studies (prospective cohort, retrospective cohort, case-control) or randomized controlled trials involving women of reproductive age (18-45 years) with RIF, DOR, PCOS, or POI, undergoing IVF or ICSI procedures. Included studies must have measured FGF levels (any isoform) in biological samples such as follicular fluid, serum, culture media, granulosa cells, or endometrial tissue. The studies needed to report at least one of the following outcomes: clinical pregnancy rate, live birth rate, implantation rate, embryo quality, fertilization rate, miscarriage rate, or oocyte yield. Only English-language publications on human subjects published between January 2014 and December 2024 were considered. Studies were excluded if they were case reports, reviews, or animal studies, or if they did not provide sufficient statistical data for effect size calculation.

Results

The systematic literature search yielded a total of 5,757 records across three databases: Scopus (N=2,579), PubMed (N=2,122), and Web of Science (N=1,056). After the removal of 4,677 records marked as ineligible by automation tools and 539 duplicate records, 541 unique articles remained for screening. The initial screening process, based on titles and abstracts, resulted in the exclusion of 522 records that did not meet our inclusion criteria. Of the 19 full-text articles assessed for eligibility, 10 were not retrievable, and 1 was excluded due to non-relevance to the research question. Ultimately, 8 studies met all inclusion criteria and were included in this systematic review. The study selection process is illustrated in the PRISMA flow diagram (Figure 1).

