

# Alterations in complement and coagulation pathways of human placentae subjected to in vitro fertilization and embryo transfer in the first trimester

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# Abstract

The mechanisms underlying the potential risks of in vitro fertilization and embryo transfer (IVF-ET) have not been fully elucidated. The aim of this study was to explore changes in the complement and coagulation pathways in placentae subjected to IVF-ET in the first trimester compared to placentae from normal pregnancies. Four placenta samples in the first trimester were obtained from patients undergoing IVF-ET owing to oviductal factors only. An additional 4 control placentae were obtained from volunteers with normal pregnancies. A GeneChip Affymetrix HG-U133 Plus 2.0 Array was utilized to analyze the changes in gene expression between the normal and IVF-ET placentae. Differentially expressed genes (DEGs) were analyzed using the Database for Annotation and Visualization and Integrated Discovery bioinformatics resource, and gene ontology enrichment analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis were conducted. Using real-time PCR, we confirmed the obtained microarray data in 10 dysregulated genes. Five of the gene products were further analyzed by immunohistochemistry (IHC) to determine their protein expression and localization. A total of fifty DEGs were identified in the complement and coagulation pathways in the IVF-ET treated placentae: 38 upregulated and 12 down-regulated. KEGG pathway analysis indicated that IVF-ET manipulation substantially overactivated the coagulation and complement pathways, while urokinase plasminogen activator- and urokinase plasminogen activator receptor-mediated trophoblastic invasion and tissue remodeling were inhibited. Furthermore, the 5 proteins analyzed by IHC were found to be localized specifically to the placenta. This is the first study to compare DEGs relating to the placental complement and coagulation pathways from patients undergoing IVF-ET treatment compared to those undergoing normal pregnancy. These findings identified valuable biomarkers and potential novel therapeutic targets to combat the unfavorable effects of IVF-ET.

**Abbreviations:** CD59 = CD59 molecule complement regulatory protein, CFD = complement factor D (adipsin), DAVID = Database for Annotation, Visualization and Integrated Discovery, DEG = differentially expressed gene, FGA = fibrinogen alpha chain, FGB = fibrinogen beta chain, FGG = fibrinogen gamma chain, GCOS = gene chip operating software, GEO = Gene Expression Omnibus, GO = gene ontology, IHC = immunohistochemistry, IVF-ET = in vitro fertilization and embryo transfer, PLAU = plasminogen activator urokinase, PLAUR = plasminogen activator urokinase receptor, PROC = protein C, qRT-PCR = quantitative real-time PCR, SERPINC1 = serpin peptidase inhibitor clade C member 1, SERPINE1 = serpin peptidase inhibitor clade E member 1, STRING = search tool for the retrieval of interacting genes, uPA = urokinase plasminogen activator, uPAR = urokinase plasminogen activator receptor.

Keywords: complement and coagulation pathways, first trimester, in vitro fertilization and embryo transfer (IVF-ET), placenta, pregnancy complication

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## 1. Introduction

Therapeutic strategies against infertility caused by various etiological factors have improved greatly in recent years, particularly in vitro fertilization and embryo transfer (IVF-ET).<sup>[1]</sup> However, even after adjusting for several confounding factors, the risk of adverse outcomes during the perinatal period, including miscarriage, premature birth, low birth weight, intrauterine growth retardation, and gestational hypertension, have been reported to be higher in IVF-ET cohorts than in subjects with spontaneous pregnancies.<sup>[2,3]</sup> In recent years, the early stages of mammalian embryonic development have been found to be very sensitive to their microenvironment, with long-term effects on fetal, postnatal, and adult health.<sup>[4,5]</sup> The concept of the developmental origins of health and disease, based on accumulating evidence that prenatal exposure to modified environmental conditions affects postnatal growth, metabolism, and disease susceptibility in adulthood, has been extended to the preimplantation stages of development.<sup>[6]</sup>

Recently, increasing research has shown that placental tissues are more sensitive than embryonic tissues to the preimplantation epigenetic dysregulation of imprinted genes.<sup>[7,8]</sup> This can lead to abnormal placental development and function with possible consequences for the developing fetus. Based on this observation, subsequent studies have proposed 2 possible scenarios to explain why these defects appeared to be restricted to the trophectoderm lineage.<sup>[9,10]</sup> On one hand, trophectoderm cells, which are in contact with the culture medium, are more strongly influenced by in vitro culture, which is responsible for a loss of imprinting in midgestation placenta.<sup>[11]</sup> On the other hand, they are also the first lineage to differentiate in the embryo as trophectoderm stem cells, from which the different cell lines in the future placenta will originate.<sup>[12]</sup> In addition to the fact that the composition of culture media differs from that of the in vivo natural environment, and despite careful manipulation, in vitro cultured trophectoderm cells are vulnerable to several environmental stressors, such as oxygen tension, pH and temperature variations during manipulation, light exposure, and shear stress linked to repeated pipetting, which may affect placental development and function.<sup>[13]</sup>

Increasing evidence supports the hypothesis that some adverse pregnancy outcomes observed after IVF-ET are due to suboptimal placenta function caused by abnormal trophoblastic invasion.<sup>[14]</sup> Notably, trophectoderm cells from blastocysts cultured in vitro showed major changes in gene expression, including the activation of stress-related pathways and the down-regulation of genes involved in placentation.<sup>[15]</sup> Furthermore, in human placentas after IVF-ET, genome-wide mRNA expression analysis identified the overexpression of genes involved in metabolism, immune response, transmembrane signaling, and cell cycle control.<sup>[16]</sup> Similarly, transcriptome data in mouse placental tissues showed that some IVF techniques may trigger the induction of genes involved in cellular proliferation and cell cycle progression.<sup>[17]</sup>

The complement and coagulation systems are 2 evolutionarily conserved and closelt related proteolytic cascades in plasma that play important roles in host defense and hemostasis, respective-ly.<sup>[18]</sup> Complement and coagulation proteins circulate in the blood as inactive precursors, but are activated upon contact with target structures. The resulting proteolytic cascade generates multiple protein cleavage products that trigger numerous events leading to the onset of inflammation and hemostasis.<sup>[19]</sup> The parallel expression of activation products for the complement

and coagulation systems has long been observed in both clinical and experimental settings. The coexistence and interplay of hemostatic and inflammatory mediators in the same microenvironment typically ensures a successful balance in the hemostatic system, leading to a state of hypercoagulability during normal pregnancy.<sup>[20]</sup> However, the dysregulation of this cascade or the presence of inhibitors in one or both systems can lead to obstetric complications with critical thrombotic and/or inflammatory complications.<sup>[21,22]</sup>

In the present study, we hypothesized that the expression of genes relating to the complement and coagulation pathways is altered in placental tissue during the first trimester after IVF-ET compared to that in placental tissue from spontaneous pregnancies. Therefore, we performed a microarray analysis to investigate and discover the potential effects of IVF-ET treatment on placental gene expression relating to the complement and coagulation pathways during early stages. The aim of this study was to explore the possible causal relationship between IVF-ET and the increased frequency of adverse pregnancy outcomes. Furthermore, an improved understanding of placental mechanisms triggered by IVF-ET may be of value in future to improve the safety of IVF-ET protocols.

# 2. Methods

#### 2.1. Study subjects

Between January 2017 and October 2018, twin to singleton fetal reduction was performed in 4 cases at a mean of  $49 \pm 6$  days into pregnancy after IVF-ET treatment (age range: 23-35 years; mean age: 30.7 years). All patients were undergoing IVF-ET due to oviductal obstructions. The quality of each male sperm was confirmed to be normal. The clinical application of assisted reproductive technology (ART) was licensed by the Ministry of Health of the People's Republic of China. The control group comprised 4 cases of unwanted twin pregnancies in the same period (age range: 24-30 years; mean age: 28.9 years). Clinical data were collected by the Department of Obstetrics and Gynecology at Beijing Jishuitan Hospital and organized in a database. The sample size of 4 for the microarrays, which is the minimal number required for statistical validity, was determined based on the availability of samples meeting the study's diagnostic criteria. Each of the 4 placental specimens from the IVF-ET group was matched to a control sample based on maternal age, and gestational age.

