



LEUKEMIA INHIBITORY FACTOR (LIF) AND LIF RECEPTOR (LIFR) GENE POLYMORPHISMS AND IMPLANTATION AND PREGNANCY OUTCOMES AFTER ASSISTED REPRODUCTION: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Background: Leukemia inhibitory factor (LIF) signals through the LIF receptor (LIFR)–gp130 complex, and mice that lack uterine LIF cannot implant their embryos. Whether variants in *LIF* or *LIFR* shape the outcome of assisted reproductive technology (ART) is still debated. **Methods:** PubMed and supplementary sources were searched up to 29 September 2026 for studies that genotyped *LIF* or *LIFR* in women treated with in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI), including women with recurrent implantation failure (RIF). Genotype counts were taken from the original tables, quality was scored with the Newcastle–Ottawa scale, and odds ratios (ORs) were pooled under six genetic models. **Results:** Eleven studies (4,556 genotyped women) were included and six entered meta-analyses. Poolable ART-outcome data existed only for *LIF* rs929271, a 3' untranslated region variant. In three cohorts (742 women), the GG genotype was linked to lower odds of failing to reach an ongoing pregnancy or live birth (GG vs TT+TG: OR 0.50, 95% CI 0.29–0.86; $I^2 = 19\%$), and in two cohorts G carriers had fewer miscarriages (OR 0.49, 0.28–0.86). The signal lost significance with the Hartung–Knapp–Sidik–Jonkman correction, rested mainly on one Brazilian center, and was absent when women with IVF failure were compared with fertile women (G vs T: OR 1.26, 0.91–1.75). Rare *LIF* variants showed no consistent effect, and no study has tested *LIFR* against ART outcomes. **Conclusions:** Certainty of evidence is very low. *LIF* or *LIFR* genotyping should not guide IVF practice until larger, ancestry-aware studies with clear outcome definitions confirm these findings.

Keywords: Leukemia inhibitory factor; LIFR; rs929271; recurrent implantation failure; in vitro fertilization; genetic polymorphism; meta-analysis.

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INTRODUCTION

Assisted reproductive technology (ART) is now a routine part of infertility care, and millions of treatment cycles are reported worldwide every year [1]. Yet the step that decides success is still poorly controlled. Many cycles end without implantation even after a good embryo is transferred, and a subgroup of women fail again and again, a pattern now called recurrent implantation failure (RIF) [2–4]. Implantation depends on a short dialogue between a competent blastocyst and a receptive endometrium, and a large share of early losses happen before a pregnancy can be seen on ultrasound [5–7]. Leukemia inhibitory factor

(LIF) sits near the center of that dialogue. Female mice without LIF make normal blastocysts, but the embryos do not implant unless LIF is given back [8,9]. In women, endometrial LIF rises in the mid-secretory phase, when the window of implantation opens, and its receptor is found on the luminal epithelium and on the blastocyst [10,11]. LIF expression is also tuned by p53, and that link first drew attention to inherited variation in the pathway [12,13].

A genetic marker of receptivity would be attractive in practice, because it can be tested once, from blood, before treatment starts. Several groups have since genotyped *LIF* in women having in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI), and a few have looked at *LIFR* in infertile women. The results do not agree. Rare coding variants turned up in a few infertile women but not in those with repeated failure [14], a common variant in the 3' untranslated region seemed to favor pregnancy [15], and other cohorts saw nothing at all [16,17]. As far as we know, no systematic review has brought these data together. We therefore reviewed every study that related *LIF* or *LIFR*

variants to implantation, pregnancy, miscarriage or RIF after ART, pooled the comparable data, and looked closely at the quality and biological plausibility of each genotype report.

2. LIF-LIFR SIGNALING AT THE MATERNAL-EMBRYONIC INTERFACE

2.1. Lessons from the mouse

In the mouse, uterine LIF appears in the endometrial glands on day 4 of pregnancy, just before the blastocyst attaches, and it follows the nidatory estrogen surge [18]. LIF-null females ovulate and their embryos develop well, yet implantation fails, and LIF itself rescues it [8]. LIF can even stand in for nidatory estrogen in making the uterus receptive [9]. Without it, genes of the attachment reaction, such as heparin-binding EGF-like growth factor, amphiregulin and cyclooxygenase-2, are expressed abnormally [19]. The glands matter too; mice that lack FOXA2-dependent glands lose LIF and fail to implant on time [20]. p53 is involved as well: it activates the *Lif* gene, and p53-deficient females have less uterine LIF and poor implantation [12,21,22].

2.2. The receptor complex and its signals

LIF binds a low-affinity receptor, LIFR, which then forms a high-affinity complex with gp130, the signal transducer shared by the IL-6 cytokine family [23,24]. Binding activates the Janus kinases on the receptor tails; these phosphorylate STAT3, and STAT3 dimers move into the nucleus [25,26]. The same complex feeds the SHP2-RAS-MAPK and PI3K-AKT routes, and STAT3 induces SOCS3, which switches the signal off again (Figure 1) [27]. Deleting gp130 or Stat3 in the uterus reproduces the implantation failure of LIF loss [28,29], and the timing is set by dual control of LIF expression and LIFR function at the onset of receptivity [30]. Loss of LIFR in the whole body is another story: mice die around birth with placental, skeletal and neural defects [31,32], and in humans biallelic null *LIFR* mutations cause Stüve-Wiedemann syndrome [33].

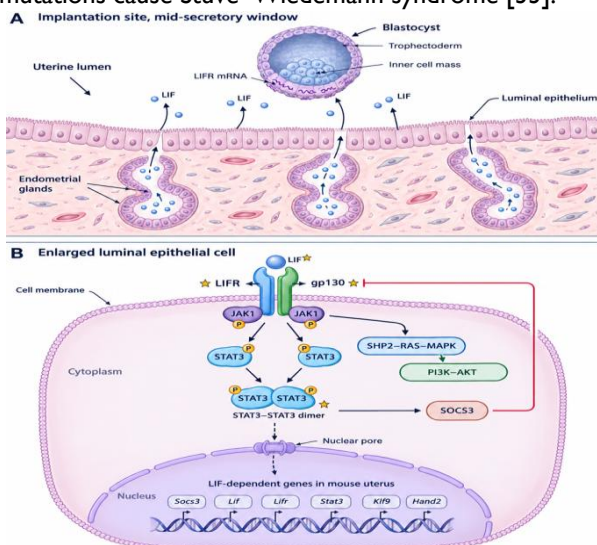


Figure 01: LIF-LIFR/gp130 signaling at the implantation site (illustrative drawing). Top: in the mid-secretory window, endometrial glands secrete LIF into the

uterine lumen, where the blastocyst, which carries *LIFR* mRNA, meets the luminal epithelium. Bottom (enlarged epithelial cell): LIF binds LIFR and gp130; JAK1 on the receptor tails phosphorylates STAT3, which dimerizes and enters the nucleus, while the complex also signals through SHP2-RAS-MAPK and PI3K-AKT, and STAT3-induced SOCS3 closes the loop. Gene names in the nucleus are LIF-dependent genes of the mouse uterus; stars mark the proteins affected by the variants reviewed here. Drawn from [8,10-12,19,20,25,30].

