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Role of *P53* p.Arg72Pro Variant in Recurrent Pregnancy Loss, Recurrent Implantation Failure and IVF Outcome

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Abstract: The role of *p53* p.Arg72Pro variant in recurrent pregnancy loss, recurrent implantation failure and IVF outcome is controversial and research so far has yielded inconsistent results. This systematic review aims to summarise the literature on the role of *TP53* p.Arg72Pro variant in recurrent pregnancy loss following natural and assisted conception. A comprehensive literature search was conducted on MEDLINE, EMBASE and CENTRAL electronic databases for literature published between 1998 and April 2020. Inclusion and exclusion criteria and search terms were established. References of retrieved articles were hand searched to identify other relevant papers including conference abstracts. In total, 9 case control studies (1041 patients), 6 case control studies (382 patients) and 7 studies (3403) were included examining the role of *TP53* p.Arg72Pro variant in recurrent pregnancy loss, recurrent implantation failure and IVF outcome respectively. Combined genotype frequencies suggest that there may be an association between Pro/Pro genotype and recurrent pregnancy loss and Arg/Pro genotype and recurrent implantation failure. However, the association between *TP53* p.Arg72Pro variant and recurrent pregnancy loss, recurrent implantation failure or IVF outcomes has not been clearly established. In conclusion, genotyping patients for the *TP53* variant may enable us to identify an aetiology for patients experiencing unexplained recurrent pregnancy loss and detect individuals at risk of recurrent implantation failure before IVF treatment is initiated. Furthermore, exploring the mechanisms of action of the p53 protein may provide us with an insight into potential treatments.

Keywords: P53, Gene Polymorphism, Gene Variant, Recurrent Miscarriage, Recurrent Implantation Failure, IVF

1. Introduction

The European Society of Human Reproduction and Embryology (ESHRE) and the American Society of Human Reproductive Medicine (ASRM) define recurrent pregnancy loss (RPL) as two or more consecutive proven pregnancy losses before 20 weeks of gestation [1]. RPL occurs in about 1% of pregnancies [2]. Recurrent implantation failure (RIF) is defined as repetitive failure to achieve a clinical pregnancy after the transfer of good quality embryos in three or more cycles of IVF treatment [3-4]. Although the pathophysiology is not fully understood, RPL is probably a disorder at the level of implantation, affecting apposition (or adplantation), adhesion or embryo invasion through the stroma of the endometrium [3], which would explain why the vast majority of miscarriages occur in the early stages of pregnancy.

RPL is a complex heterogenous disorder, the underlying pathophysiology involves many possible factors. Maternal age, endometrial pathology, infectious, endocrinological, immunological, prothrombotic disorders as well as environmental factors have all been implicated [3, 5-7]. Despite these potentially identifiable aetiological causes, up to 50% of cases of RPL remain idiopathic [3, 5-7]. Due to the fact that most pregnancy loss occurs during the implantation or early embryonic stages of development, it has been suggested that any factor which alters the intricate balance

between proliferation, angiogenesis and apoptosis may interfere with implantation or early embryonic development [8]. This intricate balance between combinations of essential mediators contributes to the success of trophoblast invasion and placental differentiation which is essential for the growth and development of the growing fetus. A disturbance of this balance may impair the chances of a successful pregnancy.

Genetic variants, may influence the balance of these mediators, thus reducing the chances of a successful pregnancy. Few clinically significant relationships between variants and RPL/RIF have been established [8-11].

TP53 is a tumour-suppressor gene that encodes p53, a transcription factor implicated in a number of cellular processes. It has a clearly established role in the regulation of apoptosis, angiogenesis and repair of DNA damage [12]. Numerous post-translational modifications regulate p53 activity. Mutation of the gene itself or loss of cell signaling upstream or downstream can cause loss of activity of p53 [12]. Research has also suggested that p53 could be a potential pregnancy mediator, and thus genetic variations of *TP53* could be a potential risk factor for idiopathic RPL and RIF [11-13].

