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Letter to the Editor

Altered proteomic profile in umbilical arterial serum from mothers with schizophrenia

Keywords:
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Schizophrenia is known to be a multi-factorial disease caused by genetic and environmental factors. Accumulating evidence has demonstrated that intrauterine exposure to inflammation (maternal immune activation; MIA) subsequently leads to psychiatric diseases, including schizophrenia, owing to fetal programming (Estes and McAllister, 2016). Previous proteomic analysis of saliva revealed that proteins involved in innate immunity are increased in subjects with schizophrenia (Iavarone et al., 2014).

Based on those findings, we hypothesized that schizophrenia during pregnancy may have prenatal effects on offspring *via* immune activation, as observed in MIA. Therefore, we studied proteomic profiles for umbilical arterial serum (UA) and maternal serum (MS) obtained from pregnant women with schizophrenia, compared with serum from control subjects.

Clinical characteristics of all subjects included in the study are shown in Supplementary Table 1. For UA, 348 proteins detected by liquid chromatography–tandem mass spectrometry (LC–MS/MS) were analyzed with the Mascot program, which identified 81 proteins as differentially expressed proteins (DEPs) (Supplementary Fig. 1; Supplementary Table 2). Enrichment analysis of Gene Ontology (GO) terms for a biological process for these DEPs pointed toward complement activation of the classical pathway ($P = 1.1 \times 10^{-41}$), followed by overall complement activation ($P = 3.3 \times 10^{-39}$; Fig. 1A). Pathway enrichment analysis also demonstrated that complement and coagulation cascades were most significant ($P = 5.9 \times 10^{-27}$; Fig. 1B). A proteomap was used to visualize the involvement of the immune system and complement activation (Fig. 1C–E). GO term annotations confirmed robust coverage (Supplementary Fig. 2). Intense mutual interaction among proteins was annotated to the immune system; the interaction involved several complement proteins (Supplementary Fig. 3A), consistent with the result of GO enrichment analysis. The Reactome map also demonstrated involvement of enriched pathways in the immune system (Supplementary Fig. 3B). Transthyretin was recognized as a protein with statistically significant fold change in cases and controls ($P = 0.040$; Supplementary Fig. 4).

Similar results were observed in MS; GO and pathway enrichment analysis revealed the highest degree of significance for complement activation of the classical pathway ($P = 1.5 \times 10^{-32}$; Supplementary Fig. 5A) and complement and coagulation cascades ($P = 5.1 \times 10^{-15}$; Supplementary Fig. 5B), respectively. The DEPs for MS and UA are not identical (Supplementary Table 3), but the pattern of upregulation or downregulation was similar to each other. The R–I plot confirmed the validity of results obtained for UA (Supplementary Fig. 6A) and MS (Supplementary Fig. 6B) by LC–MS/MS.

This is the first report in which proteomic profiles of UA and MS from pregnant women with schizophrenia were demonstrated to differ from those of healthy pregnant women. Moreover, the classical complement activation pathway was identified as most significantly enriched in UA from mothers with schizophrenia, which was equivalent to serum pattern in their mothers. These findings indicate that the complement pathway gets activated in offspring born to mothers with schizophrenia *in utero*, as observed in studies involving animal models (Guest et al., 2012). The complement pathway is involved in synapse formation and elimination. Dysregulation of the complement pathway contributes to the pathogenesis of schizophrenia (Nimgaonkar et al., 2017). However, this alteration might be a consequence of genetic risk caused by maternal schizophrenia, rather than MIA. Increased *C4A* copy number is also associated with increased risk of schizophrenia (Sekar et al., 2016). C4A was reported to be increased in blood of newborns who later developed first-onset schizophrenia (Cooper et al., 2017). These results are consistent with those presented here. C1q levels in MS (Severance et al., 2014) and brains of adult offspring (Han et al., 2017) are associated with increased risk for schizophrenia in offspring. Those findings are also in line with our results, as C1q is an initiator of the classical pathway. That activation in umbilical arterial serum might impact on not only neurodevelopment but also systemic development. dditional studies will be necessary to validate these trends over the long term.