2.3. What human studies add

Human endometrium expresses LIF across the cycle, with a clear rise in the mid- to late secretory phase, and LIF is released into uterine fluid [10,34,35]. LIF and LIFR are found in the luminal and glandular epithelium together with pinopodes, a morphological marker of receptivity [11,36], and human preimplantation embryos carry *LIFR* transcripts [10,37]. Lower epithelial LIF, or weaker LIF-STAT3 signaling, has been described in unexplained infertility and in RIF [38-43], and dormant genital tuberculosis, a cause of RIF in some settings, disturbs the same axis [44]. Endometrial LIF has been linked with ART outcome, and LIF in uterine flushing fluid predicted implantation in one IVF series [45,46]. Still, recombinant human LIF did not raise implantation in women with repeated failure [47]. The trial bears on the genetic question, because if supplying the ligand does not help, a variant that matters at all may act through timing, tissue context or receptor function rather than through the amount of LIF alone [48-51]. Interleukin-11, another gp130 cytokine, is also needed for decidualization, and the two share much of their signaling machinery [52,53]; some redundancy of this kind may blunt the effect of any single variant.

3. THE LIF AND LIFR GENES AND THE VARIANTS STUDIED

LIF lies on chromosome 22q12.2 and is read from the minus strand. Its canonical transcript (NM_002309.5) has three exons and encodes a 202-residue precursor; residues 1-22 form the signal peptide and residues 23-202 the mature four-helix cytokine (Figure 2) [26,54,55]. Exon 3 holds the last part of the coding sequence and a long 3' untranslated region (3'UTR) of about 3.2 kb. Ensembl also lists two shorter *LIF* transcripts, but their role in the endometrium is unknown [54].

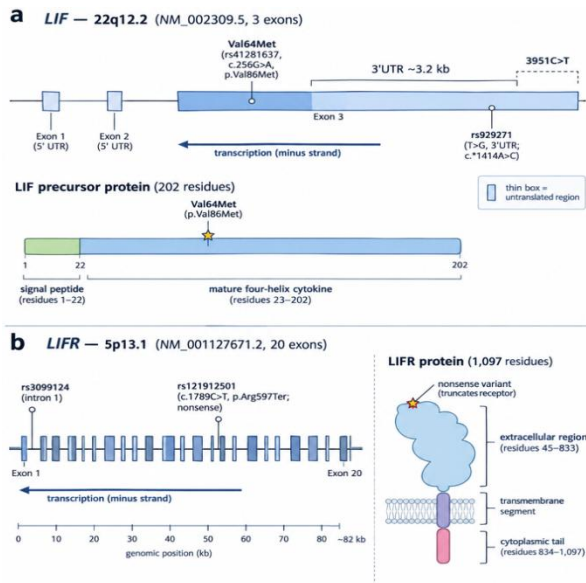


Figure 02: Structure of the *LIF* and *LIFR* genes and proteins with the variants studied in women undergoing ART. (a) *LIF* on 22q12.2 (NM_002309.5, three exons) and its 202-residue precursor. (b) *LIFR* on 5p13.1 (NM_001127671.2, 20 exons) and its 1,097-residue receptor. Gene tracks are drawn to scale in the direction of transcription (both genes lie on the minus strand); thin boxes are untranslated regions.

Positions follow the GRCh38 genome build and current Human Genome Variation Society (HGVS) names. The 3951C>T variant is shown only as a 3'UTR bracket because the original report gave no reference coordinate. Data from Ensembl, UniProt and ClinVar [54–56].

Three *LIF* variants dominate the fertility literature. The first, rs929271, is a T>G change in the 3'UTR (c.*1414A>C on the transcript). It is common, but its frequency varies a great deal: the G allele is carried by about 2% of African and 46% of South Asian chromosomes in the 1000 Genomes panel [57,58]. Its function is not settled. 3'UTR changes can alter mRNA stability or microRNA binding, and the same single-nucleotide polymorphism (SNP) has been examined in schizophrenia, in sex-specific prenatal selection and in high-altitude adaptation [59–62]. The second is a missense change in exon 3, usually written Val64Met after the mature-protein numbering; in current nomenclature it is rs41281637, c.256G>A, p.Val86Met. It is rare, below 1% of alleles in European samples, and ClinVar lists it as benign or likely benign [56,58]. The third, 3951C>T, is a 3'UTR change reported without an rs number [63].

LIFR maps to 5p13.1, spans about 82 kb and has 20 exons (NM_001127671.2). It encodes a 1,097-residue single-pass receptor with a large extracellular region (residues 45–833), one transmembrane segment and a cytoplasmic tail [55]. Two named *LIFR* variants have been studied in infertility. rs3099124 lies in intron 1, and its minor allele is uncommon (about 2% worldwide). rs121912501 is a nonsense change, c.1789C>T (p.Arg597Ter). ClinVar classes it as

pathogenic for Stüve–Wiedemann syndrome, and it was seen once among 5,008 alleles in 1000 Genomes [56,57]. That detail matters when the *LIFR* studies are read below.

4. METHODS

4.1. Protocol, search and eligibility

The review followed the PRISMA 2020 statement [64] and the STREGA guidance for genetic association data [65]. The protocol was not registered in advance. PubMed was searched on 29 September 2026 with four strings: “*LIF* polymorphism implantation failure”, “rs929271”, “leukemia inhibitory factor polymorphism IVF” and “leukemia inhibitory factor gene mutation infertile women”. Genetic studies from the Middle East and Eastern Europe often appear in regional journals, so we also used web search engines, journal websites, the OpenAlex index and the reference lists of every retrieved paper. No language or date limits were set.

Studies were eligible if they genotyped any germline *LIF* or *LIFR* variant in women undergoing IVF or ICSI with their own or donor oocytes, or in women with RIF or IVF failure defined after ART, and if they reported genotype data against implantation, clinical or ongoing pregnancy, live birth, miscarriage, ovarian response or RIF status. Outcome terms followed the international glossary [66]. Reviews, animal work, expression-only studies and studies without ART-defined participants were excluded, although the last group was kept as context.

4.2. Data extraction and appraisal

For each study we recorded country, ancestry, design, group definitions, type of ART, variant, genotyping method and genotype counts. Counts were copied from the printed tables and then re-checked by rebuilding row totals, allele counts and percentages. When a group had to be derived, for example women without an ongoing pregnancy, it was obtained by subtracting two printed numbers. Hardy–Weinberg equilibrium (HWE) in control groups was tested with an exact test [67], and allele frequencies were compared with 1000 Genomes and gnomAD data to flag implausible distributions [57,58]. Quality was scored with the Newcastle–Ottawa scale (NOS) for case–control designs; 7–9 stars were read as high, 5–6 as moderate and 0–4 as low quality [68].