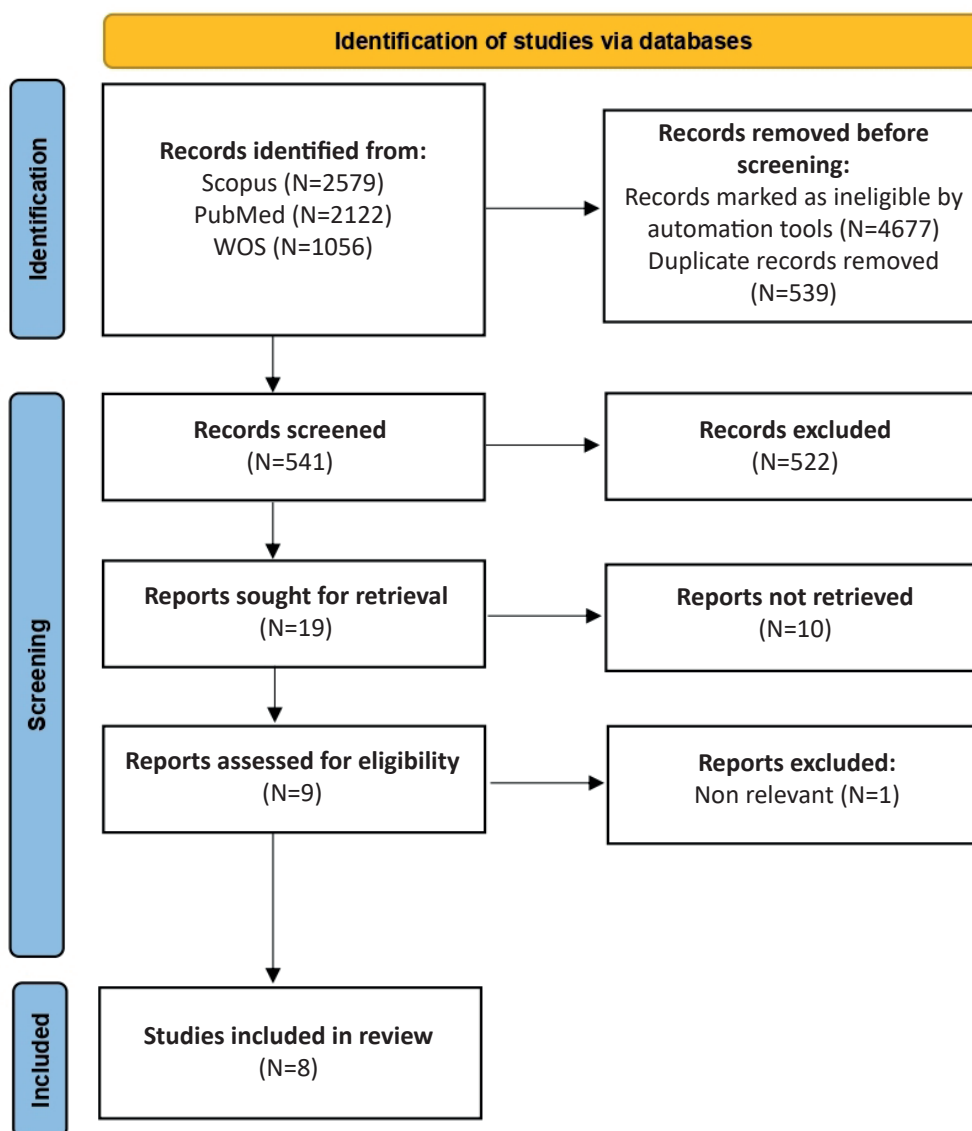


Figure 1. PRISMA flow diagram of study selection process.¹⁷

Table 1 presents a comprehensive overview of the included studies, their design, population, sample size,

FGF isoforms studied, biological samples used, detection methods, and key conclusions.

Table 1. Comprehensive overview on fibroblast growth factor (FGF) studies in reproductive medicine.

Study	Design	Population	Sample size	FGF	Biological sample	Method of detection	Conclusion
Aghajani <i>et al.</i> ⁸	RCT	Infertile women with unexplained RIF undergoing IVF	20 (10 in RIF group, 10 controls)	FGF1, FGF2, FGF13 (genes)	Endometrial biopsy	PCR array and quantitative reverse transcriptase PCR	Endometrial scratching induced significant upregulation of <i>FGF1</i> , <i>FGF2</i> , and <i>FGF13</i>
Kharamani <i>et al.</i> ⁹	Cross-sectional	Infertile women with RIF history and healthy women undergoing first IVF-ET with successful delivery	800 (400 RIF, 400 control)	FGF-1	Serum	ELISA	- FGF-1 was significantly reduced in RIF compared to controls - Significant association between <i>FGF1</i> (rs34011) promoter polymorphism and its serum concentration with RIF - The AA genotype was linked to lower FGF-1 serum levels and may be a risk factor for RIF
Abhari <i>et al.</i> ⁵	Case-control	Women undergoing ovarian stimulation for IVF	131 (56 DOR cases, 75 controls)	FGF-5	Follicular fluid	Multiplex immunoassay (Quantibody® Human Cytokine Antibody Array)	- FGF-5 was significantly lower in DOR group
Patil <i>et al.</i> ¹⁵	Case-control	Women undergoing controlled ovarian hyperstimulation for IVF	60 (30 PCOS cases, 30 controls)	FGF-2	Follicular fluid, serum and granulosa-lutein cells	ELISA for serum and follicular fluid levels, and qRT-PCR for gene expression in granulosa-lutein cells	- FGF-2 levels were significantly lower in both serum and follicular fluid levels of PCOS women compared to controls - FGF-2 transcript levels showed positive correlation with oocyte fertilization rate - <i>FGF2</i> expression was significantly lower in PCOS patients compared to controls
Liu <i>et al.</i> ¹²	Case-control	Women undergoing IVF/ICSI	72 (35 bPOI cases, 37 controls)	bFGF	Follicular fluid	Magnetic beads multiplex immunoassay (Luminex)	- bFGF was significantly higher in bPOI group compared to controls - bFGF in follicular fluid was significantly correlated with FSH, AMH, and AFC
Yland <i>et al.</i> ¹⁸	Prospective cohort	Women presenting for oocyte retrieval	34 (10 with unilateral endometrioma, 24 without endometriosis)	FGF-β	Follicular fluid	Multiplex immunoassays and Luminex bead-based antibody capture and recognition arrays	Non-significantly different between the groups

Table 1. Comprehensive overview on fibroblast growth factor (FGF) studies in reproductive medicine (*continued*).