#### 2.2. Sample collection and ethics approval

All fetal reductions were performed by the same senior physician through fetal bud aspiration under B ultrasound guidance. Four cases were selected for villi suction at the same time. Tissues were collected 30 to 45 days after embryo transfer, which is equivalent to 45 to 50 days of pregnancy. Patients in the control group were diagnosed with early intrauterine pregnancy after a bimanual examination, urine pregnancy test, and B ultrasound. All the patients had regular menstruation cycles and had not taken any steroid hormone drugs in the previous 3 months. Villi were obtained during the conventional artificial abortion operation. The villi samples were immediately separated from the specimens within 1 hour under an inverted microscope. All samples were then suspended in ice-cold PBS and subsequently stored in liquid nitrogen until total RNA extraction. A section of the remaining specimen was immersed in 4% formalin for 24 hours and then removed and rinsed under running water for 30 minutes. The villi were then subjected to routine dehydration, wax dipping, embedding, and slicing. One slice was obtained via 2-step immunohistochemical PV-9000. The study design was approved by the Ethics Committee of Beijing Jishuitan Hospital, China (Permission no 201703-11). Written informed consent to participate in this study was obtained from each individual prior to recruitment. All study participants were recruited at the Beijing Jishuitan Hospital Beijing 2017 to 2018, and were of Asian ancestry and living in Beijing.

#### 2.3. RNA extraction

Tissue homogenization and RNA extraction, as well as microarray analysis (described below), were performed by CapitalBio Corporation (Bejing, China). Tissue homogenization total RNA extraction were performed using the Macherey–Nagel Nucleo-Spin RNA II kit (Macherey–Nagel, Duren, Germany) according to the manufacturer's instructions. The RNA, extracted with ribosomal 28S and 18S RNA with a ratio of intensities of 1.5 to 1.8:1, was used for both the microarray assay and quantitative real-time PCR (qRT-PCR).

### 2.4. Microarray analysis

To compare the differentially expressed genes (DEGs) between the 2 groups, an aliquot ( $2 \mu g$ ) of total placental RNA was used to synthesize cDNA, which was subsequently transcribed to biotintagged cRNA using the MessageAmp II aRNA Amplification Kit (Ambion Inc., Carlsbad, CA). The cRNA was then fragmented to produce 35 to 200-nt strands in accordance with the manufacturer's protocols (Affymetrix, Santa Clara, CA). Microarray analysis was performed using the Affymetrix Human Genome U 133 plus 2.0 GeneChip (about 54,675 probes covering more than 32,228 transcripts and variants, representing more than 20,000 genes mapped through UniGene or via RefSeq annotations) following the manufacturer's instructions. After purification and washing, samples were incubated at 94°C for 35 minutes to fragment the RNA, followed by incubation and hybridization of the labelled amplified RNA at 45°C for 16 hours.

The arrays were washed and stained with streptavidinphycoerythrin in an Affymetrix GeneChipFluidics Station 450, and subsequently scanned on an Affymetrix GeneChip Scanner 3000 to analyze the hybridization data. The scanned images obtained were first assessed by visual inspection and then analyzed by Affymetrix GeneChip Operating Software (GCOS, v 1.4). To normalize the different arrays, dChip software was used with global scaling. For the comparative analysis, a 2-class, unpaired method developed in Significance Analysis of Microarrays software (SAM, v 3.02; Stanford University, Stanford, CA) was used to compare significantly DEGs in the IVF-ET and natural pregnancy groups.

#### 2.5. Gene expression data analysis

The microarray data of analyzed placental samples are MIAME compliant, and the raw datasets were deposited in the Gene Expression Omnibus (GEO) data repository (n=8, accession no. GSE 122214). Gene expression between IVF-ET and natural pregnancy placentas was compared and defined statistically by analysis of variance with a false discovery rate of 1%. Genes

showing a fold change of > 2 and P < .01 were considered to be differentially expressed. Fisher exact test (P < .05) was used for canonical pathway analysis. To assess the function of identified DEGs, the functional analysis and clustering tool from the Database for Annotation, Visualization and Integrated Discovery (DAVID) resource was used, as it provides a comprehensive set of functional annotation tools for investigators to understand the biological significance of a large list of genes (http://david.ncifcrf. gov). Bioinformatics tools, including DAVID v 6.7, were used to perform gene ontology (GO) functional enrichment analysis and annotation of the identified DEGs. DAVID was used to search a block of functionally related genes according to different criteria, such as GO terms for biological process, cellular component, and molecular function. The Kyoto Encyclopedia of Genes and Genomes (KEGG) Orthology-Based Annotation System (KOBAS 2.0) (http://kobas.cbi.pku.cn) was employed to identify enriched KEGG pathways based on an adjusted P value. Search tool for the retrieval of interacting genes (STRING) software was used to draw the genetic interaction network (https://string-db.org/).

#### 2.6. Microarray validation by real-time PCR

To validate the microarray results, 500 ng of the same RNA samples were reverse-transcribed using the PrimeScript RT reagent Kit (Perfect Real Time) (TaKaRa Biotechnology [Dalian] Co., Ltd., Dalian, China). Amplification reactions were conducted using SYBR Premix Ex Taq (Perfect Real Time) (TaKaRa Biotechnology [Dalian] Co., Ltd.) with an ABI PRISM 7300 system. Transcripts encoding fibrinogen beta chain (FGB), fibrinogen alpha chain (FGA), fibrinogen gamma chain (FGG), serpin peptidase inhibitor, clade C (antithrombin), member 1 (SERPINC1), protein C (inactivator of coagulation factors Va and VIIIa) (PROC), plasminogen activator urokinase (PLAU), plasminogen activator urokinase receptor (PLAUR), serpin peptidase inhibitor, clade E (nexin, plasminogen activator inhibitor type 1), member 1 (SERPINE1), CD59, and complement factor D (adipsin) (CFD) were used for microarray validation. The primers used for qRT-PCR are listed in Supplementary Table S1, http://links.lww.com/MD/D329. qRT-PCR was conducted on the above 10 genes that were found to be differentially expressed based on microarray analysis; furthermore, their functions were considered to be closely related to critical placental functions based on biological function analysis. The same RNA samples were used as those extracted from placental samples. The analysis of differences in gene expression between the study groups was performed using the Mann-Whitney U test. A value of P < .05 were considered statistically significant.

#### 2.7. Immunohistochemistry

To improve our understanding of the functions of these confirmed DEGs in controlling the complement and coagulation pathways in placenta in the IVF-ET and control groups, immunohistochemistry (IHC) was performed to analyze the activity of the related proteins using 4- $\mu$ m sliced placental paraffin sections. The placental tissue samples used for IHC staining originated from the same tissue block as those collected for RNA extraction. The following primary antibodies were used for IHC: FGB (ab232793), FGG (ab217783), SERPINC1 (ab126598), PLAU (ab133563), and PLAUR (ab82220, Abcam, Cambridge, UK). Formalin-fixed, paraffin-embedded placental

# Table 1

Characteristics of the patients in the 2 groups.							
	n	Mean age	Gestational age (day)	Gravidity	BMI (kg/m²)		
IVF-ET group	4	$30.66 \pm 3.76$	$49.44 \pm 3.14$	$1.10 \pm 1.21$	23.33±3.17		
Control group	4	$28.86 \pm 3.45$	49.35±3.23	$2.21 \pm 0.89$	22.99±2.35		
t value		0.833	0.637	0.858	1.311		
P value		.425	.529	.437	.263		

BMI = body mass index.