4.3. Statistical synthesis

For rs929271 the primary comparison set women who did not reach an ongoing pregnancy or live birth, including women with RIF, against women who did. Secondary comparisons were IVF failure versus fertile women, implantation per transferred embryo and miscarriage per clinical pregnancy. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated under allelic, dominant, recessive, homozygote, heterozygote and overdominant models, because the mode of inheritance is unknown [69–71]. Pooling used DerSimonian–Laird random effects, with inverse-variance fixed effects as a check [72]. Heterogeneity was measured with Cochran's Q and I^2 [73]. With so

few studies, we also report the Hartung–Knapp–Sidik–Jonkman (HKSJ) interval, which behaves better when the number of studies is small [74]. Sensitivity analyses dropped one study at a time and swapped the primary outcome for the alternative definitions given in the papers. Funnel plots and the Egger and Begg tests were not used, since they have little power below ten studies [75–77]. Carriage of the rare Val64Met allele was pooled with the Peto one-step method. Certainty was rated with GRADE [78]. All calculations were run in Python (NumPy and SciPy), and the extraction sheet and code are supplied as supplementary files.

5. RESULTS

5.1. Study selection

The four PubMed strings returned 48 hits, 33 of them unique, and nine further records came from other sources (Figure 3). After screening, 22 reports were assessed for eligibility and 11 studies met the criteria. Four reports could not be obtained in usable form, among them the original p53-pathway study of Kang and colleagues. Its abstract states that selected *LIF* alleles were enriched among IVF patients, mainly in women younger than 35 years, but the genotype counts could not be obtained [13]. The others were a study of recurrent pregnancy loss that genotyped rs929271 and lay outside ART in any case [79], a short letter on Val64Met and a study of p53 variants in RIF; all four are listed in the supplementary file.

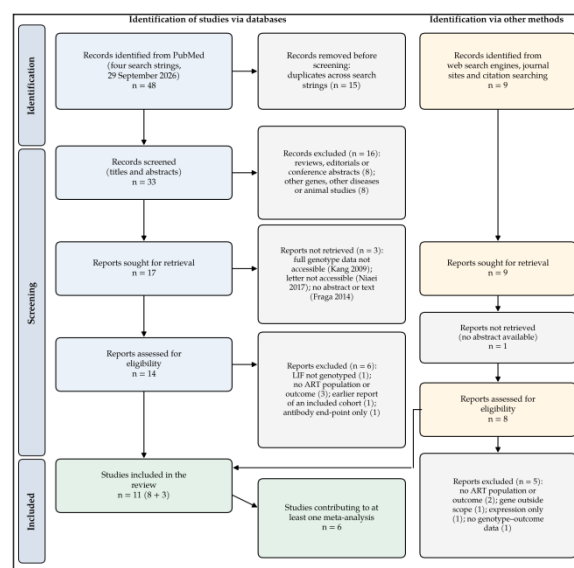


Figure 03: PRISMA 2020 flow diagram of study selection [64].

5.2. Previous studies and their characteristics

Table 1 summarizes the eleven previous studies [14–17,63,80–85]. Together they genotyped 4,556 women, although some overlap between cohorts from the same centers is likely. Five studies examined rs929271, one the 3951C>T variant, four the Val64Met mutation, and one sequenced exon 1 of *LIF*. Brazil contributed three of the rs929271 cohorts, two of them from a single center in Ribeirão Preto [15,83]; the remaining data came from Spain, Taiwan, Iran, Germany, the Czech Republic and Iraq. Quality varied widely, from 3 to 8 NOS stars.

Table 01: Characteristics of the previous studies included in the review.

Study	Country (ancestry)	Design and ART	Groups (n)	Variant(s)	Genotyping	Main finding	NOS
Steck 2004 [14]	Germany	Case–control; IVF-ET	RIF 45; unexplained infertility 50; fertile 105	<i>LIF</i> exon screen (incl. Val64Met)	SSCP, sequencing	No functional mutation in RIF; Val64Met in one woman with unexplained infertility	4
Králíčková 2007 [80]	Czech Republic	Case–control; infertility clinic incl. IVF	Infertile 399; fertile 202	Val64Met (rs41281637)	TGGE, sequencing	12 carriers (3.0%) vs none; 7 carriers later conceived with IVF	3
Novotný 2009 [81]	Czech Republic	Retrospective cohort; IVF	Carriers 15; non-carriers	Val64Met	TGGE, sequencing	Pregnancy after first IVF	3

			136			47% vs 51%	
Paskulin 2013 [16]	Brazil	Case-control; conventional IVF	IVF failure 115; endometriosis 98; fertile 134	rs929271	TaqMan	No association with IVF failure	4
Oliveira 2016 [15]	Brazil (mostly self-declared white)	Prospective cohort and case-control; ICSI	ICSI 411; fertile 83	rs929271	TaqMan, sequencing check	GG: higher implantation and ongoing pregnancy, also after adjustment	8
Alipour 2017 [63]	Iran (north)	Case-control; IVF	IVF failure 70; fertile 73	3951C>T (3'UTR)	PCR-RFLP	No association	3
Hussein 2018 [82]	Iraq	Cross-sectional; IVF	PCOS 40; non-PCOS 40	LIF exon 1	Sanger sequencing	No variant detected	NA
Vagnini 2019 [83]	Brazil	Case-control; IVF/ICSI	RIF 44; pregnant at first attempt 63; fertile 65	rs929271 (with <i>ESR1</i>)	TaqMan	TG excess and GG deficit in RIF	5
Palomares 2021 [17]	Spain (European)	Nested case-control; donor-oocyte IVF	Recipients 224 genotyped	rs929271 (p53-pathway panel)	TaqMan OpenArray	No association with implantation, pregnancy or miscarriage	8
Liu 2023 [84]	Taiwan (Han Chinese)	Cross-sectional; IVF/ICSI	Poor or suboptimal responders 1,084; normal responders 660	rs929271 (with <i>FSHR</i> , <i>AMH</i> , <i>GNRHR</i>)	TaqMan	G carriers <35 y: fewer oocytes; no pregnancy data	7
Vahdani 2025 [85]	Iran (north)	Case-control; IVF-ET	RIF 200; IVF success 200	Val64Met	Allele-specific PCR	No association; implausible genotype frequencies	3

ART, assisted reproductive technology; ET, embryo transfer; NA, not applicable; NOS, Newcastle–Ottawa scale (maximum 9 stars); PCOS, polycystic ovary syndrome; PCR-RFLP, polymerase chain reaction–restriction fragment length polymorphism; RIF, recurrent implantation failure; SSCP, single-strand conformation polymorphism; TGGE, temperature-gradient gel electrophoresis. The Králíčková 2007 entry rests on the abstract of a Czech-language article; an earlier report of the same cohort appeared in 2006 [86].

The evidence is patchy (Figure 4), and no included study examined *LIFR*. The three *LIFR* reports we found concerned women with unexplained infertility outside ART, two from one Pakistani cohort and one from a small Iranian series [87–89].

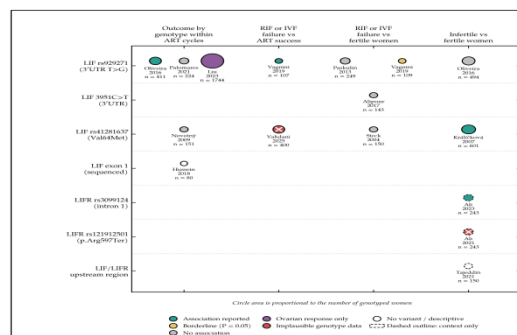


Figure 04: Evidence map of the included studies (solid outline) and of related studies outside ART (dashed outline). Rows are variants and columns are types of comparison; circle area is proportional to the number of genotyped women and the color gives the reported result.