The growing interest in *TP53* variants and RPL/RIF has drawn researchers' attention to be focused on rs1042522 polymorphism variant [chr 17: 7676154 (GRCh38.p12); NM_000546.6: c.215C>T; NP_000537.3: p.Arg72Pro], [14-15]. Studies have suggested that *TP53* p.Arg72Pro variants induce lower apoptotic activity and higher levels of G1 cell cycle arrest compared to wildtype variants [16]. This leads to inadequate trophoblastic invasion and subsequently increases the risk of RPL and RIF [17].

The primary objective of this study is to conduct a systematic review of the literature investigating the role of *TP53* p.Arg72Pro variant in recurrent pregnancy loss, recurrent implantation failure and IVF outcome.

2. Methods

A search of three electronic databases – MEDLINE, EMBASE and CENTRAL– targeting reports published between 1998 and April 2020 was conducted. The search strategy used the terms 'p53', 'p53 codon polymorphism', 'p.Arg72Pro', 'rs1042522', 'recurrent pregnancy loss', 'recurrent implantation failure', 'recurrent spontaneous abortion' and 'IVF'. The references of retrieved articles were hand searched to identify other relevant papers including conference abstracts. Studies that investigated the effects of *TP53* p.Arg72Pro (rs1042522) on recurrent implantation failure, recurrent pregnancy loss and IVF were included. Criteria for inclusion and exclusion of studies were established prior to the literature search. The main outcomes sought were the relationship between *TP53* p.Arg72Pro and recurrent implantation failure, recurrent pregnancy loss and IVF outcomes (See Appendix: Figure 1 – PRISMA Flow Diagram).

3. Results

Nine studies that examined the role of the *p53* p.Arg72Pro variant and RPL [18-26] and six studies that examined the role of this variant and RIF were retrieved [18, 20, 27-30]. The type of study, subjects included, frequency of the genotypes in the study groups and control groups are outlined in Appendix: Tables 1 and 2. Seven studies examining the role of *p53* p.Arg72Pro variant and IVF outcomes were retrieved [14, 30-35]. The results of these studies are outlined in Appendix: Table 3.

Three studies (*Firouzibadi et al., 2009, Pietrowski et al., 2004 and Lledo et al., 2013*) [18-20] report an association between the single nucleotide polymorphism and RPL. *Firouzibadi et al., 2009* report a significant difference in genotype homozygous Pro/Pro in RPL and significant differences in Pro allele frequency in the RPL group compared to the other groups (Chi-squared value 0.002) [18]. *Pietrowski et al., 2004* report a statistically significant association between carriage of Pro allele and idiopathic RPL (p=0.03) [19]. *Lledo et al., 2013* report that in RPL the frequency of Pro/Pro genotypes on the *p53* gene among women experiencing RPL was 18.5% compared to 6% in the control group (p<0.01) [20]. In contrast to this, 6 studies (*Yoon et al., 2015, Fraga et al., 2014, Kaare et al., 2009, Coulam et al., 2006, Oliveira et al., 2013 and Franco Jr et al., 2013*) report no association between the *p53* p.Arg72Pro variant and RPL [21-26].

Combining the genotype frequency study data, 48% (498/1041) RPL patients were Arg/Arg compared to 50% (514/1029) controls. 39% (410/1041) RPL patients were Arg/Pro compared to 42% (433/1029) controls. 13% (133/1041) RPL patients were Pro/Pro compared to only 8% (82/1029) controls.

Three studies (*Kay et al., 2006, Lledo et al., 2013, Firouzibadi et al., 2009*) report an association between *p53* p.Arg72Pro variant and RIF [27, 20, 18]. *Kay et al., 2006* report a significantly higher frequency of Pro72 (p=0.003) among women experiencing RIF compared with women experiencing RPL and the control group [27]. *Lledo et al., 2013* reported that the frequency of Pro/Pro genotypes on the *p53* gene among women experiencing RIF was 11.4% vs 6% in the control group (p<0.01) [20]. However, *Firouzibadi et al., 2009* report that the Arg allele frequency was significantly higher in the RIF patients than the control and RPL groups with an allelic value of 0.002 [18]. Three studies (*Goodman et al., 2009, Vagnini et al., 2013, Allanfan et al., 2015*) found no association between *p53* p.Arg72Pro variant and RIF [28-30].

