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Long non-coding RNA maternally expressed gene 3 (*MEG3*) rs4081134 gene polymorphism and preeclampsia risk

Uzun kodlayıcı olmayan bir RNA olan maternal eksprese edilen gen 3'teki (MEG3) rs4081134 gen polimorfizmi ve preeklampsi riski

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Abstract

Objective: Preeclampsia (PE), a significant challenge for health systems, is a hypertensive disorder of pregnancy. Some studies have suggested that long non-coding ribonucleic acids play a major role in the pathogenesis of PE by regulating the biological behaviors of maternal vascular smooth muscle cells and trophoblasts. In this study, the impact of the maternally expressed gene 3 (*MEG3*) rs4081134 gene polymorphism on susceptibility to PE has been evaluated.

Materials and Methods: We conducted a case-control study comprising 130 PE patients and 140 normotensive pregnant women with normal gestational outcomes genotype analysis was performed using the polymerase chain reaction-restriction fragment length polymorphism method.

Results: A significant association was evident between the AA genotype and PE risk under the recessive model, indicating that these may serve as protective factors against the development of PE. No significant relationships were detected between other genotypes, genetic models, or allelic distributions and PE risk. Additionally, among pregnant women with PE, a notable correlation was observed between newborn birth weight and the rs4081134 polymorphism in the *MEG3* gene.

Conclusion: We found a significant association between the AA genotype, as well as the recessive model of the *MEG3* rs4081134 gene polymorphism, and PE deployment. Among women diagnosed with PE, *MEG3* rs4081134 gene polymorphism was significantly associated with newborn's birth weight.

Keywords: Maternally expressed gene 3, preeclampsia, gene, polymorphism

Öz

Amaç: Sağlık sistemleri için önemli bir sorun olan preeklampsi (PE), gebeliğin hipertansif bir bozukluğudur. Bazı çalışmalar, uzun kodlayıcı olmayan ribonükleik asitlerin maternal vasküler düz kas hücrelerinin ve trofoblastların biyolojik davranışlarını düzenleyerek PE patogenezinde önemli bir rol oynadığını öne sürmüştür. Bu çalışmada, maternal eksprese edilen gen 3 (*MEG3*) rs4081134 gen polimorfizminin PE'ye yatkınlık üzerindeki etkisi değerlendirilmiştir.

Gereç ve Yöntemler: Yüz otuz PE hastası ve normal gebelik sonuçlarına sahip 140 normotansif hamile kadından oluşan bir olgu-kontrol çalışması yürütüldü ve genotip analizi polimeraz zincir reaksiyonu-restriksiyon fragment uzunluk polimorfizmi yöntemi kullanılarak gerçekleştirildi.

PRECIS: Based on our results, AA genotype and recessive model may be act as a protective factor on preeclampsia development. Furthermore, the maternally expressed gene 3 rs4081134 gene polymorphism had a significant impact on newborns' birth weight.

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Bulgular: Resesif model altında AA genotipi ile PE riski arasında bunların preeklampsi gelişimine karşı koruyucu faktörler olarak işlev görebileceğini gösteren anlamlı bir ilişki saptandı. Diğer genotipler, genetik modeller veya alel dağılımları ile preeklampsi riski arasında anlamlı bir ilişki saptanmadı. Ek olarak, preeklampsi tanısı konmuş hamile kadınlarda, yenidoğan doğum ağırlığı ile *MEG3* genindeki rs4081134 polimorfizmi arasında dikkat çekici bir korelasyon gözlemlendi.

Sonuç: AA genotipi ve *MEG3* rs4081134 gen polimorfizminin resesif modeli ile preeklampsi gelişimi arasında anlamlı bir ilişki bulduk. Preeklampsi tanısı konmuş kadınlarda, *MEG3* rs4081134 gen polimorfizmi yenidoğan doğum ağırlığı ile anlamlı bir şekilde ilişkiliydi.

Anahtar Kelimeler: Maternal eksprese edilen gen 3, preeklampsi, gen, polimorfizm

Introduction

Preeclampsia (PE), as a significant risk for mother and fetus, is specified by unprecedented hypertension (>140/90 mmHG) and proteinuria (>300 mg/24 hours) after 20 weeks of gestation, which occurs in about 3% of all pregnancies[1]. PE is divided into two main categories based on the time of diagnosis: early-onset PE (occurring before 34 weeks) and late-onset PE (occurring after 34 weeks)[2]. The increased frequency of certain maternal and fetal adverse outcomes in early-onset PE suggests that this type represents a more severe manifestation of the condition compared to late-onset PE, thus requiring particular attention[3,4]. Impacts of PE on the fetus include intrauterine growth restriction, lower birth weight, stillbirth, preterm birth, and its associated complications[5]. Maternal complications vary among individuals because of variability in organ involvement during PE. Hypertension, liver failure, renal failure, cardiomyopathy, coronary artery disease, pulmonary edema, diabetes mellitus, and stroke are some maternal outcomes of PE. Despite the advancement of our knowledge in the field of PE, Considerable progress has still not been made in the clinical context to address our challenges in exposure to PE[6,7].