5.3. rs929271: genotype data and their quality

Table 2 lists the rs929271 counts that entered the analyses. In control groups the G-allele frequency ranged from 0.30 to 0.41, close to European, admixed American and East Asian reference values (Figure 5). Two quality problems stood out. The RIF group of Vagnini et al. held a large excess of heterozygotes (32 of 44 women; exact HWE $P = 0.001$), and the fertile controls of Oliveira et al. departed slightly from equilibrium ($P = 0.04$) [15,83]. Outside ART, a study of recurrent pregnancy loss reported all 150 Iranian control women as TT, with no G allele at all [90]. Against a G frequency of 34–46% in Eurasian panels, that result is hard to explain by anything other than a genotyping problem.

Table 02: LIF rs929271 genotype data used in the meta-analyses.

Study	Comparison	TT	TG	GG	G freq. (controls)	HWE P (controls)
ART failure vs ART success (primary analysis)						
Oliveira 2016	No ongoing vs ongoing pregnancy, fresh ICSI ^a	124 / 44	138 / 64	22 / 19	0.40	0.71
Vagnini 2019	RIF vs pregnancy at first attempt	10 / 24	32 / 26	2 / 13	0.41	0.30
Palomares 2021	No ongoing vs ongoing pregnancy, donor oocytes ^a	46 / 45	48 / 53	13 / 19	0.39	0.70
IVF failure or RIF vs fertile women						
Paskulin 2013	IVF failure vs fertile	46 / 57	51 / 60	18 / 17	0.35	0.85
Vagnini 2019	RIF vs fertile (control II) ^b	10 / 29	32 / 33	2 / 3	0.30	0.14
Oliveira 2016	No ongoing pregnancy vs fertile ^{a,c}	124 / 34	138 / 45	22 / 4	0.32	0.04
Implantation per transferred embryo (implanted / transferred)						
Oliveira 2016	Fresh ICSI	87/519	107/601	31/103	–	–
Palomares 2021	Donor oocytes	81/206	84/221	30/70	–	–
Miscarriage per clinical pregnancy (miscarriages / clinical pregnancies)						
Oliveira 2016	Fresh ICSI	26/70	20/84	5/24	–	–
Palomares 2021	Donor oocytes	9/58	5/60	1/20	–	–

Genotype cells give cases / controls for the first two blocks and events / totals for the last two. ^a Case counts derived by subtracting printed ongoing pregnancies from printed genotype totals. ^b HWE in the RIF group: $P = 0.001$ (heterozygote excess). ^c Sensitivity analysis only; these fertile controls probably overlap control group II of Vagnini et al. HWE, Hardy–Weinberg equilibrium (exact test); RIF, recurrent implantation failure.

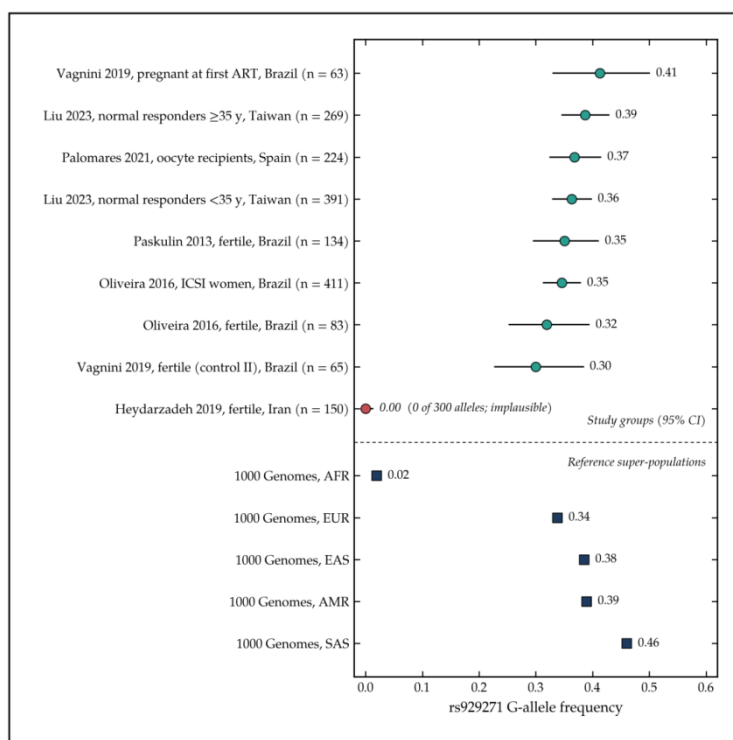


Figure 05: Frequency of the rs929271 G allele in the 1000 Genomes super-populations and in control or unselected groups of the included studies; bars are 95% Wilson confidence intervals. The outlier with no G allele comes from a

recurrent pregnancy loss study outside ART [90]. Reference data from 1000 Genomes through Ensembl [54,57]. AFR, African; AMR, admixed American; EAS, East Asian; EUR, European; SAS, South Asian.

5.4. rs929271 and pregnancy after ART

In 411 ICSI patients, Oliveira et al. found higher implantation and ongoing pregnancy rates in GG women (ongoing pregnancy per woman 46.3% vs 26.2% in TT), and the difference held after adjustment for age, mature oocytes and embryo quality [15]. In 224 donor-oocyte recipients, Palomares et al. saw the same direction for ongoing pregnancy (59.4% vs 49.5%) and miscarriage, but no difference reached significance (Figure 6) [17]. Vagnini et al. found GG in 13 of 63 women who conceived at their first attempt, against only 2 of 44 women with RIF [83]. In the same study, carrying both *LIF* TG and the *ESR1* rs12199722 AA genotype raised the odds of RIF 7.9-fold against women who conceived at the first attempt and 2.8-fold against fertile women. The combination came from a small sample, however, and has not been tested anywhere else.