Combining the genotype frequency data, 47% of patients with RIF (146/312) were Arg/Arg compared to 60% of controls (138/230). 44% (138/312) of patients with RIF were Arg/Pro compared to 33% of controls (75/230) and 9% (34/382) of patients with RIF were Pro/Pro compared to 7% (19/303) controls.

Seven studies (*Paskulin et al., 2012, Kang et al., 2009, Patounakis et al., 2008, Ghorbian et al., 2019, Chan et al., 2016, Baruffi et al., 2014, Allanfan et al., 2015*) reviewed the association between *p53* p.Arg72Pro variant and IVF outcome [14, 30-35]. Three studies (*Paskulin et al., 2012, Kang et al., 2009, Chan et al., 2016*) found an association between *p53* p.Arg72Pro variant and IVF outcome [31, 14, 34]. *Paskulin et al., 2012* report an association between p.Arg72Pro and IVF

(p=0.009) when comparing with selected and unselected controls [31]. *Kang et al., 2009* found a significantly lower implantation rate in patients homozygous Pro/Pro (19%) compared with patients carrying at least 1 allele of Arg (42%) p=0.0028, which resulted in a lower clinical pregnancy rate for patients homozygous for Pro/Pro in patients less than 35 years old [14]. In older patients there was no significant difference in implantation and pregnancy rates [14]. In contrast, *Chan et al., 2016* reported the C allele (Pro) showed a higher frequency in the clinical pregnancy group (p=0.01) and an association was found between the C allele (Pro) and IVF outcome (OR =0.83, 95% CI: 0.71+/- 0.96, p=0.01), suggesting that the Pro allele decreased the risk of pregnancy failure after IVF [34].

4. Discussion

As demonstrated the complex relationship between *p53* p.Arg72Pro variant and RPL and RIF is far from being understood. This systematic review suggests that the frequency of Pro/Pro genotype carriers compared to genotypes Arg/Pro and Arg/Arg may be higher in the RPL population compared to the control group, and the frequency of Arg/Pro genotype carriers compared to Arg/Arg and Pro/Pro may be higher in the recurrent implantation failure population compared to the control group, suggesting that this area requires further investigation.

These results are consistent with five meta-analyses examining the relationship between *p53* p.Arg72Pro variant and RPL [11, 36-39]. *Tang et al., 2011* analyzed four case control studies and concluded that women with the homozygous Pro/Pro genotype had an increased risk of RPL [11]. *Su et al., 2011* analysed four case control studies and showed that women who carried the *TP53* p.Arg72Pro variant had a higher risk of RPL in the recessive model [36]. *Chen et al., 2015* analysed six case control studies and suggested that a Pro/Pro genotype in an additive model and recessive model were associated with an increased risk of RPL compared to genotypes Arg/Arg and Arg/Pro [37]. *Zhang et al., 2016* analysed six case control studies and concluded that there is a significant association between *TP53* p.Arg72Pro and RPL in the Pro/Pro co-dominant and recessive models compared to women with genotypes Arg/Pro and Arg/Arg [38]. *Shi et al., 2017* reviewed 6 case control studies and found a significant association between recurrent pregnancy loss and *TP53* p.Arg72Pro variant [39]. However, this concordance is unsurprising as all the papers analysed similar papers due to the paucity of literature available. In contrast to this, a meta-analysis by *Wiwanitkit et al., 2011* concluded that there was no correlation between *p53* p.Arg72Pro variant and RPL, however this meta-analysis only looked at 2 case reports, both of which were included in the larger meta-analyses discussed above [40].

The relationship between *p53* p.Arg72Pro variant and RIF or IVF outcome is less clear. There are two meta-analyses examining the relationship between RIF and *p53* p.Arg72Pro variant. *Feng et al., 2016* found there was no significant association between RIF amongst patients with Pro/Pro genotype or Arg/Pro genotype compared to Arg/Arg [41], and similarly, *Wiwanitkit et al., 2011* found there was no correlation between RIF and *p53* variant [40]. Our study combining the genotype frequency data suggests that the frequency of Arg/Pro genotype carriers compared to Arg/Arg and Pro/Pro may be higher in the recurrent implantation failure population compared to the control group, which has not been shown in the previous meta-analyses. Furthermore, the studies included that examined *TP53* p.Arg72Pro and IVF outcome were contrasting, with 2 studies reporting a worse outcome with carrying the Pro allele [14, 31] compared to 1 study reporting a better outcome with carrying the Pro allele [34], highlighting the need for further research to examine the role of *p53* p. Arg72Pro variant in RIF and IVF outcome.