Table 2

### Genes differentially expressed in placenta derived from IVF-ET treatment.

Ensembl     Symbol     Gene Title     Location     Charlow       DeS00000171664     FIB     Fibringen bate chain     chr/4p3     2.3822       PES00000171664     FIB     Complement 1, subcomponent 1, subcomponent 1, chr/2p13     2.3822       PES000001764544     FIB     chr/4p3     2.3822       PES00000176454     FIB     chr/4p3     2.3822       PES00000176454     FIB     chr/4p3     2.3822       PES0000176454     FIB     chr/4p3     2.3864       PES0000176454     FIB     Complement factor 1     chr/4p3     2.3864       PES0000176245     C15     Complement factor 1     chr/4p3     2.3864       PES00000178768     CRB     Complement foorporent 1, subcomporent 2, subcomporent 2, chr/1s     chr/1g3     5.7355       PES00000178768     C10C     Complement comporent 1, subcomporent 2, chr/1s     chr/1g3     5.7355       PES00000178768     C10C     Complement comporent 1, subcomporent 2, chr/1s     chr/1g4     12.441       PES00000179788     C10C     Complement comporent 1, subcomporent 2, chr/1s     chr/1g4     12.441	Gene			Chromosomal	Fold
ENSIGUOD171644     FBB     Entingen     Extra component     chr4g28     C44.925       ENSIGUOD171560     FGA     Thiringen alpha chain     chr4g28     37.1852       ENSIGUOD1715715     PRIC     Protein C (machiteatri d'autora Va and Villa)     chr4g28     37.1852       ENSIGUOD01715715     PRIC     Protein C (machiteatri d'autora Va and Villa)     chr4g25     2.3662       ENSIGUOD0122543     CFI     Complement factor 1     chr4g25     2.3669       ENSIGU000122543     C13     Complement factor 1     chr4g21     3.3847       ENSIGU000122542     C13     Complement factor 1     chr4g26     chr1g21     3.3847       ENSIGU000122542     C13     Complement factor 11, subcomponent 1, subcompon	Ensembl	Symbol	Gene Title	Location	Change
BNB600001159403     C1R     Complement component 1, r subcomponent     chr12n13     2,2822       DNB60000115716     PR0C     Protein C functivisor of cospulation Factors Vai of Villaj     chr2n13     9,3116       DNB600000115718     PR0C     Protein C functivisor of cospulation factors Vai of Villaj     chr2n13     9,3116       DNB600000123243     CR     Complement factor 1     chr3n13     chr3n13     1,30984       DNB600000123243     CR     Complement factor 1     chr3n14     11264.463       DNB600000123243     CAPPB     Complement component 1, s subcomponent 4     chr3n14     11264.463       DNB600000123243     CAPPB     Complement component 1, g subcomponent 4     chr3n14     11264.463       DNB600001723243     CAPPB     Complement component 1, g subcomponent 4     chr3n14     11264.463       DNB600000172345     C108     Complement component 1, g subcomponent 4     chr3n12     8.466       DNB600000172345     C108     Complement component 1, g subcomponent 4     chr3n24     6.5749       DNB600000172345     C108     Complement component 1, g subcomponent 4     chr3n12     8.466       DNB600	ENSG00000171564	FGB	Fibrinogen beta chain	chr4a28	644.9783
ENEGROQUOT7560     FGA     Entringen palka chain     ont-data     ont-dat	ENSG00000159403	C1R	Complement component 1. r subcomponent	chr12p13	2.3822
ENS00000115718     PROC     Protein C     Consideration Technological Consignment Cators 1     chr2q13     9.3116       ENS00000115718     Complement factor 1     chr2q35     C.3098       ENS00000128236     C1S     Complement factor 1     chr2q13     S.7325       ENS00000128236     C1S     Complement component 1, subcomponent     chr12p13     S.7325       ENS00000128243     CAIPPS     Complement component 4, fing subcomponent, g. subcomponen	ENSG00000171560	FGA	Fibrinogen alpha chain	chr4a28	371.6853
ENSCO0000164344     KUK81     Kulliveria P, Isternia (Perchan Factor) 1     chr/q55     2.808       ENSCO0000278228     C15     Complement Longtonent 1, s subcomponent     chr/q57     3.0984       ENSCO0000278228     C15     Complement component 1, s subcomponent     chr/q57     3.0984       ENSCO0000127243     CHEP2     Caboxyperdates ES     p.obleptide     chr1g31     5.7325       ENSCO0000127247     F138     Complement component 1, q subcomponent, C chain     chr1g31     2.3747       ENSCO0000173289     C108     Complement component 1, q subcomponent, C chain     chr1g31     2.3767       ENSCO000017389     C108     Complement component 1, q subcomponent, C chain     chr1g31     2.3787       ENSCO000017801     Serpin peptidase inhibitor, clabe C (pathibiton hartor XI)     chr1g33     101.525.5118       ENSCO000017801     SERPINCI     Serpin peptidase inhibitor, clabe C (pathibiton hartor X)     chr1g33     112.55.5118       ENSCO000017827     F10     Sorpin peptidase inhibitor, clabe C (pathibiton hartor X)     chr1g33     112.55.5118       ENSCO000017827     F10     Sorpin peptidase inhibitor, clabe C (pathibiton hartor X)     chr1g31	ENSG00000115718	PROC	Protein C (inactivator of coagulation Eactors Va and VIIIa)	chr2a13	9.3116
ENSIDED/02/254/03     CF     Complement factor i     chr/dp2/1     3.0844       ENSIDED/07/01/98     F     Complement component 1, s. subcomponent     chr/dp2/1     3.0844       ENSIDED/07/01/98     F     Complement component 1, s. subcomponent     chr/dp1/1     12.8446       ENSIDED/07/01/98     Chr     Complement component 1, s. subcomponent, 1, s	ENSG00000164344	KI KB1	Kallikrein B plasma (Eletcher factor) 1	chr4q35	2,3608
ENSOD0001010     FP3     Cosaguistion factor N.     chr/d27.1     3.0084       ENSOD00018226     C1S     Complement component 1, subcomponent.     chr/301.1     126.492       ENSOD00012843     CHPB     Complement component 1, binding protein, beta     chr/301.1     124.146       ENSOD0001284278     F138     Cocaguistion factor XII, Bip objection     chr/108.1     2.43.476       ENSOD0001275389     C10B     Complement component 1, subcomponent, C chain     chr/108.1     2.9.476       ENSOD000127539     C10B     Complement component 1, subcomponent, C chain     chr/108.1     2.9.477       ENSOD000127630     PROS1     Complement component 3, beta polypetide     chr/108.1     2.9.477       ENSOD000127637     ESRPIMC1     Serpin peptidase inhibitor, clade C (antithromhin, member 1     chr/301.4     6.6379       ENSOD00012637     ESR     Complement component 6     chr/301.4     10.1463       ENSOD00012637     FG     Complement component 6     chr/301.4     10.1463       ENSOD000126387     FG     Complement component 6     chr/301.4     10.1463       ENSOD000017538     FT     Cosaguist	ENSG00000205403	CEL	Complement factor I	chr4q25	40 1378
NS600000 8226     C1S     Complement component 1, s subcomponent     chrl 2p.13     5.7325       PNS6000000866     CP82     Carboxypeuldase B2 (plasma)     chrl 2p.13     5.7325       PNS6000001232843     C4PPB     Complement component 1, b subcomponent, B chain     chrl 2p.13     2.8407       PNS600000132978     F138     Complement component 1, q subcomponent, B chain     chrl 2p.13     2.9787       PNS60000015819     C10C     Complement component 1, q subcomponent, C chain     chrl 2p.811     2.9787       PNS6000001582     C38     Complement component 1, b calubon, member 1     chrl 2p.31     2.9787       PNS60000012820     PPOD1     Serpin peptidase inhibitor, calce C (antihurchin), member 1     chrl 2p.31     2.052.51       PNS600000128275     SEPPIND1     Serpin peptidase inhibitor, calce C (antihurchin), member 1     chrl 2p.34     6.6379       PNS6000000128657     C6     Complement component 4, calubon protein 1     chrl 2p.34     6.6379       PNS60000012867     F0     Complement component 4, calubo protein 1     chrl 2p.12     1.01463       PNS60000012867     C6     Complement component 4, calubo protein 1     chrl 2p.13	ENSG00000200400	F9	Coaculation factor IX	chrXn27 1	3 0984
Excession 10.2.20     Complement component 1 is a succemponent     Ching 11, 11, 126, 452       ENGGO0000123847     C4EPB     Complement component 4 binding protein, beta     chr1g1, 11, 126, 452       ENGGO0000123847     F13B     Complement component, 1, a subcomponent, 6 chain     chr1g2, 13, 23, 2469       ENGGO0000123847     F13B     Complement component, 1, a subcomponent, 6 chain     chr1g3, 11, 22, 456       ENGGO0000123840     PROS1     Complement component, 8, beta polypeptide     chr1g3, 11, 22, 456       ENGGO000012582     CBB     Complement component, 8, beta polypeptide     chr1g3, 103, 5847       ENGGO00002582     F10     Cagulation tactx X     chr1g3, 11, 125, 5178       ENGGO0000126218     F10     Cagulation tactx X     chr1g3, 11, 125, 5178       ENGGO0000126218     F10     Cagulation tactx X     chr1g3, 11, 125, 5178       ENGGO0000126283     F14     Pleasmin agen achator, X     chr1g3, 11, 126, 156, 156       ENGGO0000126285     CLU     Cagulation factx X     chr1g3, 13, 103, 168, 148, 149, 122, 246, 158, 158, 158, 158, 158, 158, 158, 158	ENSG00000101301	C1S	Complement component 1 s subcomponent	chr12n13	5 7325