This study had certain limitations. Sample size in this study was small, which prevented analysis of various confounders that may have affected proteomic profiles. Confounders of obstetric complications, immune disorders, and feto-maternal Rh incompatibility were excluded from the analysis, but medications taken differed among subjects (Supplementary Table 4). The effects of various drugs on inflammation remain to be elucidated (Cassoli et al., 2016; Fond et al., 2017). These medications may affect the proteomic profile. Additional studies will be necessary to investigate the effects of these medications during pregnancy.

In conclusion, this study shows that complement activation was enriched in UA from mothers with schizophrenia compared to that from normal pregnant controls. Nonetheless, further study is required to determine the contribution of such changes to the pathogenesis of schizophrenia.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2018.02.024.

Abbreviations: DAVID, Database for Annotation, Visualization and Integrated Discovery; DEP, differentially expressed protein; GO, Gene Ontology; LC–MS/MS, liquid chromatography–tandem mass spectrometry; MIA, maternal immune activation; MS, maternal serum; UA, umbilical arterial serum.

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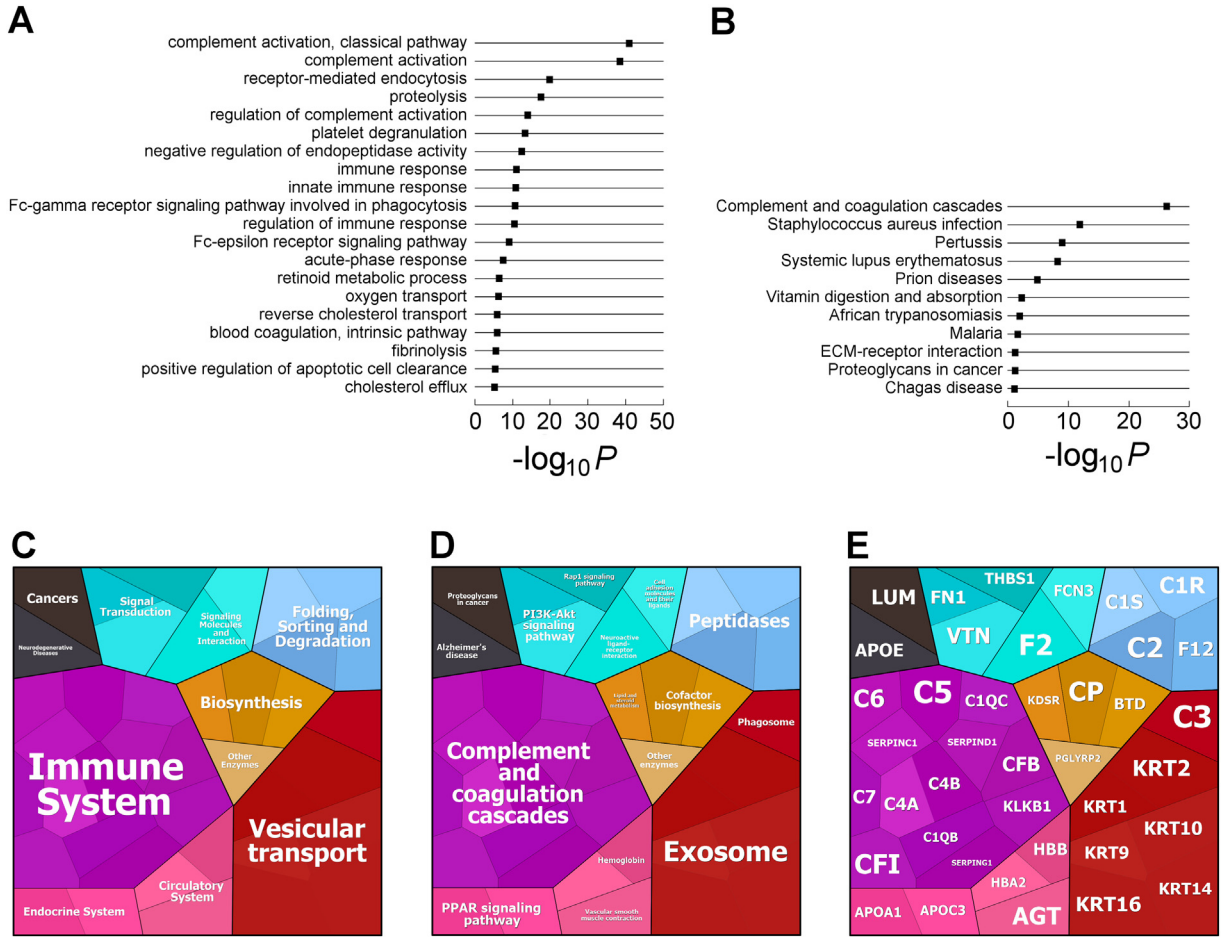