Findings including the predisposition to PE in certain molar pregnancies (where no fetus is present), along with the resolution of PE-related symptoms after childbirth, indicate that the placenta has a central role in the PE pathogenesis[8]. In contrast to late-onset PE, the underlying pathophysiology of early-onset PE is more closely related to abnormalities during placental development[9]. In normal placentation, the remodeling of maternal myometrial and decidual spiral arteries plays a pivotal role in providing sufficient uteroplacental blood flow[10]. Interstitial and endovascular extravillous trophoblasts invasion and migration to decidua of the uterus, drive spiral artery remodeling by influencing vascular smooth muscle cells (VSMCs) and endothelial cells, respectively[11]. Shallow invasion of the spiral arteries following defective placentation causes poor placental perfusion. In response to hypoxic conditions, an imbalance of angiogenic factors occurs, and proinflammatory cytokines and reactive oxygen species are released into the maternal bloodstream. These substances are key contributors to the pathogenesis of PE[12].

Non-coding ribonucleic acids (ncRNAs) are functional RNA transcripts that lack protein-coding capacity. They are divided into two subgroups: structural and regulatory. Regulatory noncoding RNAs consisting of <200 nucleotide (nt) are considered small non-coding RNAs (sncRNAs), and those with more than 200 nt are called long ncRNAs (lncRNAs) [13]. LncRNAs influence numerous biological and pathological processes within cells by modulating gene expression at various levels, including transcription and chromatin remodeling. multiple studies have demonstrated the key role of lncRNAs in the development of PE by modifying trophoblast biological behaviors, including proliferation, migration, invasion, and apoptosis[14,15]. Furthermore, using microarray and RNA-seq approaches has revealed dysregulation of lncRNAs within placental and decidual tissues from preeclamptic individuals compared to healthy controls[16,17].

Maternally expressed gene 3 (*MEG3*) is a tumor suppressor lncRNA from chromosome 14q32.2[18]. Yu et al.[19] have demonstrated lower expression of *MEG3* in placental tissue of PE compared to standard controls. In addition to, lower expression of *MEG3* decreased the migratory and invasive properties of human trophoblasts *in vitro* by attenuating the epithelial-mesenchymal transition (EMT) process. Although *MEG3* regulatory mechanism on EMT remains to be elucidated, a negative relationship between EMT and the transforming growth factor β (TGF-β)/Smad pathway has been documented upon *MEG3* dysregulation. On the other hand, it has been suggested that downregulating *MEG3* by inhibiting the Notch1 signaling pathway diminishes EMT process in trophoblasts and subsequently leads to PE as a possible mechanism of action[20]. The effects of *MEG3* in placentation are not limited to trophoblasts. On the maternal side, initiation of spiral artery remodeling requires proliferation arrest of VSMCs, induction of apoptosis, and enhanced migration of these cells. Upregulation of *MEG3* induced by factors released from uterine natural killer cells facilitates these essential alterations of VSMCs in the maternal spiral arteries of the uterus[21,22].

Regarding the significance of *MEG3* in healthy placentation, this study aimed to evaluate the involvement of the *MEG3* rs4081134 gene polymorphism in PE susceptibility.

Materials and Methods

Participants Data

We conducted a case-control study comprising 130 PE patients and 140 healthy pregnant women. All participants were recruited from among pregnant women seeking prenatal

care at the obstetrics clinic of Ali-ebn Abitaleb Hospital, which is affiliated with Zahedan University of Medical Sciences in Iran. Patients in the case group were determined to have PE according to diagnostic criteria which was defined as unprecedented systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg measured twice separately. Additionally, protein excretion in urine higher than 300 mg in a 24-hour urine specimen was present in all patients after 20 weeks of pregnancy. All participants with diabetes, gestational diabetes, chronic hypertension, chronic kidney disease, cardiovascular disease, hyperthyroidism, or who smoked were excluded from the study. All participants provided written informed consent, and the study protocol received approval from the Ethics Committee of Zahedan University of Medical Sciences (approval number: IR.ZAUMS.REC.1399.239, date: 09.08.2020).