Endeductodo     Charles     Calados/penducto C	ENSCOOD00102320	010	Carbovypontidase R2 (plasma)	chr12q14 11	126 4642
Endocionol 2.05.3     Complement 2 Min. B polyspital     chrl p.2.     2.0.97       ENGOD0001 23:57     F138     Coaguitation factor 3 Min. B polyspitale     chrl p.3.     2.3.75       ENGOD0001 23:59     C102     Complement component 1, g subcomponent C, chain     chrl p.3.     2.9787       ENGOD000125:52     C88     Complement component 3, last polyspitale     chrl p.3.     6.6739       ENGOD000125:52     C88     Complement component 6, last polyspitale     chrl p.3.     6.6739       ENGOD000126:51     F10     Coaguitation factor X     chrl p.3.     chrl p.3.     6.6379       ENGOD000126:51     F10     Coaguitation factor X     chrl p.3.     chrl p.3.     6.6379       ENGOD00013:567     F6G     Complement component 6     chrl p.3.     chrl p.3.     chrl p.3.     chrl p.3.     4.10.7464     10.7426       ENGOD000013:567     F6G     Complement component 7.     state polyspitale     chrl p.3.     chrl p.3.     4.119.7254       ENGOD000015783     F7     Coaguitation factor 11 (thrombin) receptor     chrl p.3.     4.119.7254       ENGOD0000157503     C3     Complement comp	ENSC0000000000000000	CARDR	Complement compensat 4 hinding protein beta	chr1q22	2 20/17
Endocuo01422/6     F135     Complement component 1, g subcomponent, B chain     chr1p36.12     3.4769       ENSG0000173369     C102     Complement component 1, g subcomponent, B chain     chr1p36.11     2.9787       ENSG00000159189     C102     Complement component 1, g subcomponent, B chain     chr1p36.11     2.9787       ENSG0000017601     SERPINC1     Serpin peptidase inhibitor, cade 6 (antithromhi, member 1     chr13q14     8.486       ENSG0000017601     SERPINC1     Serpin peptidase inhibitor, cade 6 (antithromhi, member 1     chr3q11.2     8.486       ENSG0000017601     F10     Coaguitatin factor X     chr13q24     6.6379       ENSG0000013858     F10     Coaguitatin factor X     chr3q27     105.7426       ENSG00000176578     F6     Coaguitatin factor X     chr3q27     105.7426       ENSG00000175793     F7     Coaguitatin factor VII (serum protrionchin conversion accelerator)     chr13q34     10.8168       ENSG00000175731     G8A     Cornojement Component 3.     chr13q13.3     10.1275       ENSG00000175731     G8A     Complement component 3.     chr13q13.3     3.5395       ENSG00000167713	ENCC00000142070		Completient component 4 binding protein, beta	chi 1432	3.0047
ENCODUCT 73:39     C108     Complement component 1, et succemponent 2, etcl polypeptide     chr1p32, chr12, 2, 2,3787       ENSCODUCT 15:59     C10     Complement component 3, etcl polypeptide     chr1p32, chr12, 2,3787       ENSCODUCT 15:50     CRS     Camplement component 3, etcl polypeptide     chr1p32, chr12, 2,3787       ENSCODUCT 15:50     SERPINC1     Serpin peptidase inhibitor, clade 0 (hepant cofactr), member 1     chr1q32, chr324, chr3	ENSG00000170000	FI3D C10D	Coaguiation lactor XIII, B polypeptide	CIII 143 I	12.1410
ENECUDUOU 199199     CIUL     Complement component 1, q subcomponent 0, cet publication control particle     chr17p32     6.4718       ENSS00000015552     CB     Complement component 8, beta publication cator 0, member 1     chr17p32     6.4718       ENSS00000012620     PROS1     Protein 5 (alpha)     chr12p31     152.511       ENSS000000128218     F10     Coaguitation factor X     chr13p34     6.6379       ENSS000000128357     C6     Complement component 6     chr13p34     10.1483       ENSS000000124828     F10     Coaguitation factor X     chr13p34     10.1483       ENSS00000124368     PLAT     Plasminogen activator, tissue     chr6p12     12.0615       ENSS0000001745573     F7     Coaguitation factor XI (secure orthronic noversion accelerator)     chr4p324     419.7254       ENSS00000157530     F7     Coaguitation factor XI (thronbin) receptor-like 2     chr5q13     3.1891       ENSS000001672730     C3     Complement component 3     chr5q13     3.1891       ENSS000001672730     C3     Complement component 3     chr5q33     5.5395       ENSS00000016771     MRL2     Manna-bindi	ENSG00000173369	CIQB	Complement component 1, q subcomponent, B chain	CHE1p36.12	3.4769
ENSEQUOUD1218/2     CdB     Complement component 3, labta polypeptide     chr1p32     6.4718       ENSCOUDD014560     PROS1     Protein S (apha)     chr1q32     103.884       ENSCOUDD0145610     PROS1     Serpin peptidase inhibitor, cdade 0 (inpain ordacion, member 1     chr1q32     103.884       ENSCOUDD014561     F10     Coagulation factor X     chr13q34     6.6379       ENSCOUDD014581     F10     Coagulation factor X     chr13q34     6.6379       ENSCOUDD014588     FNG1     King1     chr3q27     105.7426       ENSCOUDD014588     F7     Coagulation factor VII (serum prothrombin conversion accelerator)     chr3q24     10.8186       ENSCOUDD015753     F7     Coagulation factor VII (serum prothrombin conversion accelerator)     chr3q24     10.8186       ENSCOUDD015730     C3     Complement component 3     chr1913.3     4.0571       ENSCOUDD015730     C3     Complement component 3.3     chr1913.3     4.0571       ENSCOUDD015730     C3     Complement component 3.3     chr193.3     5.5395       ENSCOUDD015730     F8     Coagulation factor II (thrombin) receptor like 2     <	ENSG00000159189	CIQU	Complement component I, q subcomponent, C chain	CNT1p36.11	2.9787
ENSGU00001764:00     PHOSI     Protein S (apina)     chr/sq11.2     8.486       ENSGU0000176701     SERPINC1     Serpin peptidase inhibitor, clade () (antifurmothin), member 1     chr12a3     103.5847       ENSGU0000176218     F10     Coagulation factor X     chr13q34     6.6379       ENSGU000013837     C6     Complement component 6     chr5q13     10.1463       ENSGU0000174568     PLAT     Plasminogen activator, fisuse     chr6q12     12.0615       ENSGU0000174557     F66     Fibrinopen garma chain     chr4q28     419.7254       ENSGU0000174585     CLU     Clasterin     chr6q13     3.1981       ENSGU000017685     CLU     Clasterin     chr6q13     3.1981       ENSGU0000176730     C3     Complement component 8, alpha polypeptide     chr6q13     3.1981       ENSGU000167730     C3     Complement component 8, alpha polypeptide     chr6q13     3.1981       ENSGU000017873     F12     Coagulation factor II (thrombin) receptor     chr6q28     5.5395       ENSGU000016471     MBL2     Mannes-binding lectin (protein C) 2, soluble     chr10q11.2     3.2084	ENSG0000021852	C8B	Complement component 8, beta polypeptide	chr1p32	6.4/18
ENS00000017601     SERPINC1     Serpin peptidase inhibitor, clade C (partifrombin), member 1     chr1q23     103.5847       ENS0000003993     SERPIND1     Serpin peptidase inhibitor, clade D (partin colactor), member 1     chr13q34     6.6379       ENS00000039537     C6     Complement component 6     chr13q12     10.1463       ENS000000113869     RNG1     Kninogen 1     chr3q27     105.7426       ENS000000113869     RNG1     Kninogen and colarity     chr4q28     10.1463       ENS000000113869     RNG1     Caugulation factor VI (serum prothrombin conversion accelerator)     chr1q24     10.57426       ENS00000017593     F7     Coagulation factor VI (serum prothrombin conversion accelerator)     chr13q34     10.8186       ENS00000164220     F2RL2     Coagulation factor II (thrombin) receptor-like 2     chr5q13     3.1891       ENS0000015730     C3     Complement component 3     chr19p13.3     4.0571       ENS000000157131     F2     Coagulation factor XI (Hogeman factor)     chr5q33     5.3355       ENS00000157131     F2     Coagulation factor XI (Hogeman factor)     chr5q33     10.1275       ENS00000167219 </td <td>ENSG00000184500</td> <td>PROS1</td> <td>Protein S (alpha)</td> <td>chr3q11.2</td> <td>8.486</td>	ENSG00000184500	PROS1	Protein S (alpha)	chr3q11.2	8.486