Fig. 1. Proteomic analysis of umbilical arterial serum between patients with schizophrenia and controls. A, Gene Ontology (GO) enrichment analysis for a biological process. Top 20 proteins (in terms of statistical significance) are shown. B, pathway enrichment analysis. C–E, Proteomaps, low level (C), middle level (D), and high level (E) of GO annotation, where graphical areas of each protein reflect the magnitude of the average fold change for cases over controls.

Conflict of interest

The authors declare no conflicts of interest to disclose.

Contributors

T.K. designed the study, oversaw data analyses, and edited the manuscript. Y.M. conducted clinical assessment, experiments, and analyses of data, and wrote the initial draft of the manuscript. T.U., K.I., T.N., and H.T. assisted with clinical assessment and data interpretation. F.K. provided assistance with data interpretation and edited the manuscript.

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References

Cassoli, J.S., Guest, P.C., Santana, A.G., Martins-de-Souza, D., 2016. Employing proteomics to unravel the molecular effects of antipsychotics and their role in schizophrenia. Proteomics Clin. Appl. 10 (4), 442–455.

Cooper, J.D., Ozcan, S., Gardner, R.M., Rustogi, N., Wicks, S., van Rees, G.F., Leweke, F.M., Dalman, C., Karlsson, H., Bahn, S., 2017. Schizophrenia-risk and urban birth are associated with proteomic changes in neonatal dried blood spots. Transl. Psychiatry 7 (12), 1290.

Estes, M.L., McAllister, A.K., 2016. Maternal immune activation: implications for neuropsychiatric disorders. Science 353 (6301), 772–777.

Fond, G., Resseguier, N., Schurhoff, F., Godin, O., Andrianarisoa, M., Brunel, L., Bulzacka, E., Aouizerate, B., Berna, F., Capdevielle, D., Chereau, I., D'Amato, T., Dubertret, C., Dubreucq, J., Faget, C., Gabayet, F., Lancon, C., Llorca, P.M., Mallet, J., Misdrahi, D., Passerieux, C., Rey, R., Schandrin, A., Urbach, M., Vidailhet, P., Boyer, L., Leboyer, M., FACE-SZ (FondaMental Academic Centers of Expertise for Schizophrenia) group, 2017. Relationships between low-grade peripheral inflammation and psychotropic drugs in schizophrenia: results from the national FACE-SZ cohort. Eur. Arch. Psychiatry Clin. Neurosci. https://doi.org/10.1007/s00406-017-0847-1.

Guest, P.C., Urday, S., Ma, D., Stelzhammer, V., Harris, L.W., Amess, B., Pietsch, S., Oheim, C., Ozanne, S.E., Bahn, S., 2012. Proteomic analysis of the maternal protein restriction rat model for schizophrenia: identification of translational changes in hormonal signaling pathways and glutamate neurotransmission. Proteomics 12 (23–24), 3580–3589.

Han, M., Zhang, J.C., Hashimoto, K., 2017. Increased levels of C1q in the prefrontal cortex of adult offspring after maternal immune activation: prevention by 7,8-dihydroxyflavone. Clin. Psychopharmacol. Neurosci. 15 (1), 64–67.

Iavarone, F., Melis, M., Platania, G., Cabras, T., Manconi, B., Petruzzelli, R., Cordaro, M., Siracusano, A., Faa, G., Messana, I., Zanasi, M., Castagnola, M., 2014. Characterization of salivary proteins of schizophrenic and bipolar disorder patients by top-down proteomics. J. Proteomics 103, 15–22.