Successful trophoblast invasion and embryonic development is regulated by a careful balance between mediators involved in proliferation and apoptosis. [17, 38, 42-43]. The p53 protein has an important role in regulating the cell cycle, apoptosis and protecting the genome [36] and is necessary for successful invasion of trophoblast cells [38]. *P53* variant changes the functional activity of p53, (17, 43). The C allele variant causes Arg to be replaced by Pro. The Arg72 variant is better than the Pro72 variant at inducing apoptosis and suppressing cellular transformation [11], the Pro72 variant induces a higher level of G1 cell cycle arrest than the Arg72 variant and induces a lower level of apoptotic activity [11, 38]. This may result in inadequate trophoblastic invasion and therefore lead to an increased risk of RPL or RIF in Pro carriers. Furthermore, the p53 protein is involved in the regulation of leukaemia inhibitory factor (LIF), an important cytokine that influences the receptivity of the endometrium and implantation of the blastocyst [11]. Arg72 has been shown to be more active than Pro72 in activating LIF and therefore Pro carriers may have an increased risk of RPL or RIF through altered p53 activity and reduced LIF [11].

Although we have included a comprehensive systematic overview of the literature and combined genotype frequency results, there are differences in the inclusion and exclusion criteria of the patient groups recruited into the studies, which does not allow statistical combination of the results. In the RPL group, some studies recruited patients with 2 consecutive pregnancy losses [18, 20-22, 24-26], however other studies included only 3 or more consecutive pregnancy losses [19, 23]. Furthermore the gestation limit of the previous miscarriages, method of diagnosis of previous miscarriage, pregnancy history and the diagnostic tests performed prior to confirmation of idiopathic RPL varied significantly between the studies. Similarly, in the RIF group some studies recruited patients with 2 consecutive IVF cycle failures [18, 27, 30] or IVF failure after 4 cleaved good quality embryos [20, 29] or IVF failure after 8 cleaved embryos or 4 blastocysts [28]. Similarly, the control groups between the studies are dissimilar for example two studies recruited postmenopausal women [19, 21] with the remainder recruiting premenopausal women. This heterogeneity between the studies suggests that results should be considered with caution.

Literature has shown that the allele frequencies of *p53* variant vary according to populations with different ethnic backgrounds. It seems that the Pro allele is the ancestral allele

and it has around a 60% frequency in African populations compared to around 25-35% frequency in Caucasian and Asian populations [45]. The case control studies have been conducted in various countries including South Korea [21], Brazil [22, 25-26, 29, 31, 35], Iran (18, 30, 33), Finland [23], Austria [19], USA [24, 28, 27, 14, 32], Spain [20] and China [34] and therefore they include a wide range of ethnicities. Furthermore, it is likely that different *p53* genotypes in different populations may be associated with different risks of RPL/RIF. However despite this association, a firm conclusion cannot be reached on the impact of *p53* variant in different populations, as it is difficult to account for environmental confounding factors that may exist in particular ethnic groups and subsequently influence the pregnancy outcome. This highlights the importance of stratification of the results according to ethnicity, which was not performed in all the research studies and also reflects the need for well-matched control groups in any future studies.

Advancing maternal age is associated with reduced oocyte quality, which may contribute to recurrent implantation failure, and therefore we would expect that RIF may be a more significant cause for subfertility in younger patients with unexplained subfertility compared to older patients. Literature suggests that the association of *p53* variants with reduced fertility mainly occurs in younger patients and the association is reduced with advancing maternal age, suggesting that it may also be important to consider stratification according to maternal age in any future research [43].

The p53 pathway is complex network with negative and positive regulators of p53, for example MDM 2, MDM4 and Hausp [44]. Each of these regulators also have genetic variants which can further effect the p53 pathway and could impact implantation and other aspects of fertility [44]. This highlights the complexity in investigating the role of *p53* variant in RIF/RPL, it may be that in future research studies, patients and control groups are investigated for a number of variants simultaneously to enable us to further understand this pathway and its' association with RPL, RIF and IVF outcome.