ENS00000009937     SERPIND1     Serpin peptidase inhibitor, clade D (heparin cofactor), member 1     chr2211.21     152.5118       ENS00000003937     C6     Complement component 6     chr13034     66.373       ENS0000011388     KN01     Kininogen 1     chr3027     105.7426       ENS0000011366     PLAT     Plasmiogen activator, issue     chr3027     10.57426       ENS00000017579     F7     Coagulation factor VI (serum porthornbin onversion accelerator)     chr407121     12.3905       ENS000000175793     F7     Coagulation factor VI (serum porthornbin) receptor-like 2     chr3013     3.1981       ENS00000016731     CAA     Complement component 3, alpha polypeptide     chr1913.3     4.0571       ENS00000015730     C3     Complement component 3     chr1913.3     4.0571       ENS0000015730     C3     Complement component 3     chr1921.3     1.0175       ENS0000015730     C3     Coagulation factor II (thrombin) receptor     chr633     5.5395       ENS0000015671     MBL2     Manaes-binding lectin (protein C) 2, sluble     chr1921.3     1.0175       ENS00000015710     F8     Coagulation	ENSG00000117601	SERPINC1	Serpin peptidase inhibitor, clade C (antithrombin), member 1	chr1q23	103.5847
ENS00000126218     F10     Caqualation factor X     chr13q34     6.6379       ENS000000039537     C6     Complement component 6     chr5p13     10.1463       ENS00000014389     PLAT     Plasminogen activator, tissue     chr3p12     12.0615       ENS00000017557     F6G     Fibrinogen garma chain     chr4p12     12.0615       ENS00000017583     F7     Coagulation factor IVI (serum prothombin conversion accelerator)     chr3p24     10.8166       ENS000001764220     F2RL2     Coagulation factor II (thrombin) receptor-like 2     chr5p13     3.1981       ENS0000015730     C3     Complement component 3     chr1p22     8.3894       ENS0000015730     C3     Complement component 3     chr1p31     13.916       ENS00000128710     MBL2     Mannose-binding lectin (proticin C) 2, soluble     chr10q11.2     13.9146       ENS00000118710     F8     Coagulation factor VII, proceagulant component     chr6q26     85.2698       ENS0000017214     PLG     Plasminogen     chr6q26     85.2698       ENS0000001724     MASP2     Mannos-binding lectin serino epidase 2     chr19q33     <	ENSG00000099937	SERPIND1	Serpin peptidase inhibitor, clade D (heparin cofactor), member 1	chr22q11.21	152.5118
ENS020000039357     C6     Complement component 6     chr6p13     10.1463       ENS020000113889     KNG1     Mininogen 1     chr3p27     105.7426       ENS02000117357     FGG     Fibrinogen gamma chain     chr4p28     110.1463       ENS02000117357     FGG     Environment component 6, alpha polypeptide     chr3p12     12.20615       ENS020000175793     F7     Coagulation factor II (frombin) receptor-like 2     chr3p13     3.1981       ENS02000015713     CGA     Complement component 8, alpha polypeptide     chr1p13.3     4.0571       ENS02000015730     C3     Complement component 3, alpha polypeptide     chr1p13.3     4.0571       ENS02000015730     C3     Congulation factor II (frombin) receptor - Ike 2     chr5q13     10.1275       ENS02000013187     F12     Coagulation factor II (frombin) receptor     chr5q33     5.5395       ENS020000185010     F8     Coagulation factor II (frombin) receptor     chr6q26     85.2698       ENS02000018771     SERPINA1     Serpin peptidase inhibitor, clade F     chr1p3.3     2.3218       ENS020000197749     SERPINA1     Serpin peptidase inhibitor,	ENSG00000126218	F10	Coagulation factor X	chr13q34	6.6379
ENS600000113889     KNG1     Kininogen ativator, tissue     chr3q27     105.7428       ENS600000171557     FG6     Fibrinogen gamma chain     chr4q28     419.7254       ENS600000171557     FG6     Fibrinogen gamma chain     chr3q34     10.8186       ENS600000171557     FG     Coagulation factor II (thrombin) receptor-like 2     chr3q34     10.8186       ENS600000157593     F7     Coagulation factor II (thrombin) receptor-like 2     chr5q13     3.1981       ENS60000015731     CBA     Complement component 3     chr19p13.3     4.0571       ENS600000157131     CBA     Complement component 3     chr19p13.3     4.0571       ENS600000157131     CBA     Complement component 3     chr19p13.3     4.0571       ENS600000181104     F2P     Coagulation factor XII (Hageman factor)     chr19g13.3     4.0571       ENS600000018104     F2P     Coagulation factor VIII, procagulant component 6     chr19g13     4.3519       ENS6000000188010     F8     Coagulation factor VIII, procagulant component 2     chr14g28     4.3519       ENS60000019724     MASP2     Marana-binding lectin serine peptidase inhi	ENSG0000039537	C6	Complement component 6	chr5p13	10.1463
ENS2000010171557     FGG     Flasminogen activator, tissue     chr6p12     12.0615       ENS00000017553     F7     Coagulation factor VII (serum prothrombin conversion accelerator)     chr1q32     10.8186       ENS00000017533     F7     Coagulation factor VII (serum prothrombin conversion accelerator)     chr6q21     12.3905       ENS000000157131     CGA     Complement component 3, alpha polypeptide     chr1q12     3.1981       ENS000000157131     CGA     Complement component 3, alpha polypeptide     chr1q12     13.9146       ENS000000131187     F12     Coagulation factor VII (Hageman factor)     chr6q13     10.1275       ENS000000131187     F12     Coagulation factor VII (Hageman factor)     chr6q26     85.2698       ENS000000131187     F12     Coagulation factor VII, proceagulant component 5     chr1q21.     10.1275       ENS000000185010     F8     Coagulation factor VII, proceagulant component 5.     chr1q32.     4.3519       ENS000000187711     SERPINA2     MASP2     Mannan-binding lectin serine petidase 1.4076, member 2     ENS00000009774     MASP2     A.3519       ENS00000018771     SERPINA2     Serpin peptidase inhibitor, clad	ENSG00000113889	KNG1	Kininogen 1	chr3q27	105.7426
ENSG00000171557     FGG     Fibringen gamma chain     chr4q28     (419.7254       ENSG00000120885     CLU     Coagulation factor VII (serum prothrombin conversion accelerator)     chr1q34     10.8186       ENSG00000120885     CLU     Clusterin     chr5q13     3.1981       ENSG0000015731     CGA     Complement component 8, alpha polypeptide     chr1q32     8.3894       ENSG00000125730     C3     Complement component 3     chr19p13.3     4.0571       ENSG00000125730     C3     Complement component 3     chr10q11.2     13.9146       ENSG00000125741     MBL2     Mannose-binding lectin (protein C) 2, soluble     chr10q11.2     13.9146       ENSG00000181104     F2R     Coagulation factor VIII, fromobiny receptor     chr5q13     10.1275       ENSG00000185010     F8     Coagulation factor VIII, proceagulant component 4     chr1q26.3     4.3519       ENSG000000724     MASP2     Mannan-binding lectin serine peptidase 10.1275     ENSG000000787     MASP2     chr1q21.3     11.3.0954       ENSG000000727     SERPINP12     Serpin peptidase inhibitor, clade F     chr1q22.1     113.0954       ENS	ENSG00000104368	PLAT	Plasminogen activator, tissue	chr8p12	12.0615
ENSG00000157583     F7     Coagulation factor VII (serum prothrombin conversion accelerator)     chr13034     10.8186       ENSG0000016422     CLU     Coagulation factor VII (formbin) receptor-like 2     chr6q13     3.1981       ENSG00000157131     CGA     Complement component 8, alpha polypeptide     chr19p13.3     4.0571       ENSG00000165771     MBL2     Mannose-binding lectin (protein C) 2, soluble     chr19p13.3     4.0571       ENSG00000165471     MBL2     Mannose-binding lectin (protein C) 2, soluble     chr19p13.3     4.0571       ENSG00000152194     PLG     Coagulation factor VIII (hrombin) receptor     chr6q13     10.1275       ENSG00000182010     F8     Coagulation factor VIII, procagulant component 4     chr4q28     2.4595       ENSG00000182010     F8     Coagulation factor VIII, procagulant component 5     chr4q33     7.3218       ENSG0000016664     C5     Complement component 5     chr4q33     7.3218       ENSG00000167711     SERPINF2     Serpin peptidase inhibitor, clade F     chr17p13     3.2308       ENSG0000016664     C5     Costomplement factor H     chr4q33     7.3218       ENSG000000	ENSG00000171557	FGG	Fibrinogen gamma chain	chr4q28	419.7254