Nimgaonkar, V.L., Prasad, K.M., Chowdari, K.V., Severance, E.G., Yolken, R.H., 2017. The complement system: a gateway to gene-environment interactions in schizophrenia pathogenesis. Mol. Psychiatry 22 (11), 1554–1561.

Sekar, A., Bialas, A.R., de Rivera, H., Davis, A., Hammond, T.R., Kamitaki, N., Tooley, K., Presumey, J., Baum, M., Van Doren, V., Genovese, G., Rose, S.A., Handsaker, R.E., Schizophrenia Working Group of the Psychiatric Genomics Consortium, Daly, M.J., Carroll, M.C., Stevens, B., McCarroll, S.A., 2016. Schizophrenia risk from complex variation of complement component 4. Nature 530 (7589), 177–183.

Severance, E.G., Gressitt, K.L., Buka, S.L., Cannon, T.D., Yolken, R.H., 2014. Maternal complement C1q and increased odds for psychosis in adult offspring. Schizophr. Res. 159 (1), 14–19.

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Supplementary data

Material and Methods

Ethical statement

This study was permitted by the Ethics committee of Nagoya University (Nagoya, Japan; permission number 2015-0471). We used the pre-existing samples and information. Thus, we provided disclosure of information on the methods of this study, and gave the subjects an opportunity for rejection of participation in this study, in accordance to the ethical guidelines by the Japanese Ministry of Health, Labor and Welfare.

Subjects

In this study, we enrolled six pregnant women (cases) who were diagnosed with schizophrenia before pregnancy and as many pregnant women without any maternal or fetal complications (controls). All of them were admitted to our hospital, Nagoya University Hospital (Nagoya, Japan) and delivered their babies at the Department of Obstetrics, from April 2013 to April 2016. Controls were matched with cases regarding age, gestational age at delivery, mode of delivery, and neonatal sex. We excluded cases with any obstetric complication,

including preterm birth, gestational diabetes, and preeclampsia, from this study. In fact, cases with deteriorated schizophrenia during pregnancy were also excluded. In both groups, any obstetric complications including preeclampsia, preterm birth, gestational diabetes mellitus, immune disorders, or feto-maternal Rh incompatibility, which may be involved in immune activation, were not included. Supplementary Table 1 summarizes their clinical characteristics. We compared the clinical characteristics of cases and controls by the Student's *t*-test or the χ^2 test using IBM SPSS Statistics for Windows, version 24.0 (IBM Corporation, Armonk, NY). We collected the maternal peripheral blood during the third trimester of pregnancy (for 5 of 6 case–control pairs) and the umbilical arterial blood during delivery, with written informed consent obtained from all participants in advance. The umbilical artery is the fetal blood ejected from the fetal heart. After centrifugation for 10 min at 4°C, the serum was isolated and stored at −80°C until the proteomic analysis.

Sample preparation

The frozen umbilical arterial serum samples were thawed at 4°C, and their total protein concentrations were assessed by the BCA assay (BCA Protein

Assay Kit; Pierce, Thermo Fisher Scientific Inc., Waltham, MA), using bovine serum albumin for obtaining the standard curve. Then, the samples were diluted to 500 μg/mL. To 100 μL of diluted samples, we added 133 mg of guanidine hydrochloride (Wako, Osaka, Japan) and 10 μL of Milli-Q water. After that, we added 20 μL of 3 M Tris–HCl (pH 8.5). Furthermore, 10 μL of 0.1 M dithiothreitol (Pierce, Thermo Fisher Scientific Inc.) was added (final concentration, 5 mM) and incubated for 30 min at room temperature to reduce protein disulfides. Similarly, 10 μL of 0.2 M iodoacetamide (Pierce, Thermo Fisher Scientific Inc.) was added and incubated for 60 min at room temperature in the dark for alkylation of cysteine residues. Then, we added 600 μL of ice-chilled methanol (Cica, Tokyo, Japan) and 150 μL of ice-chilled chloroform (Cica), both mixed by inversion. Finally, we added 450 μL of ice-chilled Milli-Q and mixed by inversion, centrifuged these at 15,000 rpm for 10 min at 4°C, and removed the upper phase. Then, we added 450 μL of ice-chilled methanol, mixed by inversion, centrifuged these at 15,000 rpm for 10 min at 4°C, and removed the supernatant. The obtained pellets were dried by centrifugal concentration under vacuum (CentriVap Mobile System, Labconco, Kansas City, MO), and dissolved in 10 μL of 6 M urea, to which we added 40 μL of 0.1 M Tris–HCl (pH 8.5) and mixed.