Genotyping

After drawing blood samples from all participants, the samples were stored in K2-EDTA-containing tubes. Peripheral leukocyte deoxyribonucleic acid (DNA) was extracted from 500 µL of blood using the salting-out method and stored at -20 °C until further use. The forward primer (5ı-TTTCTTGTAGCTGCCTCCTCC-3ı) and the reverse primer (5ı-CGTCTGTTGGCTGTGAGTGAATGA-3ı) were used to amplify the desired gene fragment by polymerase chain reaction (PCR). The PCR mixture consisted of 7.5 µL master mix Red 2x, 0.82 forward primers, 0.82 reverse primer, 4.86 µL H_2O, and one µL of DNA. The PCR program was set for 40 cycles, with denaturation at 95 °C for 30 seconds, annealing at 65 °C for 40 seconds, and extension at 72 °C for 35 seconds. 2.7 µL H_2O, 0.3 µL Ndel enzyme, and one µL H_2O were added to 6 µL of PCR product for *MEG3* rs4081134 genotypic determination[23]. After overnight incubation at 37 °C, the microtube contents were separated by gel electrophoresis.

Statistical Analysis

Statistical analysis was performed using SPSS Statistics version 26.0 (SPSS Inc., Chicago, IL, USA). The independent-samples t-test was used to compare demographic and clinical characteristics between the two groups. For women with PE versus healthy controls, odds ratios with 95% confidence intervals were computed for various genotypes, genetic models, and alleles. furthermore, chi-square test and one-way analysis of variance were used to compare PE clinical characteristics in different genotypes of case group. Results with p-values were defined as statistically significant.

Results

Demographic and Clinical Characteristics of PE Patients and Controls

Table 1 demonstrates the demographic and clinical characteristics of the two groups. All precipitants were matched respect to the maternal age (26.7±5.6 and 27.75±6.65 in the control and PE groups, respectively, p=0.164). Significant differences were found between the two groups in birth weight, systolic blood pressure, and diastolic blood pressure. The frequencies of mild and severe PE were 52.3% and 47.7%, respectively. Moreover, 55.4% of participants had early-onset PE, while 44.6% had late-onset PE.

The Correlation Between *MEG3* rs4081134 Gene Polymorphism and PE Susceptibility

As shown in Table 2, the genotype frequencies for GG, GA, and AA were 61.6%, 36.9%, and 1.5% in the PE group and 57.1%, 35.8%, and 7.1% in the control group. A significant association with PE risk was found for both the AA genotype and the recessive model, indicating that they may be protective against the development of PE. Other genotypes, genetic models, and allelic distributions were not significantly associated with PE risk.

Relationship of The Clinical and Demographic Characteristics of PE Patients with *MEG3* rs4081134 Gene Polymorphism

The average maternal age [mean ± standard deviation (SD), years] for the GG, GA and AA genotypes was 28.53±6.78, 26.64±6.4 and 23±5.65, sequentially, which was not statistically significant (p=0.180). The average gestation age (mean ± SD, weeks) for GG, GA and AA genotypes was 36.10±3.61, 35.48±3.91 and 36±2.82, respectively, which was not statistically significant (p=0.66). A significant relationship was found between birth weight (mean ± SD, grams) and the *MEG3* rs4081134 gene polymorphism (p=0.043). The average birth weight for GG, GA and AA genotypes was 2879.38±628.18, 2576.04±817.15 and 3225±318.19, respectively. Moreover, there was no significant correlation between the *MEG3* rs4081134 polymorphism and other clinical characteristics in patients with PE (Table 3).

Discussion

Prior research has supported the involvement of lncRNAs such as *MEG3* in the pathogenesis of PE. Through alternative splicing, various isoforms of *MEG3* are generated. To date, 12 isoforms of *MEG3* have been described. Among them, *MEG3* has been well-reputed[24]. Based on information extracted from GenBank, this isoform contains exons 1-4 and 8-10. The studies have not identified any functional open reading frame (ORF) in the *MEG3* isoforms. The functional studies of ORFs revealed that one ORF does not mediate the functions of *MEG3* . In other words, the whole-length sequence of *MEG3* is needed for essential functions of this ncRNA[25]. Gene expression profiling of *MEG3*-knockdown mice revealed increased expression of genes that contribute to angiogenesis, including vascular endothelial growth factor alpha and its receptor. Angiogenesis is a pivotal step in tumor growth. Therefore, it seems that *MEG3* is involved in procedures that contribute to tumor suppression[24]. *MEG3* interacts with