5. Conclusion

This systematic review has demonstrated that the frequency of Pro/Pro genotype carriers may be higher in the RPL population and the frequency of Arg/Pro genotype carriers may be higher in the RIF population. Genotyping patients for the *TP53* variant may enable us to identify an aetiology for patients experiencing unexplained RPL and also detect individuals at risk of RIF before IVF treatment is initiated. Furthermore, exploring the mechanisms of action of the p53 protein will provide us with an insight into potential treatments of RPL and RIF.

Appendix

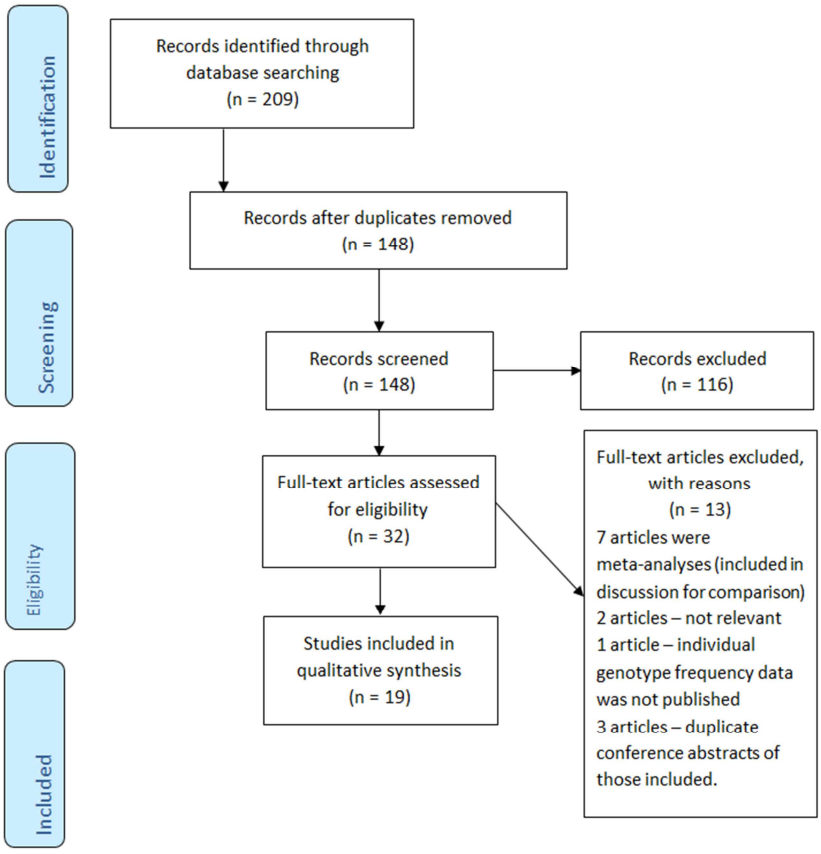

Figure 1. *PRISMA Flow Diagram.*

Table 1. *Details of Studies Included in the Review: Recurrent Pregnancy Loss.*

Authors	Subjects	Location	Genotype frequencies			Conclusion
			Arg/Arg (%)	Arg/Pro (%)	Pro/Pro (%)	
Yoon et al., 2015	Study: 294 women with RPL Control: 300 postmenopausal women	South Korea	RPL: 42.9% (126/294) Control: 39.3% (118/300)	RPL: 44.9% (132/294) Control: 51% (153/300)	RPL: 12.2% (36/294) Control: 9.7% (29/300)	No significant differences in the genotype distributions or allele frequencies
Fraga et al., 2014	Study: 120 women with RPL Control: 143 fertile women	Southern Brazil	RPL: 47.5% (57/120) Control: 50.3% (72/143)	RPL: 39.2% (47/120) Control: 42% (60/143)	RPL: 13.3% (16/120) Control: 7.7% (11/143)	No significant difference in the genotype distributions or allele frequencies
Firouzabadi et al., 2009	Study: 97 women with RPL Control: 32 premenopausal women	Iran	RPL: 23.7% (23/97) Control: 12.5% (4/32)	RPL: 42.3% (41/97) Control: 65.6% (21/32)	RPL: 34% (33/97) Control: 21.9% (7/32)	Significant difference in women homozygous Pro/Pro and in Pro allele freqency in RPL compared to the other groups
Kaare et al., 2009	Study: 46 women with RPL Control: 191 women	Finland	RPL: 45.6% (21/46) Control: 55.5% (106/191)	RPL: 47.8% (22/46) Control: 40.3% (77/191)	RPL: 6.5% (3/46) Control: 4.2% (8/191)	No significant difference in the genotype distributions or allele frequency
Pietrowski et al., 2004	Study: 175 women with RPL Control: 143 postmenopausal women	Austria	RPL: 47.4% (83/175) Control: 58% (83/143)	RPL: 40% (70/175) Control: 35% (50/143)	RPL: 12.6% (22/175) Control: 7% (10/143)	Statistically significant association between carriage of Pro allele and RPL
Coulam et al., 2006	Study: 205 women with RPL Control: 21 premenopausal women with 2+ livebirths	USA	RPL: 68.8% (141/205) Control: 61.9% (13/21)	RPL: 26.8% (55/205) Control: 38.1% (8/21)	RPL: 4.4% (9/205) Control: 0%	No significant difference in the genotype or allele frequencies