Then, trypsin (Trypsin Gold, Mass Spectrometry Grade; Promega, Madison, WI) was diluted to 1 μg/μL with 50 mM acetic acid (Cica), 1 μL of which was added to the mixture and incubated for 16 h at 37°C for digestion. Subsequently, these samples were desalted and concentrated with C18 solid phase extraction tips (AMR, Tokyo, Japan) and a mixture of acetonitrile (ACN; Cica) and trifluoroacetic acid (TFA; Cica). Finally, eluted samples were dried by centrifugal concentration under vacuum and dissolved in 50 μL of 5% ACN with 0.1% TFA.

Liquid chromatography–tandem mass spectrometry

We performed nanoelectrospray tandem mass analysis using a Q Exactive Hybrid Quadrupole-Orbitrap Mass Spectrometer (Thermo Fisher Scientific Inc.) in combination with an Advance LC System (Bruker Corporation, Billerica, MA). Then, samples were injected onto the Advance LC System equipped with a MonoCap C18 0.1 mm in diameter and 150 mm in length (GL Sciences Inc., Tokyo, Japan). We conducted reversed-phase chromatography with a linear gradient (0 min, 5% B; 100 min, 50% B) of solvent A (2% ACN with 0.1% formic acid) and solvent B (90% ACN with 0.1% formic acid) at an estimated flow rate of 500 nL/min. Then, ionization was performed by a

CaptiveSpray source (Bruker Corporation) with a capillary voltage at 1.4 kV and temperature of 250°C. A precursor ion scan was carried out using a 400–1600 mass to charge ratio (m/z) before the MS/MS analysis. Finally, multiple MS/MS spectra were submitted to the Mascot program, version 2.5.1 (Matrix Science Inc., Boston, MA) for the MS/MS ion search.

Bioinformatic data analysis

We set a two-fold change in the value of area calculated by the Mascot program in one or more case-control pairs as the threshold for the protein abundance ratio to identify differentially expressed proteins (DEPs), referring to the previous report (Pan et al., 2015). We analyzed proteins detected in all cord blood or maternal blood samples. Furthermore, we used a bioinformatic web tool, Database for Annotation, Visualization and Integrated Discovery (DAVID, http://david.abcc.ncifcrf.gov, and version 6.8), with default settings for carrying out subsequent analyses. The Gene Ontology (GO) annotation was conducted for DEPs. With annotated DEPs, we performed the enrichment analysis of GO terms for biological processes and then that of the KEGG pathway. Proteomap was generated to visualize the differential contribution of biological pathways

(http://bionic-vis.biologie.uni-greifswald.de/, version 2.0). We used another bioinformatic web tool, STRING (http://www.string-db.org/, version 10), to perform protein–protein interaction analysis called the Interactome analysis. Of note, STRING generated a map of protein–protein interaction of DEPs with default settings. Finally, the pathway database analysis of DEPs was performed with a web tool, Reactome (http://www.reactome.org/, version 59).

Reference

Pan, H.T., Guo, M.X., Xiong, Y.M., Ren, J., Zhang, J.Y., Gao, Q., Ke, Z.H., Xu, G.F., Tan, Y.J., Sheng, J.Z., Huang, H.F., 2015. Differential proteomic analysis of umbilical artery tissue from preeclampsia patients, using iTRAQ isobaric tags and 2D nano LC-MS/MS. J. Proteomics 112, 262-273.