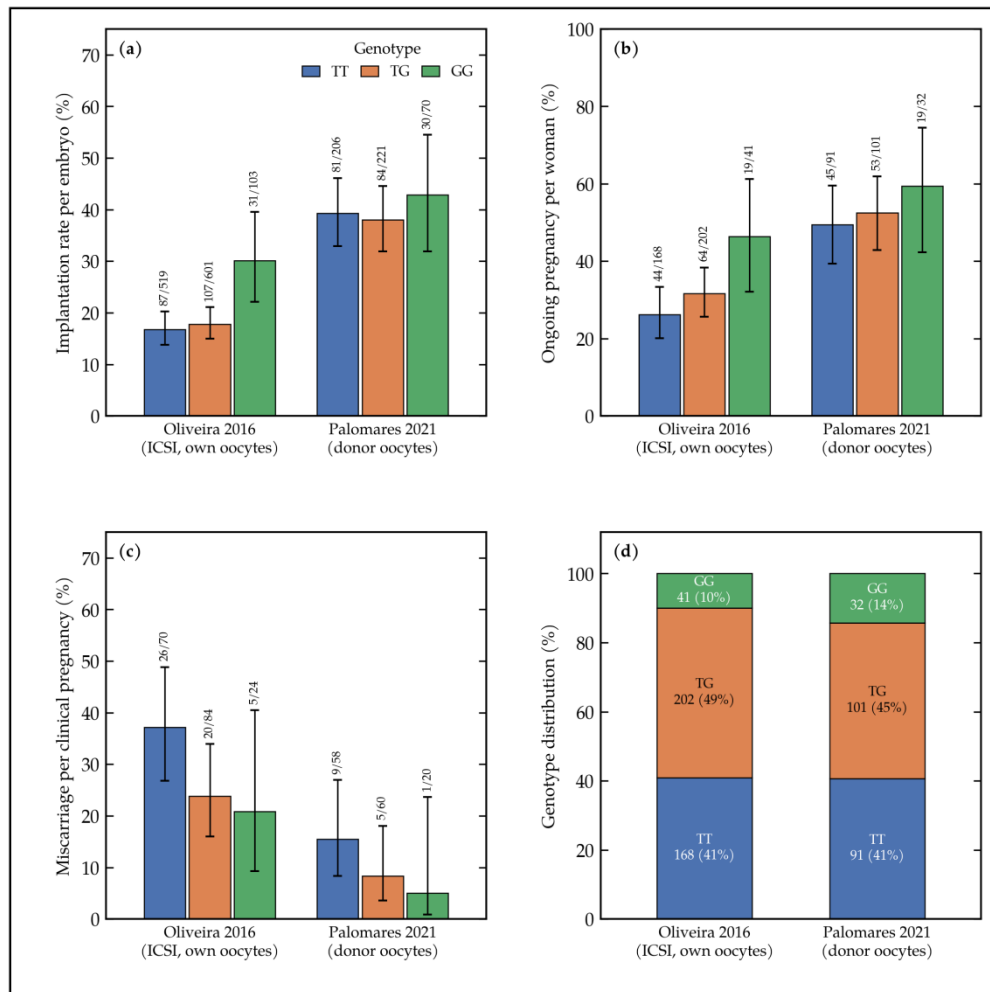


Figure 06: ART outcomes by rs929271 genotype in the two cohorts that reported outcomes per genotype: (a) implantation rate per transferred embryo, (b) ongoing pregnancy per woman, (c) miscarriage per clinical pregnancy and (d) genotype distribution. Oliveira et al. data are from fresh ICSI cycles and Palomares et al. data from first donor-oocyte cycles. Error bars are 95% Wilson confidence intervals; labels above the bars give events/total [15,17].

Pooled across the three cohorts (742 women), the GG genotype was associated with about half the odds of ART failure (recessive model OR 0.50, 95% CI 0.29–0.86; $I^2 = 19\%$), and GG versus TT gave a similar value (OR 0.49, 0.30–0.82; $I^2 = 0\%$) (Figure 7; Table 3). The allelic model was weaker (OR 0.78, 0.63–0.98), and the dominant model showed nothing (OR 0.95, 0.55–1.62; $I^2 = 61\%$). The heterozygote and overdominant models were highly heterogeneous ($I^2 = 71\%$ and 78%), a result driven by the heterozygote excess in the Vagnini RIF group.

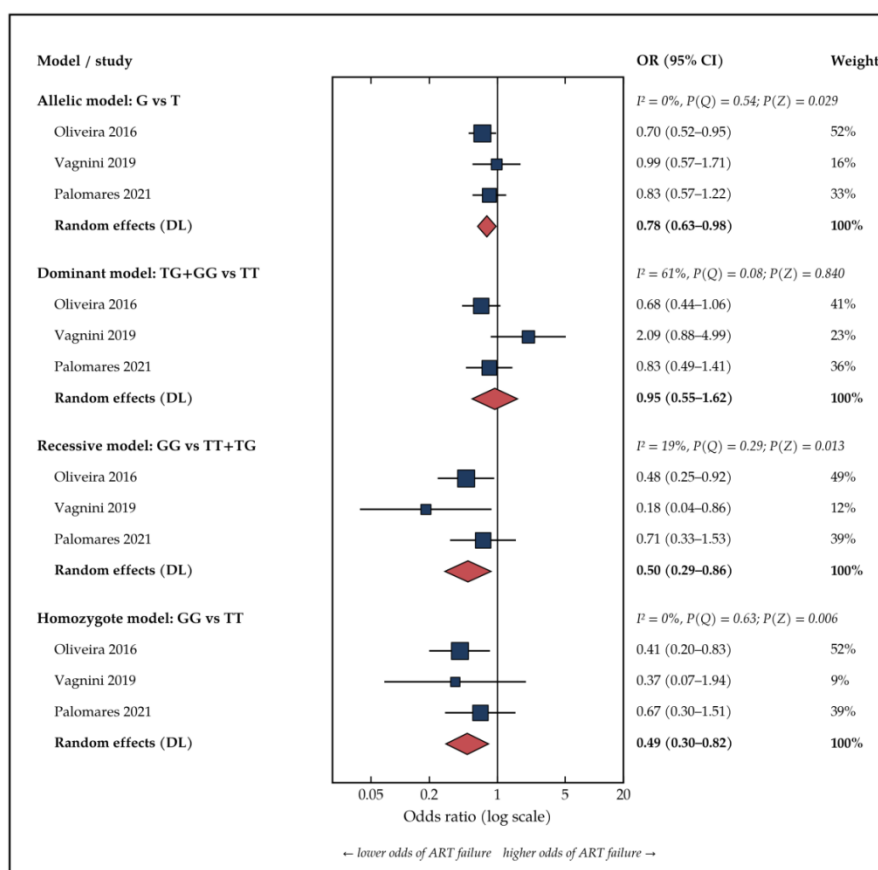


Figure 07: Forest plots of the association between *LIF* rs929271 and ART failure (no ongoing pregnancy or live birth, including RIF) under four genetic models. Squares are study odds ratios, sized by random-effects weight; diamonds are DerSimonian–Laird pooled estimates.

Table 03: Pooled odds ratios for *LIF* rs929271 and *LIF* Val64Met, with heterogeneity and certainty of evidence.