ENSG0000120885     CLU     Clusterin     chr8p21     12.3905       ENSG0000164220     F2RL2     Coagulation factor II (thrombin) receptor-like 2     chr1p32     8.3894       ENSG000015731     CGA     Complement component 3     chr1p31.3     4.0571       ENSG000015730     C3     Complement component 3     chr1p31.3     4.0571       ENSG0000165471     MEL2     Mannose-binding lectin (protein (°), 2, soluble     chr1p33.3     5.5395       ENSG0000131187     F12     Coagulation factor III (thrombin) receptor     chr5q33     5.5395       ENSG00000122194     PLG     Plasminogen     chr6q26     85.2698       ENSG000001724     MASP2     Mannaru-binding lectin serine peptidase 2     chr1p36.3     4.3519       ENSG0000016804     C5     Complement component 5     chr9q33     7.3218       ENSG0000018020     F2H     Coagulation factor III (thrombin)     celepta2     chr1p36.3     4.3519       ENSG0000018724     MASP2     Mannaru-binding lectin serine peptidase 2     chr1p36.3     4.3519       ENSG0000018724     SERPINP4     Serpin peptidase inhibitor, clade A lalpha-1 antiprotei	ENSG00000057593	F7	Coagulation factor VII (serum prothrombin conversion accelerator)	chr13q34	10.8186
ENSG0000164220     F2RL2     Coagulation factor II (thrombin) receptor-like 2     chr5q13     3.1981       ENSG0000157131     CGA     Complement component 8, alpha polypeptide     chr19p13.3     4.0571       ENSG0000155730     C3     Complement component 3     chr19p13.3     4.0571       ENSG0000165471     MBL2     Mannose-binding lectin (protein C) 2, soluble     chr10q11.2     13.9146       ENSG0000122194     F12     Coagulation factor XII (Hagman factor)     chr5q13     10.1275       ENSG00000122194     PLG     Plasminogen     chr6q26     85.2698       ENSG00000185010     F8     Coagulation factor VIII, procoagulant component     chr19g33.3     7.33218       ENSG0000018604     C5     Complement component 5     chr19g33.3     7.33218       ENSG00000167711     SERPINP2     Serpin peptidase inhibitor, clade F     chr17p13     3.2308       ENSG00000009724     F2     Coagulation factor II (thrombin)     chr14g32.1     113.0954       ENSG00000167711     SERPINA1     Serpin peptidase inhibitor, clade F     chr17p13     3.2308       ENSG00000197249     SERPINA1     Serpin peptidase i	ENSG00000120885	CLU	Clusterin	chr8p21	12.3905
ENSG00000157131     CBA     Complement component 8, alpha polypeptide     chr1p32     8.3894       ENSG0000125730     C3     Complement component 3     chr19p13.3     4.0571       ENSG00000156371     MBL2     Manose-binding lectic (protein C) 2, soluble     chr10g11.2     13.9146       ENSG0000131187     F12     Coagulation factor XII (Hageman factor)     chr5q13     10.1275       ENSG00000185010     F8     Coagulation factor VIII, procoagulant component     chr6q26     85.2698       ENSG00000185010     F8     Coagulation factor VIII, procoagulant component 5     chr1g3.3     4.3519       ENSG0000016804     C5     Complement component 5     chr1g3.3     73.3218       ENSG000001724     MASP2     Mannan-binding lectin serine peptidase 2     chr1q32.4     113.0954       ENSG0000016804     C5     Complement factor H     chr1q32     6.0606       ENSG000001724     Serpin peptidase inhibitor, clade F     chr1q32.4     113.0954       ENSG00000019724     Serpin peptidase inhibitor, clade F     chr1q32.4     0.0414       ENSG00000019724     SERPINA1     Serpin peptidase inhibitor, clade F     chr1q42.	ENSG00000164220	F2RL2	Coagulation factor II (thrombin) receptor-like 2	chr5q13	3.1981
ENSG00000125730     C3     Complement component 3     chr19p13.3     4.0571       ENSG00000165471     MBL2     Mannose-binding lectin (protein () 2, soluble     chr10q11.2     13.9146       ENSG00000181104     F2R     Coagulation factor XII (Hageman factor)     chr5q33     5.5395       ENSG00000181104     F2R     Coagulation factor XII (Hrombin) receptor     chr5q13     10.1275       ENSG0000009724     MASP2     Manna-binding lectin serine peptidase 2     chr19a5.3     4.3519       ENSG0000009724     MASP2     Manna-binding lectin serine peptidase 2     chr19a5.3     4.3519       ENSG00000016604     C5     Complement component 5     chr19q3.3     7.3218       ENSG00000017249     SERPINA1     Serpin peptidase inhibitor, clade F     chr19q3.1     113.0954       ENSG0000000971     CFH     Complement factor H     chr19q3.2     113.0954       ENSG00000138210     F2     Coagulation factor II (frombin)     chr114g2.1     113.0954       ENSG00000197249     SERPINA1     Serpin peptidase inhibitor, clade F     chr19q3.2     0.0824       ENSG00000197249     SERPINB2     Serpin peptidase in	ENSG00000157131	C8A	Complement component 8, alpha polypeptide	chr1p32	8.3894
ENSG0000165471     MBL2     Mannose-binding lectin (protein C) 2, soluble     chr1011.2     13.9146       ENSG0000131187     F12     Coagulation factor XII (Hageman factor)     chr5033     55.395       ENSG0000122194     F2R     Coagulation factor XII (Hageman factor)     chr5033     10.1275       ENSG0000122194     PLG     Plasminogen     chr6026     85.2698       ENSG00000122194     MASP2     Mannar-binding lectin serine peptidase 2     chr1026.3     4.3519       ENSG0000016804     C5     Complement component 5     chr9033     73.3218       ENSG0000017711     SERPINF2     Serpin peptidase inhibitor, clade F     chr17p13     3.2308       ENSG00000187249     SERPINA1     Serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 1     chr14q32.1     113.0954       ENSG00000180210     F2     Coagulation factor II (thrombin)     chr11q32     0.0824       ENSG00000196352     CD55     CD55     molecule, decay accelerating factor for complement (Cormer blood group)     chr13q21     0.4944       ENSG0000011422     PLAUR     Plasminogen activator, urokinase receptor     chr13q21.3     0.4944 <td>ENSG00000125730</td> <td>C3</td> <td>Complement component 3</td> <td>chr19p13.3</td> <td>4.0571</td>	ENSG00000125730	C3	Complement component 3	chr19p13.3	4.0571
ENSG0000131187F12Coagulation factor XII (Hageman factor)chr5q335.5395ENSG0000181104F2RCoagulation factor XII (Hormbin) receptorchr5q1310.1275ENSG0000122194PLGPlasminogenchr6q2685.2698ENSG0000185010F8Coagulation factor VIII, procoagulant componentchr4v282.44995ENSG0000106804C5Complement component 5chr1v3284.3519ENSG0000107711SERPINF2Serpin peptidase inhibitor, clade Fchr1v17913.2308ENSG00000197249SERPINA1Serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 1chr1q326.0606ENSG00000197249SERPINA1Serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 1chr1q326.0606ENSG00000197249SERPINA1Serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 1chr1q326.0606ENSG00000197249SERPINA1Serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 1chr1q320.0824ENSG00000197249SERPINA1Serpin peptidase inhibitor, clade B (oragulation factor II (thrombin)chr1q320.0824ENSG0000019725CD55CD55molecule, decay accelerating factor for complement (Cromer blood group)chr1q320.0824ENSG0000011122PLAURPlasminogen activator, urokinasechr1q1210.0444ENSG00000122861PLAUPlasminogen activator, urokinasechr1q220.3828ENSG00000122861PLAUCD59Complement fact	ENSG00000165471	MBL2	Mannose-binding lectin (protein C) 2. soluble	chr10a11.2	13,9146
ENSG0000181104F2RCoagulation factor II (thrombin) receptorchr5q1310.1275ENSG0000122194PLGPlasminogenchr6q2685.2698ENSG00001285010F8Coagulation factor VII, procoagulant componentchr4q282.4595ENSG0000106804C5Complement component 5chr9q3373.3218ENSG00001167711SERPINF2Serpin peptidase inhibitor, clade Fchr17p133.2308USG00000197249SERPINF2Serpin peptidase inhibitor, clade Fchr1q32113.0954ENSG0000197249SERPINA1Serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 1chr1q326.0606ENSG00000197249SERPINA1Serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 1chr1q320.0606ENSG00000197249SERPINA1Serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 1chr1q320.0606ENSG0000019724F2Coagulation factor II (thrombin)chr1q320.0824ENSG00000196352CD55CD55 molecule, decay accelerating factor for complement (Cromer blood group)chr1q320.0824ENSG00000197632SERPINB2Serpin peptidase inhibitor, clade B (valburnin), member 2chr1q32.0.0044ENSG00000197632SERPINB2Serpin peptidase inhibitor, clade B (valburnin), member 2chr1q32.0.0044ENSG00000197632SERPINB2Serpin peptidase inhibitor, clade B (valburnin), member 2chr1q32.0.0044ENSG00000197632SERPINB2Serpin peptidase inhibitor, clade B (valburnin), member 2c	ENSG00000131187	F12	Coagulation factor XII (Hageman factor)	chr5q33	5.5395
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	ENSG00000178726	THBD	Thrombomodulin	chr20p11.2	0.1825