Lledo et al., 2013	Study: 54 women with RPL Control: 83 oocyte donors	Spain	RPL: 51.9% (28/54) Control: 65.1% (54/83)	RPL: 29.6% (16/54) Control: 28.9% (24/83)	RPL: 18.5% (10/54) Control: 6% (5/83)	In RIF and RPL patients R72P on *p53* gene is more prevalent
Oliveira et al., 2013	Study: 23 couples with RPL Control: 55 couples with 2 livebirths	Brazil	RPL: 39.1% (9/23) Control: 54.5% (30/55)	RPL: 56.5% (13/23) Control: 34.6% (19/55)	RPL: 4.4% (1/23) Control: 10.9% (6/55)	No significant difference in genotype or allele frequencies
Franco Jr et at., 2013	Study: 27 women with RPL Control: 61 women with 2 livebirths	Brazil	RPL: 37% (10/27) Control: 55.7% (34/61)	RPL: 51.9% (14/27) Control: 34.5% (21/61)	RPL: 11.1% (3/27) Control: 9.8% (6/61)	No significant difference in genotype or allele frequency
		TOTAL	RPL: 48% (498/1041) Control: 50% (514/1029)	RPL: 39% (410/1041) Control: 42% (433/1029)	RPL: 13% (133/1041) Control: 8% (82/1029)	

Table 2. *Details of Studies Included in the Review: Recurrent Implantation Failure.*

Author	Subjects	Location	Genotype Frequencies			Conclusion
			Arg/Arg (%)	Arg/Pro (%)	Pro/Pro (%)	
Firouzabadi et al., 2009	Study: 70 women with RIF Control: 32 premenopausal women	Iran	RIF: 42.9% (30/70) Control: 12.5% (4/32)	RIF: 40% (28/70) Control: 65.6% (21/32)	RIF: 17.1% (12/70) Control: 21.9% (7/32)	Arg allele frequency was significantly higher in the RIF patients than in the control and RPL groups
Goodman et al., 2009	Study: 70 women with RIF Control: 73 fertile women	USA	Data not available	Data not available	RIF: 9% (6/70) Control: 1% (1/73)	No significant difference in genotype or allele frequencies
Kay et al., 2006	Study: 70 women with RIF Control: 20 fertile women	USA	RIF: 47% (33/70) Control: 62% (13/20)	RIF: 46% (32/70) Control: 38% (8/20)	RIF: 7% (5/70) Control: 0%	The frequency of Pro72 was significantly higher in RIF
Lledo et al., 2013	Study: 44 women with RIF Control: 83 oocyte donors	Spain	RIF: 40.9% (18/44) Control: 65.1% (54/83)	RIF: 47.7% (21/44) Control: 28.9% (24/83)	RIF: 11.4% (5/44) Control: 6% (5/83)	In RIF patients R72P on *p53* gene is more prevalent
Vagnini et al., 2013	Study: 108 couples with RIF Control: 55 couples with 2	Brazil	RIF: 45.5% (49/108)	RIF: 49.1% (53/108)	RIF: 5.5% (6/108) Control: 10.9%	No significant difference in genotype or allele frequencies