Model	OR (95% CI), random effects	P	I ² (%)	OR (95% CI), fixed effect (inverse variance)	Certainty (GRADE)
ART failure vs ART success (k = 3; 742 women)					
G vs T	0.78 (0.63–0.98)	0.029	0	0.78 (0.63–0.98)	Very low ^{1,2}
TG+GG vs TT	0.95 (0.55–1.62)	0.84	61	0.85 (0.62–1.16)	Very low ^{1,2,3}
GG vs TT+TG	0.50 (0.29–0.86) [†]	0.013	19	0.51 (0.32–0.82)	Very low ^{1,2}
GG vs TT	0.49 (0.30–0.82) [‡]	0.006	0	0.49 (0.30–0.82)	Very low ^{1,2}
TG vs TT	1.14 (0.58–2.21)	0.71	71	0.96 (0.69–1.34)	Very low ^{1,2,3}
TG vs TT+GG	1.39 (0.69–2.81)	0.36	78	1.14 (0.84–1.55)	Very low ^{1,2,3}
IVF failure or RIF vs fertile women (k = 2; 358 women)					
G vs T	1.26 (0.91–1.75)	0.17	9	1.25 (0.92–1.70)	Very low ^{1,2}
TG+GG vs TT	1.63 (0.68–3.90)	0.28	68	1.40 (0.91–2.17)	Very low ^{1,2,3}
GG vs TT+TG	1.23 (0.63–2.40)	0.54	0	1.23 (0.63–2.40)	Very low ^{1,2}
GG vs TT	1.38 (0.68–2.82)	0.37	0	1.38 (0.68–2.82)	Very low ^{1,2}
Embryo not implanted (k = 2; 1,720 transferred embryos)					
GG vs TT+TG	0.63 (0.37–1.07)	0.090	59	0.62 (0.44–0.86)	Very low ^{1,2,3}
TG+GG vs TT	0.89 (0.71–1.12)	0.34	0	0.89 (0.71–1.12)	Very low ^{1,2}
Miscarriage per clinical pregnancy (k = 2; 316 clinical pregnancies)					
TG+GG vs TT	0.49 (0.28–0.86)	0.013	0	0.49 (0.28–0.86)	Very low ^{1,2}
GG vs TT+TG	0.56 (0.22–1.43)	0.23	0	0.56 (0.22–1.43)	Very low ^{1,2}
LIF Val64Met carriage, infertile vs fertile women (k = 2; 801 women)					
Carrier vs non-carrier	Peto 4.87 (1.53–15.47)	0.007	–	–	Very low ^{1,2,4}

[†] HKSJ 95% CI 0.14–1.74 ($P = 0.14$). [‡] HKSJ 95% CI 0.23–1.04 ($P = 0.056$). Reasons for downgrading: ¹ risk of bias; ² imprecision; ³ inconsistency; ⁴ indirectness (outcome is infertility, not ART success). Odds ratios above 1 mean higher odds of the adverse outcome. HKSJ, Hartung–Knapp–Sidik–Jonkman; RIF, recurrent implantation failure.

The recessive signal was not robust (Figure 8d). With the HKSJ method the interval widened to 0.14–1.74. Leaving out Oliveira et al. gave OR 0.43 (0.12–1.56), whereas leaving out either of the other two studies kept the estimate significant. Using cumulative fresh-plus-frozen outcomes for Oliveira et al. and clinical pregnancy for Palomares et al. gave OR 0.51 (0.24–1.10).

5.5. Implantation, miscarriage and comparison with fertile women

At the embryo level, GG went with fewer non-implanted embryos under the fixed-effect model (OR 0.62, 0.44–0.86), but not under random effects (OR 0.63, 0.37–1.07; $I^2 = 59\%$) (Figure 8b). Miscarriage per clinical pregnancy was lower in G carriers in both cohorts (TG+GG vs TT: OR 0.49, 0.28–0.86; $I^2 = 0\%$) (Figure 8c). When women with IVF failure were compared with fertile women, no model reached significance (allelic OR 1.26, 0.91–1.75) (Figure 8a) [16,83], and adding the Oliveira cohort, whose controls probably overlap those of Vagnini et al., changed little (OR 1.15, 0.90–1.45). In Han Chinese women, G carriers younger than 35 years yielded fewer oocytes than TT women (median 14 vs 16), and the G allele was more common in young poor responders; pregnancy outcomes were not reported [84].

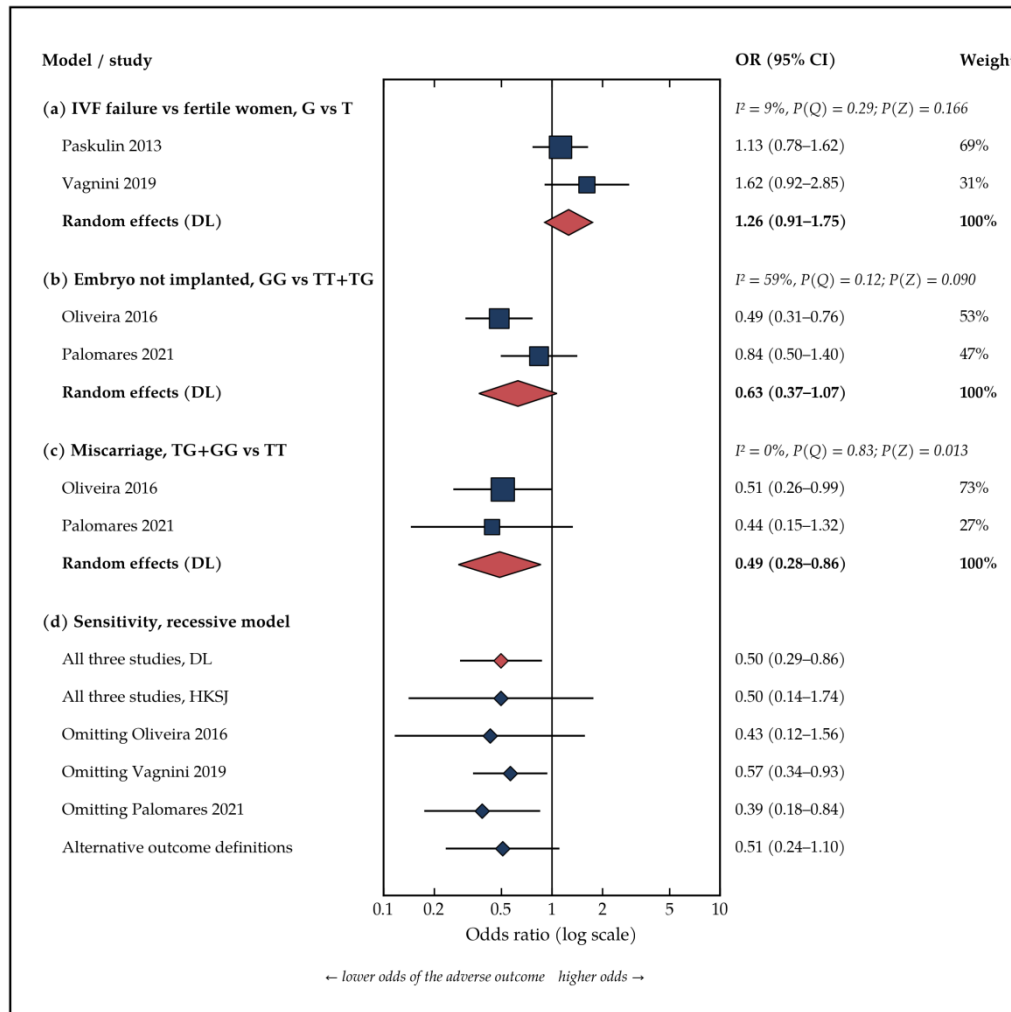


Figure 08: Secondary and sensitivity analyses for *LIF* rs929271: (a) women with IVF failure or RIF versus fertile women; (b) embryos that did not implant, per transferred embryo; (c) miscarriage per clinical pregnancy; (d) sensitivity of the recessive model for ART failure, with the Hartung–Knapp–Sidik–Jonkman (HKSJ) interval, leave-one-out estimates and alternative outcome definitions.