some targets, through which multiple genes involved in the TGF-β pathway are regulated[26]. The decreased or lost level of *MEG3* was associated with some cancers including pituitary adenomas and meningioma[27,28]. The studies showed that *MEG3* is likely to regulate the p53 protein in different ways. For example, the *MEG3* could block MDM2 transcription, leading to inhibiting the degradation of p53[29]. While many studies confirmed the tumor suppressor role of *MEG3*, primarily through activation and accumulation of p53, there is evidence of an association between knockdown *MEG3* and activation of p53 and metastasis[30].

MEG3 is a key participant in several cancer-related signaling pathways, including Wnt, PI3k/Akt/mTOR, WT1, and TGF-β. Additionally, the serum level of *MEG3*, as well as several single-nucleotide polymorphisms in this ncRNA, serves as a biomarker for specific cancers[31,32]. *MEG3* contributes to the response of cancer cells to chemotherapy agents. An expression study on non-small cell lung carcinoma demonstrated an association between reduced *MEG3* levels and unfavorable responses to cisplatin treatment. In addition, *MEG3* improved the sensitivity of chemotherapy drug response in correlation with miR-21-5p[33].

Bone morphogenetic protein (BMP) and its receptors, *BMPR1* and *BMPR2*, form a tetrameric structure that triggers specific signal cascades. BMP signals through *BMPRs* induce several alterations that are assumed to result in cell proliferation, differentiation, and metastasis[34]. The evidence shows that *BMPR2* is involved in embryonic development and angiogenesis and appears to be correlated with hypertension. The study by Andruska et al.[35] showed a link between *BMPR2* gene mutations and pulmonary hypertension. The expression profile of the placental tissue of PE women showed an increase in miR-21 expression[36,37]. Overexpression of miR-21 inhibitors induced proliferation and invasion of trophoblast cells. These results are consistent with the findings from in silico analysis, which confirmed *BMPR2* as a key direct target of miR-21. Furthermore, *MEG3* has decreased in the placentas of PE participants. Based on bioinformatics results, *MEG3* acts as a molecular sponge that regulates miR-21. Therefore, it is not surprising that the downregulation of *MEG3* led to increased miR-21 expression in women with PE. Conclusively, *MEG3* , acting as a sponge for miR-21, regulates the expression of *BMPR2* and thereby improves trophoblast proliferation. Therefore, *MEG3* is involved in a regulatory mechanism that prevents premature ejaculation (PE)[38]. These do not bear on the *MEG3* effects in the pathogenesis of PE. It is suggested that *MEG3* is involved in metastasis by expression regulation of elements that contribute to the metastasis process, including nuclear factor kappa B, caspase, and Bax[39]. The documents showed that *MEG3* blocked cell proliferation by targeting Notch1 in endometrial carcinoma cells. In addition, Notch1 downregulation in PE promotes

Table 1. Demographic and clinical characteristics of preeclampsia patients and controls

Variable	Controls	PE	p-value
Maternal age (mean ± SD, years)	26.7±5.6	27.75±6.6	0.164
Gestation age (mean ± SD, weeks)	38.56±1.4	35.87±3.7	<0.0001
Birth weight (mean ± SD, g)	3131.93±396.4	2772.69±714.5	<0.0001
SBP (mean ± SD, mmHg)	108.31±8	152.91±16.3	<0.0001
DBP (mean ± SD, mmHg)	69.82±8	88.62±22.7	<0.0001
Proteinuria (n, %)			
Trace	-	11 (8.5%)	
1+	-	43 (33.1%)	
2+	-	35 (26.9%)	
3+	-	35 (26.9%)	
4+	-	6 (4.6%)	
Severity			
Mild		68 (52.3%)	
Severe		62 (47.7%)	
Onset			
Early-onset		72 (55.4%)	
Late-onset		58 (44.6%)	

PE: Preeclampsia, SD: Standard deviation, SBP: Systolic blood pressure, DBP: Diastolic blood pressure

trophoblast cell apoptosis. Consistent with these findings, the evaluation of the expression of *MEG3* and Notch1 showed decreased levels in PE subjects compared with their regular counterparts, promoting apoptotic processes. On the other hand, *MEG3* enhancement showed the opposite effect and promotes cell proliferation and inhibits cell apoptosis[20].