Supplementary Figure legend

Supplementary Fig. 1. Differentially expressed proteins (DEPs) in the umbilical arterial serum. For all 81 DEPs that demonstrated over a two-fold change, the ratio of area value in liquid chromatography–tandem mass spectrometry analysis of case over control is shown in binary logarithm with normalization. Component proteins are listed in a descending ratio: the most overexpressed at the top and the most repressed at the bottom.

Supplementary Fig. 2. A coverage of gene ontology annotations of the umbilical arterial serum.

Supplementary Fig. 3. The database analysis of proteomic differential expression in the umbilical arterial serum. A, Interactome map. A majority of differentially expressed proteins (DEPs) have a close relation to each other, which means they are enriched in specific pathways, immune system-associated pathways in this study. B, Reactome map. It visualizes that DEPs are enriched in the immune system.

Supplementary Fig. 4. A volcano plot of differentially expressed proteins in the cord blood. P values for area values calculated by the Student's t-test in decadic logarithm are shown in comparison to their average ratio in binary logarithm.

Transthyretin (TTR) was the only protein that demonstrated a statistically significant differential expression (P = 0.04).

Supplementary Fig. 5. The proteomic analysis of the maternal serum between cases of schizophrenia and controls. A, Gene ontology enrichment analysis for a biological process. Top 20 proteins in terms of statistical significance are shown. B, The pathway enrichment analysis.

Supplementary Fig. 6. The R–I plot of differentially expressed proteins of the cord blood (A) and maternal blood (B), where intensity and ratio are the sum and the difference of binary logarithm of the average area value in liquid chromatography–tandem mass spectrometry of each case and that of counterpart control, respectively.

Supplementary Table 1 Characteristics of subjects for umbilical arterial serum and maternal serum analysis.

Umbilical arterial serum	Case (n = 6)	Control (n = 6)	*P*
Maternal age[a], yr	31.4 ± 6.2 (23.0-38.3)	31.4±6.2 (22.8-38.2)	.962*
BMI[a], kg/m^2	28.8 ± 3.5 (26.2-35.5)	24.1 ± 2.1 (20.1-27.1)	.018*
Gestational age[a], wk	40.4 ± 1.0 (38.6-41.4)	40.3 ± 1.1 (38.1-41.1)	.851*
Peripartum blood loss[a], g	592.8 ± 306.6 (300-1100)	857.1 ± 765.1 (200-2033)	.460*
Mode of delivery[b]			
Vaginal	5	5	1.000**
Cesarean	1	1	
Parity[b]			
Primiparous	5	4	.505*
Multiparous	1	2	
Marriage[b]			
Yes	3	6	.046*
No	3	0	
Employment[b]			
Yes	2	4	.248*
No	4	2	
Smoking during pregnancy[b]			
Yes	1	0	.296*
No	5	6	
Alcohol during pregnancy[b]			
Yes	0	1	.296*
No	6	5	
Psychotropics at delivery[b]			
Prescribed	5	0	.003*
Not prescribed	1	6	
Outcomes of neonates			
Sex[b]			
Male	3	3	1.000**
Female	3	3	
Birthweight[a], g	3047 ± 229 (2818-3468)	3148 ± 317 (2756-3444)	.544*
Height[a], cm	49.8 ± 1.1 (48.0-51.0)	50.3 ± 1.2 (49.0-52.0)	.468*
Head circumference[a], cm	32.9 ± 1.2 (31.0-34.2)	33.4 ± 1.8 (31.0-36.0)	.549*
Chest circumference[a], cm	32.2 ± 1.4 (30.0-34.0)	32.0 ± 1.2 (30.0-33.0)	.761*
APGAR score at 1 min[a]	8.0 ± 0.0 (8-8)	9.0 ± 0.0 (9-9)	N/A

APGAR score at 5 min[a]	9.2 ± 0.4 (9-10)	9.5 ± 0.6 (9-10)	.260*
Maternal serum	**Case (n = 5)**	**Control (n = 5)**	***P***
Maternal age[a], yr	32.5 ± 6.2 (23.0-38.3)	32.3 ± 6.2 (22.8-38.2)	.960
Gestational age at sample collection[a], wk	37.0 ± 0.4 (36.7-37.7)	36.4 ± 1.3 (34.6-38.1)	.353
Gestational age at delivery[a], wk	40.3 ± 1.2 (38.6-41.4)	40.3 ± 1.2 (38.1-41.1)	.971
Birthweight[a], g	3093 ± 223 (2914-3468)	3226 ± 282 (2768-3444)	.433

N/A, Not available. *Student's *t*-test. **χ^2 test. [a]Data shown as Mean ± SD (minimum–maximum). [b]Data shown as number (%).