5.6. Rare and other LIF variants

The first mutation screen of *LIF* found three heterozygous point mutations in 74 nulligravid infertile women and no coding change in controls [91]. Val64Met was later found in 12 of 399 infertile Czech women (3.0%) and in none of 202 fertile controls [80,86]. Pooling this cohort with the German data [14] gave a Peto OR of 4.87 (1.53–15.47) for carriage in infertile women, but the estimate rests on 13 carriers (Table 4). Carriage did not predict IVF success: 7 of 15 carriers (47%) and 70 of 136 non-carriers (51%) conceived in their first cycle (OR for failure 1.21, 0.42–3.53) [81]. Steck et al. found no functional mutation among 45 women with RIF [14].

The most recent study reported Val64Met heterozygosity in 72–76% of 400 Iranian women, together with lower serum LIF in women with RIF [85]. The allele does not exceed about 3% in any gnomAD population [58], and the genotype counts depart grossly from HWE ($P < 10^{-15}$), so a technical artifact is the likeliest explanation and the study was not

pooled. The 3951C>T variant was not linked to IVF failure in northern Iran (allelic OR 1.21, 0.73–2.00) [63], and sequencing of *LIF* exon I in 80 Iraqi IVF patients, half of them with polycystic ovary syndrome, found no variant [82].

Table 04: Rare *LIF* variants and *LIFR* (and gp130) variants: reported findings and plausibility checks.

Variant	Study	Setting and groups	Genotype data	Reported result	Our appraisal
<i>LIF</i> Val64Met (p.Val86Met; rs41281637)	Steck 2004 [14]	Germany; RIF 45, unexplained infertility 50, fertile 105	Carriers 0/45, 1/50, 0/105	No functional mutation in RIF	Single carrier; small groups
<i>LIF</i> Val64Met	Králíčková 2007, 2006 [80,86]	Czech Republic; infertile 399, fertile 202	Carriers 12 vs 0	More carriers among infertile women ($P = 0.01$); 7 carriers conceived with IVF	Abstract-level data; allele classed benign or likely benign in ClinVar
<i>LIF</i> Val64Met	Novotný 2009 [81]	Czech Republic; IVF, carriers 15, non-carriers 136	Pregnant after first IVF: 7/15 vs 70/136	No overall difference; fewer pregnancies in carriers with idiopathic infertility or endometriosis (1/7 vs 18/37)	Very small subgroups; pregnancy not defined
<i>LIF</i> Val64Met	Vahdani 2025 [85]	Iran; RIF 200, IVF success 200	GG/GA/AA 52/145/3 vs 44/152/4	No association; lower serum <i>LIF</i> in RIF	Heterozygosity 72–76% and HWE $P < 10^{-15}$; genotyping error likely
<i>LIF</i> 3951C>T	Alipour 2017 [63]	Iran; IVF failure 70, fertile 73	CC/CT/TT 28/37/5 vs 33/37/3	No association	No rs number; loose case definition
<i>LIF</i> exon I	Hussein 2018 [82]	Iraq; IVF, PCOS 40, non-PCOS 40	No variant found	–	Only exon I examined
<i>LIF</i> and <i>LIFR</i> upstream regions	Tajeddin 2021 [89]	Iran; infertile 100, controls 50 (no ART)	One <i>LIF</i> and one <i>LIFR</i> variant in cases, none in controls	Descriptive	Printed rs numbers could not be matched; outside ART
<i>LIFR</i> rs3099124	Ali 2023 [88]	Pakistan; unexplained infertility 81, fertile 162 (no ART)	Counts not accessible	Genotype distribution differed ($\chi^2 = 28.2$)	Same cohort as Ali 2021; outside ART
<i>LIFR</i> rs121912501 (p.Arg597Ter)	Ali 2021 [87]	Pakistan; unexplained infertility 81, fertile 162 (no ART)	Counts not accessible	TT OR 5.42; CT OR 3.10	Pathogenic null allele of Stüve–Wiedemann syndrome; implausible
gp130 rs747379809, rs754547662	Ali 2026 [92]	Pakistan; unexplained infertility 135, fertile 177 (no ART)	Monomorphic in all women	No association	Outside ART; co-receptor gene

HWE, Hardy–Weinberg equilibrium; PCOS, polycystic ovary syndrome; RIF, recurrent implantation failure.

5.7. *LIFR* variants

No study related *LIFR* variants to implantation or pregnancy after ART. In Pakistani women with unexplained infertility, Ali et al. reported strong associations with the nonsense variant rs121912501 (TT genotype OR 5.42; CT OR 3.10) and, in the same 81 cases and 162 controls, with the intronic rs3099124 [87,88]. The first result is biologically implausible. rs121912501 is an ultra-rare pathogenic allele, and a woman homozygous for a *LIFR* null variant would be expected to have Stüve–Wiedemann syndrome, a severe and often lethal disorder, rather than isolated infertility [33,56]. An Iranian upstream-sequencing study found one *LIF* and one *LIFR* variant in 2 of 100 infertile women and none in 50 controls [89]. In the Pakistani setting, two gp130 variants were monomorphic in both cases and controls [92].

5.8. Risk of bias and certainty of evidence

Three studies scored as high quality, one as moderate and six as low; one descriptive sequencing study could not be scored (Table 5). The usual weaknesses were unmatched ages, no adjustment for embryo quality, unreported genotyping call rates and, in some studies, groups defined by a single failed cycle. With GRADE, every pooled estimate

was rated as very low certainty. All were downgraded for risk of bias and imprecision, the five estimates with marked heterogeneity also for inconsistency, and the Val64Met estimate for indirectness (Table 3).

Table 05: Newcastle–Ottawa quality assessment of the included studies.

Study	S1	S2	S3	S4	C1	C2	E1	E2	E3	Total
Steck 2004	★	–	–	★	–	–	★	★	–	4
Králíčková 2007 ^a	–	–	–	★	–	–	★	★	–	3
Novotný 2009	–	–	★	–	–	–	★	★	–	3
Paskulin 2013	★	–	–	★	–	–	★	★	–	4
Oliveira 2016	★	★	★	★	★	★	★	★	–	8
Alipour 2017	–	–	★	–	–	–	★	★	–	3
Hussein 2018	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Vagnini 2019	★	–	★	★	–	–	★	★	–	5
Palomares 2021	★	★	★	★	★	–	★	★	★	8
Liu 2023	★	★	★	★	★	–	★	★	–	7
Vahdani 2025	★	–	★	–	–	–	–	★	–	3

S1, adequate case definition; S2, representativeness of cases; S3, selection of controls; S4, definition of controls; C1, comparability for age; C2, comparability for embryo quality or another key factor; E1, validated genotyping; E2, same method in cases and controls; E3, call rate or quality control reported. ★ criterion met; –, not met or not reported; NA, not applicable (descriptive sequencing without comparison groups). ^a Scored from the abstract only.

6. DISCUSSION

6.1. Reading the rs929271 signal

This review found one consistent pattern and a lot of uncertainty around it. Women homozygous for the G allele of rs929271 were less likely to leave ART without a pregnancy. The effect followed a recessive shape, pointed the same way in all three cohorts, and fitted with fewer miscarriages in G carriers. That coherence is encouraging, but the pooled estimate leans on one center, loses significance with small-sample methods, and disappears when IVF failures are set against fertile women. With 742 women the analysis had little power for a genotype carried by 10–14% of patients, and first reports of genetic associations tend to overstate their effects [93,94]. There is no mechanism yet either. rs929271 lies about 1.4 kb downstream of the stop codon, its regulatory effect has only been predicted in silico [60], and no study has measured endometrial LIF mRNA or protein by genotype, so for now the association is statistical rather than biological.