tissues from the control group were deparaffinized, re-hydrated, and sectioned into 4- $\mu$ m slices. All IHC staining has conducted according to the manufacturer's instructions. Imaging was performed with the Olympus BX60 microscope using Olympus DP71 digital camera and CellA imaging software (Olympus Optical, Tokyo, Japan).

# 3. Results

#### 3.1. Patient characteristics

There were no statistical differences between the 2 groups of women in terms of age, gestational age, or body mass index (Table 1).

#### 3.2. Cluster analysis of microarray data

A total of fifty DEGs related to the complement and coagulation signaling pathways were identified. Among them, 38 transcripts were up-regulated, and 12 transcripts were down-regulated in the placenta during the first trimester between the IVF-ET and natural pregnancy samples. Interestingly, the majority of DEGs were up-regulated (76%), while only 24% of the genes were down-regulated in the early placenta after IVF-ET treatment (Fig. 1A and B, Table 2). Hierarchical clustering was applied to the microarray data and a very clear separation was observed in the gene expression profiles between IVF-ET and natural pregnancy samples in the same period; the 2 groups were distinctly clustered into 2 different groups (Fig. 1A). In addition, principal component analysis demonstrated a similar pattern between the IVF-ET and natural pregnancy placental gene expression (Fig. 1C).

#### 3.3. GO pathway and network analysis

The functional enrichment analysis of DEGs related to the complement and coagulation signaling pathways revealed that the observed genes also participated in more than 200 statistically over-represented GO categories (Fig. 1D). All DEGs and their functions in the complement or coagulation

signaling pathways are shown in Figure 2. For the complement pathway, the up-regulation of genes relating to the classical, lectin, and alternative pathways was observed. Crucial extrinsic pathway, intrinsic pathway, and fibrinolytic genes within the coagulation system were widely up-regulated, whereas important genes relating to cell adhesion, invasion, migration, and proliferation were down-regulated (Fig. 2). In addition to participating in the complement and coagulation signaling pathways, these 50 DEGs also participated in multiple other broad signaling pathways, including Staphylococcus aureus infection (n=13, false discovery rate [FDR]:  $P=2.11 \times 10^{-23}$ ), systemic lupus erythematosus (n=10, FDR:  $P=2.02 \times 10^{-13}$ ), prion diseases (n=7, FDR:  $P=2.03 \times 10^{-12}$ ), pertussis (n=7, FDR  $P=2.69 \times 10^{-10}$ ), Chagas disease (American trypanosomiasis) (n=4, FDR:  $P=6.83 \times 10^{-5}$ ), platelet activation (n=4, FDR:  $P = 1.27 \times 10^{-4}$ ), neuroactive ligand-receptor interaction  $(n=4, \text{ FDR: } P=2.37 \times 10^{-4})$ , phagosome (n=3, FDR: P=.36%), hematopoietic cell lineage (n=2, FDR: P=1.32%), and AGE-RAGE signaling pathway in diabetic complications (n=2, FDR: P=1.85%) (Supplementary Table S2, http://links. lww.com/MD/D329).

The 50 DEGs were also mapped using STRING online software (Fig. 3). Their transcripts were widely distributed in the nucleus, cytoplasm, and cell membrane of placental cells. Bioinformatics analyses of the data suggest that various



Figure 2. Schematic representation of genes in the placental complement and coagulation pathways affected by in vitro fertilization-embryo transfer (IVF-ET). All the differentially expressed genes analyzed here were found to affect the placental complement and coagulation pathways in IVF-ET samples during the first trimester. Red represents up-regulation; dark green represents down-regulation; light green represents no significant change.



Figure 3. Gene interaction networks in placental complement and coagulation pathways affected by in vitro fertilization-embryo transfer (IVF-ET) in the first trimester. All 50 differentially expressed genes were used as input for STRING analysis and a network was built. Differentially expressed genes based on high confidence are shown.

molecular and cellular functions were affected, and show their link to pregnancy complications.

obtained previously; this confirmed the observed fold changes from our microarray analysis.

#### 3.4. Validation by real-time PCR

To validate the microarray results, qRT-PCR was performed. Because their biological functions were mostly related to the placenta, ten of the fifty DEGs were selected to confirm their expression (Fig. 4). qRT-PCR data confirmed the up-regulation of FGB, FGA, FGG, SERPINC1, and PROC, as well as the down-regulation of PLAU, PLAUR, SERPINE1, CD59, and CFD in placenta from IVF-ET samples. Among the 10 tested genes, we observed a significant correlation with the results

#### 3.5. Immunohistochemistry

To locate differentially expressed proteins related to the complement and coagulation signaling pathways in human placenta during the first trimester, 5 genes, representing different critical functions in these signaling pathways, were selected for IHC analysis: FGB, FGG, SERPINC1, PLAU, and PLAUR. These 5 proteins were found to be located in either the cytoplasm or on the cell membrane of trophoblasts in placental villous tissues (Fig. 5).







Figure 5. Immunohistochemistry showing the cellular localization of fibrinogen beta chain (FGB), FG gamma chain (FGG), serpin peptidase inhibitor C1 (SERPINC1), plasminogen activator urokinase (PLAU), and PLAU receptor (PLAUR) in placental villus tissues obtained from *in vitro* fertilization-embryo transfer (IVF-ET) and healthy samples in the first trimester. (A) All proteins were located in either the cytoplasm or the cell membrane of trophoblasts. (B) Immunohistochemical analysis of the number of positively stained cells expressing the 5 genes in the IVF-ET and control groups. \* indicates P < .05; \*\* indicates P < .01, Scale bar=50  $\mu$ m.

#### 4. Discussion

There is substantial evidence supporting the hypothesis that several adverse pregnancy outcomes observed after ART are due to suboptimal placentation caused by abnormal trophoblast function.<sup>[23,24]</sup> Indeed, in humans, after adjusting for several confounding factors, the risk of spontaneous abortion was found to be higher in ART cohorts than in spontaneous pregnancies.<sup>[25]</sup> Notably, human studies found an increased risk of gestational hypertension, preeclampsia, placenta previa, and placental abruption in ART patients.<sup>[26]</sup> A number of studies have previously examined and identified alterations in gene expression in placental tissues after IVF-ET treatment.<sup>[27,28]</sup> A small study investigated the global gene expression in 3 term placentas from IVF-ET pregnancies compared to that in 3 placentas from spontaneous pregnancies. They found 18 DEGs and classified them according to their role in biological process in immune response, transmembrane transport, metabolism, oxidative stress, cell differentiation, and other processes.<sup>[16]</sup> Furthermore, several studied on the placental transcriptome after IVF-ET in animals have revealed comparable results.<sup>[29]</sup> The aim of our study was to investigate changes in the complement and coagulation pathways due to ART, and how this would affect placental formation and function to result in placenta-related adverse pregnancy outcomes.