Supplementary Table 2 List of differentially expressed proteins in umbilical arterial serum.

UniProt Accession Number	Protein name	Gene symbol	MW	Gene locus	Log_2R	*P*	Gene ontology for biological process
P35908	Keratin, type II cytoskeletal 2 epidermal	*KRT2*	65.39	12q13.13	0.982	0.227	cellular process, multicellular organismal process, developmental process, locomotion, single-organism process, localization, cellular component organization or biogenesis
P25311	Zinc-alpha-2-glycoprotein	*AZGP1*	34.24	7q22.1	0.964	0.135	immune system process, metabolic process, cellular process, biological adhesion, multicellular organismal process, single-organism process, regulation of biological process, response to stimulus, localization, biological regulation
P02533	Keratin, type I cytoskeletal 14	*KRT14*	51.53	17q21.2	0.931	0.182	cellular process, multicellular organismal process, developmental process, single-organism process, response to stimulus, cellular component organization or biogenesis
P02763	Alpha-1-acid glycoprotein 1	*ORM1*	23.50	9q32	0.896	0.223	cellular process, multicellular organismal process, single-organism process, regulation of biological process, response to stimulus, localization, biological regulation
P08779	Keratin, type I cytoskeletal 16	*KRT16*	51.24	17q21.2	0.848	0.257	immune system process, cellular process, multicellular organismal process, developmental process, locomotion, single-organism process, regulation of biological process, response to stimulus, localization, biological regulation, cellular component organization or biogenesis
P13645	Keratin, type I cytoskeletal 10	*KRT10*	58.79	17q21.2	0.803	0.321	cellular process, multicellular organismal process, developmental process, single-organism process
P19652	Alpha-1-acid glycoprotein 2	*ORM2*	23.59	9q32	0.796	0.251	cellular process, single-organism process, regulation of biological process, response to stimulus, localization, biological regulation
P00734	Prothrombin	*F2*	69.99	11p11.2	0.723	0.064	immune system process, metabolic process, cellular process, signaling, multicellular organismal process, developmental process, growth, locomotion, single-organism process, regulation of biological process, response to stimulus, localization, biological regulation, cellular component organization or biogenesis
Q8NG11	Tetraspanin-14	*TSPAN14*	30.67	10q23.1	0.585	0.354	metabolic process, cellular process, signaling, single-organism process, regulation of biological process, response to stimulus, localization, biological regulation, cellular component organization or biogenesis
P00748	Coagulation factor XII	*F12*	67.75	5q35.3	0.577	0.356	immune system process, metabolic process, cellular process, multicellular organismal process, single-organism process, regulation of biological process, response to stimulus, biological regulation
P04004	Vitronectin	*VTN*	54.27	17q11.2	0.517	0.165	immune system process, metabolic process, cellular process, biological adhesion, signaling, multicellular organismal process, developmental process, locomotion, single-organism process, regulation of biological process,