The direction of the finding also sits uneasily with earlier work. Kang et al. reported that selected LIF alleles were enriched among IVF patients younger than 35 years [13], and Liu et al. found the G allele more often in young poor responders [84]. If one allele raised the chance of needing IVF yet helped implantation once an embryo was transferred, it would fit the antagonistic pleiotropy that Kang et al. proposed for the p53 pathway [13,21]. We offer this only as a hypothesis; the two observations come from different populations and end points, and neither has been replicated.

6.2. Endometrium or embryo?

Nearly all studies genotyped only the woman. In autologous IVF the embryo inherits half of the maternal genotype, so a maternal effect cannot be separated from an embryonic one. The donor-oocyte cohort of

Palomares et al. helps here, because the recipient's genotype acts on the endometrium but not on the embryo [17]. Its estimates were weaker, that is closer to 1, than those of the autologous studies and not significant. This could mean that part of the Brazilian effect worked through the embryo, or simply that 224 recipients were too few. No study genotyped embryos or partners, and none measured endometrial LIF alongside genotype. Ovarian response complicates the picture further: Liu et al. linked the G allele with fewer oocytes in young women [84], and fewer oocytes means fewer embryos to choose from. In autologous cycles such an effect could hide, or mimic, an endometrial one, which is one more reason to adjust for embryo number and quality.

6.3. Why the studies disagree

Several features of this literature explain much of the conflict. First, phenotypes differed. RIF meant three failed attempts with at least five good embryos in one study [83], at least one failed cycle in another [16] and an unspecified “unsuccessful IVF history” in a third [63], while current guidance asks for a clearer, prognosis-based definition [2–4]. Second, no study controlled for embryo ploidy, the main driver of implantation failure. Third, genotype quality was uneven. Two reports gave frequencies that cannot be matched with population data, one for LIF Val64Met and one for a pathogenic LIFR allele [85,87], and a third reported no rs929271 G allele at all [90]. Allele-specific and tetra-primer PCR assays are cheap, but they need sequencing of a subset, duplicate genotyping and HWE checks, as STREGA recommends [65].

Fourth, ancestry was ignored. The G allele of rs929271 is rare in African populations and common in Asian ones (Figure 5), so estimates from admixed Brazilian samples may not carry over to Middle Eastern or African women, yet none of the included studies adjusted for ancestry. Finally, overlapping samples are

likely. Oliveira et al. and Vagnini et al. share a center and several authors, and their fertile controls were recruited in the same way. With all of these problems in play, the current data cannot separate a real but modest effect from a false positive.

The rs929271 story also looks much like that of other candidate genes proposed for RIF, from VEGF and p53 to the estrogen receptors [95]. Many began with a small positive study from a single center and were later weakened or left without replication. That is the pattern one expects when the prior probability of a true association is low and power is limited [93,94].

6.4. Implications and next steps

For now, *LIF* or *LIFR* genotyping has no place in the work-up of implantation failure or in embryo-transfer decisions. The data cannot even say whether rs929271 changes *LIF* expression in the endometrium. Future studies should use the definitions of RIF proposed by the European Society of Human Reproduction and Embryology (ESHRE) [4], transfer euploid embryos where possible, genotype women, partners and ideally embryos, report call rates and HWE, adjust for age and embryo quality, and be large enough to detect an OR of about 1.5 under a recessive model. Table 6 sets out a minimum set of items. Donor-oocyte and gestational-carrier cycles are natural experiments for separating maternal and embryonic effects, and they deserve wider use [95,96].

Clinicians may still meet couples who bring *LIF* results from commercial genetic panels. The present data support a simple message. A GG, TG or TT result does not shift the chance of success enough to change the treatment plan, and it should not replace established steps such as embryo selection, uterine assessment and the structured work-up for RIF [4].

Table 06: Minimum design and reporting items proposed for future *LIF* and *LIFR* studies in ART.

Domain	Minimum item
Phenotype	Define RIF as in the ESHRE good practice recommendations [4]; report the number of cycles, embryo stage and number of embryos transferred; use live birth or ongoing pregnancy per woman as the main end point.
Embryo factors	Record euploidy (preimplantation testing) or at least morphology grade, and analyze euploid transfers separately.
Endometrium	Record endometrial preparation (natural, hormone-replaced or stimulated) and, where possible, endometrial or uterine-fluid <i>LIF</i> measured in the same women.
Genotyping	Use validated assays; confirm at least 10% of calls by sequencing; report call rate, duplicate concordance and HWE in controls.
Ancestry	Report ancestry, compare allele frequencies with 1000 Genomes or

	gnomAD, and adjust for genetic ancestry in admixed samples.
Design	Genotype partners and, where feasible, embryos; use donor-oocyte or gestational-carrier cycles to separate maternal and embryonic effects.
Analysis	Pre-specify the genetic model; adjust for age, body mass index, embryo quality and number transferred; report raw genotype counts per woman and per embryo.
Size and sharing	Plan for an OR of about 1.5 under a recessive model; declare overlapping samples; share genotype counts so that the data can be pooled.

HWE, Hardy–Weinberg equilibrium; OR, odds ratio; RIF, recurrent implantation failure.

6.5. Limitations of this review

The search covered PubMed and web sources but not Scopus, Web of Science or Embase, and four reports could not be obtained, including the full data of Kang et al. [13]. A single reviewer extracted the data, although every count was re-checked against row totals and printed percentages. Most ORs were unadjusted. With three studies in the main analysis, publication bias could not be tested and the between-study variance was estimated poorly. Embryo stage, fresh versus frozen transfer and endometrial preparation could not be explored as modifiers, because no study reported them by genotype.

7. CONCLUSION

LIF is essential for implantation in animals, and endometrial *LIF* signaling is disturbed in some women with RIF, yet the genetic evidence from ART is thin. This review located eleven relevant studies, and only *LIF* rs929271 had enough ART-outcome data to pool. The GG genotype was associated with roughly half the odds of ART failure, and G carriage with fewer miscarriages, but the finding came mostly from one center, did not survive small-sample correction, and was not seen when women with IVF failure were compared with fertile women. Rare *LIF* variants, Val64Met included, did not change IVF success, and no study has yet tested *LIFR* against ART outcomes. The two *LIFR* associations published so far come from one small cohort outside ART, and one of them rests on implausible genotype data. Overall, the certainty of evidence is very low, and *LIF* or *LIFR* genotyping should not be offered to guide IVF or ICSI. Larger, ancestry-aware studies with strict RIF definitions, euploid embryo transfer, verified genotyping and, where possible, donor-oocyte designs are needed before any clinical use can be considered.

8. Funding

Nil

9. CONFLICTS OF INTEREST

Not Declared

10. DATA AVAILABILITY

The genotype counts extracted for this review and the analysis script are provided as supplementary files.

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Not Declared.

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