Study	Design	Population	Sample size	FGF	Biological sample	Method of detection	Conclusion
Liu <i>et al.</i> ⁶	Cross-sectional	Infertile women undergoing first IVF/ICSI, aged 20-37 years	75 (43 PCOS cases, 32 non-PCOS controls)	FGF-13	Follicular fluid	ELISA	- The prevalence of elevated FGF-13 was significant among PCOS patients - FGF13 is associated with androgen levels and oocyte developmental competence in PCOS patients - MII oocyte rate negatively correlated with FGF-13 in PCOS patients
Vithoulkas <i>et al.</i> ¹⁹	Randomized prospective comparative study	IVF patients aged 35-40 (mean age 36.5)	90	FGF-1, FGF-2	Supernatants from embryo cultures	Milliplex factor-specific magnetic-bead panels with phycoerythrin fluorescent factor-specific antibodies using immunofluorescence cytometry technology	- FGF-2 was not detected in samples of group II (standard culture) but was present in samples of group I (co-culture) and C (cumulus cells alone) - FGF-1 was only detectable in very low concentrations in group I and C, ranging from 0.5 to 1.5 pg/mL

Note: RCT: randomized controlled trial, RIF: repeated implantation failure, IVF: in vitro fertilization, ET: embryo transfer, ELISA = enzyme-linked immunosorbent assay, DOR: diminished ovarian reserve, PCOS: polycystic ovary syndrome, qRT-PCR: quantitative reverse transcription polymerase chain reaction, bPOI: biochemical premature ovarian insufficiency, FSH: follicle-stimulating hormone, AMH: anti-Müllerian hormone, AFC: antral follicle count, ICSI: intracytoplasmic sperm injection, MII: metaphase II.

Discussion

The role of FGFs, since past two decades till nowadays, in female reproductive conditions is a complex and area of rich research. In the current systematic review, the involvement of several FGF isoforms in conditions such as polycystic ovary syndrome (PCOS), repeated implantation failure (RIF), diminished ovarian reserve (DOR), and biochemical premature ovarian insufficiency (bPOI) was evidenced based on the overall assessment of the included studies.

The molecular mechanisms underlying FGF signaling in reproductive tissues involve complex, interconnected pathways (Figure 2). Three main FGF isoforms, FGF-1, FGF-2, and FGF-13, work together with their specific receptors (FGFR1-3) to activate specific but overlapping signaling cascades. Upon ligand binding, these receptors trigger three primary pathways: the MAPK pathway,

which regulates cell proliferation, migration, and survival; the PI3K/AKT pathway, crucial for angiogenesis; and the STAT pathway, which controls cellular differentiation.²⁰⁻²³ These molecular cascades ultimately influence three key reproductive processes: follicular development, corpus luteum function, and oocyte maturation.^{24,25} This complex signaling network helps explain these systematic review findings, particularly the diverse effects observed when specific FGF isoforms are dysregulated. For instance, the reduced FGF-2 levels observed in PCOS patients may compromise both MAPK-mediated cellular survival and PI3K-dependent angiogenesis, potentially contributing to the observed luteal phase deficiencies.²⁶⁻²⁸ Similarly, the association between FGF-13 and androgen levels in PCOS may be mediated through STAT-dependent differentiation pathways affecting steroidogenic cells.⁶