In the present study, we evaluated the association between the *MEG3* rs4081134 variant and PE risk in an Iranian population. according to the results, we did not observe a statistically significant correlation between the allelic frequency of rs4081134 and the risk of PE in our sample, likely due to the small sample size.

Table 2. The genotypic and allelic distribution of *MEG3* rs4081134 gene polymorphism in PE and control

	PE, n (%)	Control, n (%)	p-value	OR (95% CI)
***MEG3* rs4081134**				
GG	80 (61.6)	80 (57.1)		1
GA	48 (36.9)	50 (35.8)	0. 874	0.96 (0.58-1.58)
AA	2 (1.5)	10 (7.1)	0.026	0.2 (0.04-0.94)
Dominant (GA + AA vs. GG)	50 (38.4) 80 (61.6)	60 (42.9) 80 (57.1)	0.463	0.83 (0.51-1.36)
Recessive (AA vs. GG + GA)	2 (1.5) 128 (98.5)	10 (7.1) 130 (92.9)	0.026	0.2 (0.44-0.94)
Over dominant (GA vs. GG+AA)	48 (36.9) 82 (63.1)	50 (35.8) 90 (64.2)	0.836	1.05 (0.64-1.73)
Allele				
G	208 (80%)	210 (75%)		1
A	52 (20%)	70 (25%)	0.181	0.75 (0.49-1.12)

PE: Preeclampsia, OR: Odds ratio, CI: Confidence interval, *MEG3*: Maternally expressed gene 3

Table 3. Association between clinical characteristics of PE patients and *MEG3* rs4081134 gene polymorphism

Variable	GG	GA	AA	p-value
Maternal age (mean ± SD, years)	28.53±6.78	26.64±6.4	23±5.65	0.180
Gestation age (mean ± SD, weeks)	36.10±3.61	35.48± 3.91	36±2.82	0.660
Birth weight (mean ± SD, g)	2879.38±628.18	2576.04±817.15	3225±318.19	0.043
SBP (mean ± SD, mmHg)	152.56±16.05	152.98±17.15	165±7.07	0.572
DBP (mean ± SD, mmHg)	87.40±24.87	89.97±19.12	105±7.07	0.491
Proteinuria (n, %)				
Trace	8 (10%)	3 (6.3%)	0	0.249
1+	26 (32.5%)	17 (35.4%)	0	
2+	20 (25%)	15 (31.3%)	0	
3+	20 (25%)	13 (27%)	2 (100%)	
4+	6 (7.5%)	0	0	
Severity				
Mild (n, %)	42 (52.5%)	26 (54.2%)	0	0.323
Severe (n, %)	38 (47.5%)	22 (45.8%)	2 (100%)	
Onset				
Early-onset (n, %)	42 (52.5%)	29 (60.4%)	1 (50%)	0.675
Late-onset (n, %)	38 (47.5%)	19 (39.6%)	1 (50%)	

SD: Standard deviation, PE: Preeclampsia, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, *MEG3*: Maternally expressed gene 3

To our knowledge, this study is the first to investigate whether *MEG3* rs4081134 is associated with the risk of PE. previous studies have evaluated the association of *MEG3* rs4081134 and the risk of some tumors, including papillary thyroid carcinoma[40], neuroblastom[41], and lung cancer[42].

Study Limitations

In the current study, we faced several challenges, including the small size of the study population and technical limitations. It is recommended that future work evaluate the expression levels of *MEG3* and its downstream targets, such as miR-21 or *FOXM1*, as key participants in the proliferation of placental cells.

Conclusion

We found a significant relationship between the AA genotype of the *MEG3* rs4081134 polymorphism and the risk of PE development. Furthermore, there *MEG3* rs4081134 gene polymorphism showed a significant relationship with newborn's birth weight in patients with PE.

Ethics

Ethics Committee Approval: The study protocol received approval from the Ethics Committee of Zahedan University of Medical Sciences (approval number: IR.ZAUMS.REC.1399.239, date: 09.08.2020).
Informed Consent: All participants provided written informed consent.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.S., H.D., M.N., H.S.G., M.G., M.Z., M.S., Concept: S.S., H.D., M.N., H.S.G., M.G., M.Z., M.S., Design: S.S., H.D., M.N., H.S.G., M.G., M.Z., M.S., Data Collection or Processing: S.S., H.D., M.N., H.S.G., M.G., M.Z., M.S., Analysis or Interpretation: Literature Search: S.S., H.D., M.N., H.S.G., M.G., M.Z., M.S., Writing: S.S., H.D., M.N., H.S.G., M.G., M.Z., M.S.
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