The complement and coagulation cascades are not only parts of the innate immune system, but also effectors of antibodymediated immunity.<sup>[30]</sup> The major biological functions of these systems include defense against infections, connecting the innate and adaptive immunity, and the clearance of immune complexes and apoptotic cells.<sup>[31]</sup> The complement cascade, when activated by the classical, mannose-binding lectin, or alternative pathways, deposits several split products on the cell membrane, ultimately creating a cytotoxic cell lysis complex.<sup>[32]</sup> The complement split products also include free circulating anaphylatoxins such as C3a and C5a, which can initiate inflammation and tissue injury.<sup>[33]</sup> Dysregulation or over-activation of these systems are emerging as associated factors in many pregnancy complications.<sup>[34]</sup> In our study, a total of fifty DEGs related to the complement and coagulation signaling pathways were identified in the placenta during first trimester in pregnancy after IVF-ET therapy compared to placenta samples from natural pregnancies. We mapped these DEGs to the complement and coagulation pathways, and the results showed that these systems were over-activated and uncontrolled. The classical, mannose-binding lectin, and alternative pathways in the complement cascade were all over-activated in early placental tissue after IVF-ET treatment compared to those from natural pregnancy.

In our study, the C3, C5, and CD59 genes, which are known to play a role in the complement cascade, were confirmed to be significantly differently expressed in the placenta between the 2 groups. The expression levels of C3 and C5 in IVF-ET placentae were significantly higher compared to placentae from natural pregnancies, while CD59 expression was significantly lower. The alternative pathway is triggered by the spontaneous hydrolysis of internal thioester bonds within C3 and C5 in the fluid phase, leading to the formation of C3a and C5a. C3a and C5a, which are known as anaphylatoxins, are pleiotropic inflammatory mediators.<sup>[35]</sup> The complement cascade is controlled by several soluble membrane-bound factors, including CD59, which inhibits the complement pathway at the feto-maternal interface.<sup>[36]</sup> In a model of spontaneous abortion, C3a and C5a were shown to be required for triggering abortion; C5a in particular was found to be critical for the induction of abortion.<sup>[37]</sup> Our data were also consistent with those of previous studies in humans investigating C3a, C5a and CD59 levels. A recent study reported that women with unexplained fetal death displayed elevated levels of plasma C3a and C5a compared to those in healthy women.<sup>[38]</sup> Our research further confirms that this factor at the feto-maternal interface triggered the hyperactivation of the complement cascade after IVF-ET treatment. In addition, similar studies have reported a significant association of elevated C3a and C5a levels and decreased CD59 levels with various pregnancy complications, including gestational hypertension, preterm delivery, and intrauterine growth restrictions.<sup>[39,40]</sup> Our research adds important evidence that excessive complement activation in complicated pregnancies may be associated with many pre-existing conditions, which are triggered by IVF-ET treatment.

The coagulation system is a component of the homeostatic process and a major contributor to thrombosis. Pregnancy is a physiological hypercoagulable state, and the body must prepare the mother for the hemostatic challenge of delivery.<sup>[41]</sup> In addition, cytotrophoblast differentiation and fusion to syncytiotrophoblasts requires the initiation of apoptosis and the exposure of negatively charged phospholipids on their membrane surface.<sup>[42]</sup> The need for the rapid inhibition of hemorrhaging in the placental intervillous spaces during gestation explains the procoagulant nature of trophoblasts.<sup>[43]</sup> Although these conditions are heterogeneous in their pathophysiology, hereditary and acquired thrombophilia has been shown to be associated with recurrent pregnancy loss and gestational vascular complications.<sup>[44]</sup> In the present study, KEGG pathway analysis revealed that the coagulation cascade was significantly activated through the intrinsic and extrinsic pathways in placentae after IVF-ET treatment compared to that in placentae from natural pregnancy. In early IVF-ET placentae, a state of hypercoagulability and the local formation of thrombi in the microvasculature draining the site of embryo implantation provide a competent barrier to protect the embryo from the maternal immune system. Apart from its direct role in preventing contact with maternal circulation, the coagulation system can be viewed as an intermediary that converts mechanical information from the embryo implantation site into biochemical signals that trigger cell responses, resulting in vascular biological and inflammatory responses, as well as platelet aggregation.<sup>[45]</sup> Therefore, an overactivated coagulation system in IVF-ET early placentae may be a protective compensatory mechanism for the survival of the semiallogeneic fetus. However, IVF-ET treatment may destroy the balance and exceed the compensatory range of the coagulation cascade, resulting in reduced nutrient supply to the embryo and increased thrombophilia-associated pregnancy complications. Moreover, the protein-protein interact network and co-expression analysis derived from STRING database also revealed that some key genes were actively interacted with each other and might be valuable biomarkers and potential novel therapeutic targets against the unfavorable effects of IVF-ET.

To our knowledge, the present study provides evidence for the first time that although the parallel over-activation of the fibrinolysis and complement systems has been observed, the expression of urokinase plasminogen activator (uPA) and urokinase plasminogen activator receptor (uPAR) was significantly reduced at the transcriptional and protein levels in placentae after IVF-ET in the first trimester compared to samples from natural pregnancies. uPA and its receptor uPAR are central molecules for uPA/uPAR/plasmin-dependent proteolysis and plasmin-dependent extracellular proteolysis.<sup>[46]</sup> To our knowledge, this is the first study to analyze uPA and uPAR expression and localization in the early human placenta after IVF-ET treatment. These distinctive expression patterns were closely associated with their possible individual functions during the IVF-ET implantation process. Decreased expression of uPA and its receptor uPAR is thought to cause impaired trophoblast invasion and expansion, and may also affect the function of massive tissue remodeling in the interstitial endometrium during the process of uterine angiogenesis and degeneration of the epithelial plaque after IVF-ET treatment.<sup>[47]</sup> Abnormal trophoblast invasion in IVF-ET leads to incomplete uterine vascular conversion, an inadequate fetal blood supply, and a pathological hypoxia milieu. This placental defect after IVF-ET treatment is associated with the persistence of a pro-inflammatory environment and is considered to be a failure of maternal immune tolerance, which is required for normal implantation.

This study examined the molecular mechanisms of IVF-ETinduced alterations to the complement and coagulation signaling pathways in early placenta. We found that the convergence between the complement system and the clotting system extend far beyond the chemical nature of the complement and coagulation pathways, both of which displayed an over-activated proteolytic cascade in early placentae after IVF-ET treatment compared to that in placentae from natural pregnancies. Multiple regulatory loops linking both systems were simultaneously activated to synchronize an effective response by the placenta to disrupt the IVF-ET process. Most often, this cooperative and clearly beneficial effort ensures the elimination of interference by IVF-ET technology to embryo implantation and prevents immediate abortions. However, when some regulatory mechanisms controlling complement activation or hemostasis failure, the complement and coagulation pathways become harmful, significantly contributing to various pregnancy complications, for which only complex therapies targeting multiple molecules can be effective.<sup>[48]</sup> Indeed, in most case, pregnancies obtained through IVF-ET can be carried to term with no obvious immediate adverse outcomes.<sup>[49]</sup> This supports the hypothesis that initial defective trophoblast functions could trigger placental adaptive response during pregnancy.

One limitation of this study was the small number of samples investigated in each group. These samples were selected from a cohort of 8 samples collected prospectively for this work. Although the sample size was small, only significantly DEGs (>2-fold) were reported and significant signal pathways were analyzed. These data allow future work to be directed toward the interference of placental formation and function, resulting in placenta-related adverse pregnancy outcomes in IVF-ET. Another limitation was that we could not formally localize the expression of more proteins through IHC, which would improve our understanding of the functional importance of these changes. Further work is needed to determine the biological plausibility of the observed variations in gene expression; however, if our results are consistent with future findings and translate to protein expression in maternal serum, they may still be of value in predicting abnormal outcomes in later pregnancy.

#### 5. Conclusion

Our study offers a comprehensive view of dysregulated gene networks in the placental complement and coagulation signaling pathways influenced by IVF-ET treatment, although the detailed regulatory patterns were not explored. Another important result of our study was the discovery of the negative effects on trophoblast invasion, expansion, and tissue remodeling in early placentae after IVF-ET treatment through these 2 systems. Although these interconnections make it difficult to precisely define, separate, and classify biological processes, our data will enable us to focus on a small number of key genes and pathways that need to be better elucidated. Future studies with a larger sample size, focusing on these molecular and biological pathways, may lead to the development of molecular tests to predict adverse outcomes in first trimester. An improved understanding of the equilibrium between complement-mediated immune responses and thrombotic mechanisms triggered by IVF-ET may improve the safety and effectiveness of IVF-ET protocols.

### Author contributions

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- Writing review & editing: Liang Zhao.

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