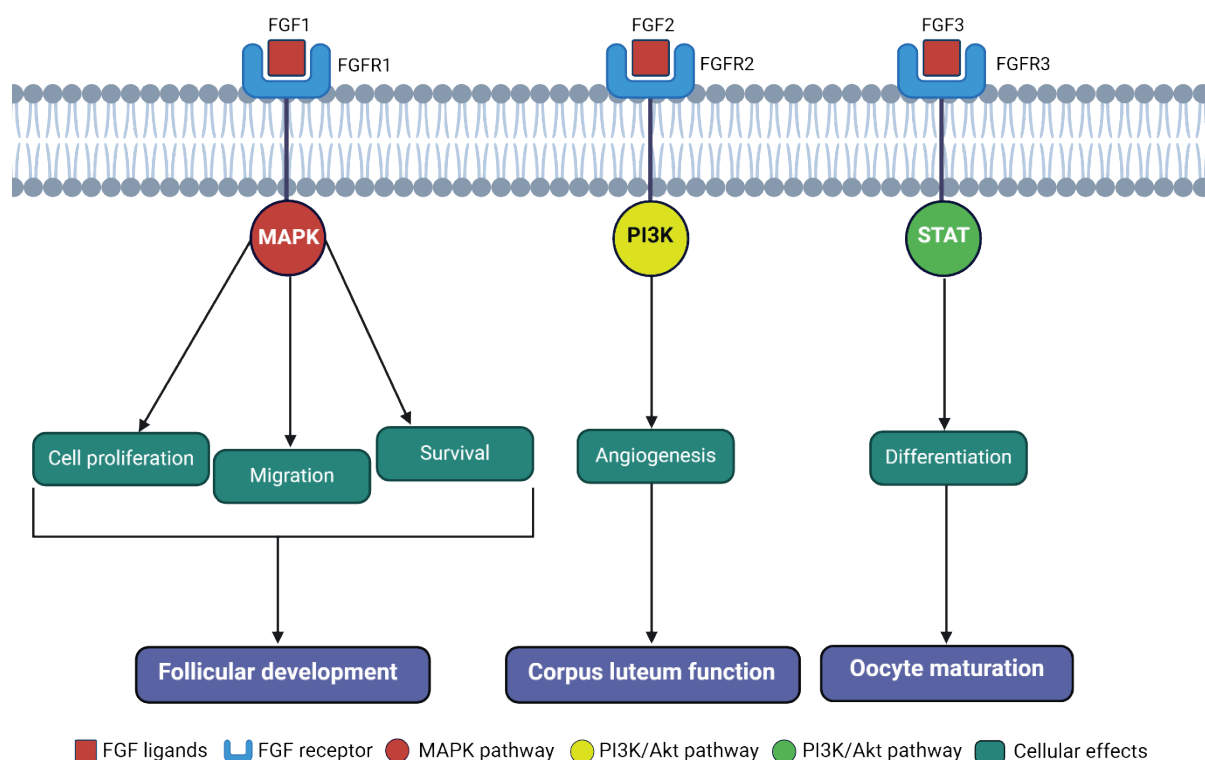


Figure 2. Molecular mechanisms of FGF signaling in reproductive tissues. These cascades regulate cellular processes, including proliferation, angiogenesis, and differentiation, ultimately influencing follicular development, corpus luteum function, and oocyte maturation (purple boxes). Arrows indicate signaling direction.

One of the most important findings relates to the role of FGF-2 (also known bFGF) in ovarian function and PCOS. The FGF-2 was differently reported in some previous studies,^{27,29} however, in the last 10 years, research has observed significantly lower levels of FGF-2 in both serum and follicular fluids of women with PCOS compared to controls.¹⁵ Patil *et al.*, in their study, showed that this downregulation extends to the gene expression level in granulosa-lutein cells (GLCs) of PCOS patients.¹⁵ Moreover, the concurrent reduction in FGFR1 protein expression in these cells hints a possible disturbance in the FGF-2 signaling pathway in PCOS.¹⁵ Taken together, these findings oppose earlier notions about FGF-2's role in

PCOS and draw attention to the need for more research into the complex interaction between FGFs and ovarian function in this disorder. The involvement of reduced FGF-2 signaling in PCOS are especially interesting when considering its known roles in angiogenesis and corpus luteum function. The observed reduction of FGF-2 and FGFR1 in PCOS patients may correlate with decreased vascularization of the corpus luteum, possibly explaining some of the luteal phase deficiencies and recurrent miscarriages observed in this population.¹⁵ Furthermore, the positive correlation between FGF-2 transcript levels in GLCs and oocyte fertilization rates rise attention to the probable role for FGF-2 in determining oocyte quality and

developmental potential.¹⁵ The relationship between FGF signaling and reproductive outcomes has been further supported by recent follicular fluid studies. Vithoulkas *et al.* (2017) examined women undergoing IVF and reported the presence of FGF-2 in embryo co-culture systems may contribute to improved embryo development and quality.¹⁹ These findings together suggest that FGF isoforms, besides their usefulness as biomarkers, play active roles in maintaining embryo development during assisted reproductive procedures. The observation that FGF-2 levels are reduced in co-culture conditions, possibly due to embryo consumption or metabolism, and this indicates a direct functional role in early embryonic development.

In the context of repeated implantation failure (RIF), this review found a possibly necessary role for FGF-1. Studies have concluded lower serum FGF-1 levels in women with RIF compared to controls, and a specific SNP in the *FGF1* promoter (rs34011) was associated with increased RIF risk.⁹ The correlation between this genetic variant and lower serum FGF-1 levels provides a potential mechanistic link between FGF-1 dysregulation and implantation failure. Additionally, the upregulation of *FGF1*, *FGF2*, and *FGF13* after endometrial scratching in RIF patients confirms that these growth factors may have a role in the reported benefits of this procedure.⁸ These findings collectively point to the potential of FGF-targeted therapies in improving implantation rates in RIF patients.