Author	Subjects	Location	Genotype Frequencies			Conclusion
			Arg/Arg (%)	Arg/Pro (%)	Pro/Pro (%)	
Allanfan et al., 2015	livebirths Study: Group 2: 20 women with RIF Control: 40 women successfully pregnant after IVF	Iran	Control: 54.5% (30/55) RIF: 80% (16/20) Control: 92.5% (37/40)	Control: 34.6% (19/55) RIF: 20% (4/20) Control: 7.5% (3/40)	(6/55) none	No significant difference in genotype or allele frequencies
		TOTAL	RIF: 47% (146/312) Control: 60% (138/230)	RIF: 44% (138/312) Control: 33% (75/230)	RIF: 9% (34/382) Control: 7% (19/303)	

Table 3. *Details of Studies Included in the Review: IVF Outcome.*

Author	Subjects	Location	Genotype Frequencies			Conclusion
			Arg/Arg (%)	Arg/Pro (%)	Pro/Pro (%)	
Paskulin et al., 2012	Study: 115 women post IVF failure Control: 134 fertile women	Brazil	IVF: 54.8% (63/115) Control: 66.4% (89/134)	IVF: 30.4% (35/115) Control: 29.9% (40/115)	IVF: 14.8% (17/11%) Control: 3.7% (5/134)	*TP53* PEX4 C allele is a risk factor for IVF failure
Kang et al., 2009	Study: 272 women with unexplained infertility Control: 1071 Women recruited into the WISE study	USA	IVF: 44.5% (121/272) Control: 61% (653/1071)	IVF: 44.8% (122/272) Control: 33.3% (357/1071)	IVF: 10.7% (29/272) Control: 5.7% (61/1071)	*p53* allele encoding Proline at codon 72 was significantly enriched over arginine at codon 72 in IVF patients
Patounakis et al., 2008	Study: Genotype and allele frequencies of 1056 female patients undergoing first fresh non donor IVF cycle and for 2 subsequent IVF cycles if no implantation occurred	USA	IVF cycle 1: 45% (476/1056) IVF cycle 2: 46% (132/289) IVF cycle 3: 51% (37/72)	IVF cycle 1: 44% (463/1056) IVF cycle 2: 45% (129/289) IVF cycle 3: 40% (29/72)	IVF cycle 1: 11% (117/1056) IVF cycle 2: 10% (28/289) IVF cycle 3: 8% (6/72)	No significant difference in genotype or allele frequencies
Ghorbian et al., 2019	Study: 100 patients with IVF failure Control: 100 patients with a natural pregnancy	Iran	Study: 10% (10/100) Control: 47% (47/100)	Study: 72% (72/100) Control: 50% (50/100)	Study: 2% (2/100) Control: 3% (3/100)	No significant difference in genotype or allele frequencies
Chan et al., 2016	Study: 1450 IVF patients Control: 250 fertile women	China	Study: 24.9% (362/1450) Control: 26% (65/250)	Study: 51% (747/1450) Control: 53.2% (133/250)	Study: 23.5% (341/1450) Control: 20.8% (52/250)	The C allele is a protective factor in IVF outcome
Baruffi et al., 2014	Study: 390 couples subjected to IVF/ICSI	Brazil	Study group: 49% (192/390) Implantation rate: 19.6%	Study group: 43.6% (170/390) Implantation rate: 18.6%	Study group: 7.2% (28/390) Implantation rate: 13.9%	No correlation with clinical outcomes after IVF/ICSI
Allanfan et al., 2015	Study: Group 1: 20 women (no pregnancy after 2 cycles of IVF) Control: 40 women successfully pregnant after IVF	Iran	Group 1: 75% (15/20) Control: 92.5% (37/40)	Group 1: 25% (5/20) Control: 7.5% (3/40)	None	No association with RIF

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