The role of FGF-13, a less-studied member of the FGF family, has also come to light in this review. High expression levels of FGF-13 in adult female ovaries and its detection in human follicular fluid indicate an important function in ovarian physiology.^{6,8} Attractively, elevated follicular fluid FGF-13 levels were associated with higher androgen levels and increased ovarian volume in PCOS patients while negatively correlating with mature oocyte rates.⁶ These observations direct that FGF-13 may be involved in the hormonal and morphological changes characteristic of PCOS, although the exact mechanisms require deeper elucidation.

Another interesting isoform of the FGF family that has been mentioned in recent studies is FGF-5. The analysis of follicular fluid from women with diminished ovarian reserve showed significantly different levels of FGF-5 in DOR patients compared to controls.⁵ This may point to its probable role in ovarian reserve regulation. However, as current evidence regarding FGF-5's specific function in reproductive disorders remains limited, more in-depth work is needed to fully understand its mechanistic involvement and potential clinical significance in ovarian pathologies.

In cases of diminished ovarian reserve (DOR) and biochemical premature ovarian insufficiency (bPOI), the review has revealed some unexpected findings. Contrary to what might be expected in conditions of reduced ovarian function, FGF-2 (or bFGF) levels were found to be significantly elevated in the follicular fluid of women with bPOI compared to controls.¹² This elevation positively correlated with FSH levels and negatively with AMH and antral follicle count, the matter draw attention

to a potential compensatory mechanism in response to declining ovarian function.¹² These findings emphasize the complex and sometimes paradoxical nature of growth factor regulation in reproductive disorders and underline the need for careful interpretation of such biomarkers in clinical settings.

This review suggests several possible clinical applications: serum FGF-1 levels may be used as a predictive biomarker for implantation failure risk, particularly in patients carrying specific genetic variants. In PCOS cases, monitoring FGF-2 and FGF-13 levels might help identify patients at higher risk for luteal phase deficiency. For DOR patients, FGF-5 assessment could complement existing ovarian reserve markers. These molecular markers could enhance current diagnostic options. However, it is necessary to acknowledge that standardization of measurement techniques and establishment of clear clinical thresholds is important before routine clinical implementation.

Still, and while these findings help us better understand FGFs in reproductive disorders, we must acknowledge some important limitations. First, many studies only show that certain changes happen together, but don't prove that one causes the other. Second, several studies looked at small groups of patients, which makes it harder to be sure the results apply to everyone. Third, since most research focused on just one or two types of FGF at a time, we might be missing the bigger picture of how all FGFs work together in reproductive health. Moving forward, we need larger studies that look at all types of FGFs at once and how they interact with other growth factors in reproductive tissues.

Conclusion

Fibroblast Growth Factors (FGFs) play various and important roles in female reproductive disorders. This systematic review showed several significant findings across different conditions. In PCOS, contrary to earlier research, FGF-2 levels are significantly reduced in both serum and follicular fluid which suggests its possible role in the pathogenesis of the syndrome. For patients with repeated implantation failure (RIF), lower serum FGF-1 levels and specific genetic variants in the *FGF1* promoter appear to increase risk, which points to possible therapeutic targets. Moreover, the elucidation of FGF-13's association with androgen levels and ovarian volume in PCOS patients and FGF-5's altered expression in diminished ovarian reserve (DOR) cases further demonstrates the broad involvement of different FGF isoforms in reproductive dysfunction. Future research should prioritize three key methodological improvements: 1) multi-center studies with larger sample sizes, 2) comprehensive proteomic analysis examining all FGF isoforms simultaneously rather than individual molecules, and 3) integration of genomic and proteomic data through systematic pathway analysis. These enhancements would provide more robust and complete understanding of FGF networks in reproductive disorders. To summarize, FGF levels could be useful for the monitoring/management of reproductive disorders

and possibly predict IVF outcomes. However, limitations such as small sample sizes and the focus on individual FGF isoforms indicate the need for larger, more comprehensive studies examining the entire FGF family and their interactions.

Conflict of interest

The author has no conflict of interest.

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