							response to stimulus, localization, biological regulation, cellular component organization or biogenesis
P02753	Retinol-binding protein 4	*RBP4*	23.00	10q23.33	0.510	0.161	reproduction, immune system process, metabolic process, cellular process, reproductive process, signaling, multicellular organismal process, developmental process, growth, single-organism process, regulation of biological process, response to stimulus, localization, biological regulation
P06681	Complement C2	*C2*	83.21	6p21.33	0.471	0.330	immune system process, metabolic process, cellular process, single-organism process, regulation of biological process, response to stimulus, localization, biological regulation, cellular component organization or biogenesis
P00450	Ceruloplasmin	*CP*	122.13	3q24-q25.1	0.448	0.523	metabolic process, cellular process, single-organism process, localization, biological regulation
P51884	Lumican	*LUM*	38.40	12q21.33	0.448	0.409	metabolic process, cellular process, multicellular organismal process, developmental process, single-organism process, regulation of biological process, response to stimulus, biological regulation, cellular component organization or biogenesis
P02766	Transthyretin	*TTR*	15.88	18q21.33	0.441	0.040	metabolic process, cellular process, single-organism process, localization, biological regulation, cellular component organization or biogenesis
P01031	Complement C5	*C5*	188.19	9q33.2	0.420	0.382	immune system process, metabolic process, cellular process, signaling, multicellular organismal process, developmental process, locomotion, single-organism process, regulation of biological process, response to stimulus, localization, biological regulation
P04264	Keratin, type II cytoskeletal 1	*KRT1*	66.00	12q13.13	0.413	0.617	immune system process, metabolic process, multicellular organismal process, developmental process, single-organism process, regulation of biological process, response to stimulus, biological regulation
P01011	Alpha-1-antichymotrypsin	*SERPINA3*	47.62	14q32.13	0.404	0.559	metabolic process, cellular process, multicellular organismal process, single-organism process, regulation of biological process, response to stimulus, localization, biological regulation
P02649	Apolipoprotein E	*APOE*	36.13	19q13.32	0.376	0.414	metabolic process, cellular process, signaling, multicellular organismal process, developmental process, growth, locomotion, single-organism process, regulation of biological process, response to stimulus, localization, multi-organism process, biological regulation, cellular component organization or biogenesis, detoxification
P01019	Angiotensinogen	*AGT*	53.12	1q42.2	0.368	0.336	reproduction, behavior, metabolic process, cellular process, reproductive process, signaling, multicellular organismal process, developmental process, growth, locomotion, single-organism process, regulation of biological process, response to stimulus, localization, multi-organism process, biological regulation, cellular component organization or biogenesis
P02749	Beta-2-glycoprotein 1	*APOH*	38.27	17q24.2	0.329	0.561	metabolic process, cellular process, multicellular organismal process, developmental process, locomotion, single-organism process, regulation of biological process, response to stimulus, localization, biological regulation

P01780	Immunoglobulin heavy variable 3-7	*IGHV3-7*	12.93	14q32.33	0.320	0.514	immune system process, metabolic process, cellular process, signaling, single-organism process, regulation of biological process, response to stimulus, localization, biological regulation
P04430	Immunoglobulin kappa variable 1-16	*IGKV1-16*	12.61	2p11.2	0.301	0.615	immune system process, metabolic process, cellular process, signaling, single-organism process, regulation of biological process, response to stimulus, localization, biological regulation
P01619	Immunoglobulin kappa variable 3-20	*IGKV3-20*	12.55	2p11.2	0.291	0.353	immune system process, metabolic process, cellular process, signaling, single-organism process, regulation of biological process, response to stimulus, localization, biological regulation
P43251	Biotinidase	*BTD*	61.09	3p25.1	0.273	0.611	metabolic process, cellular process, multicellular organismal process, developmental process, single-organism process
P04217	Alpha-1B-glycoprotein	*A1BG*	54.22	19q13.43	0.271	0.527	cellular process, single-organism process, localization
P01024	Complement C3	*C3*	187.03	19p13.3	0.258	0.517	immune system process, metabolic process, cellular process, signaling, multicellular organismal process, developmental process, single-organism process, regulation of biological process, response to stimulus, localization, biological regulation, cellular component organization or biogenesis
P00751	Complement factor B	*CFB*	85.48	6p21.33	0.251	0.710	immune system process, metabolic process, regulation of biological process, response to stimulus, biological regulation
P00736	Complement C1r subcomponent	*C1R*	80.07	12p13.31	0.240	0.685	immune system process, metabolic process, regulation of biological process, response to stimulus, biological regulation
P01766	Immunoglobulin heavy variable 3-13	*IGHV3-13*	12.50	14q32.33	0.232	0.698	immune system process, metabolic process, cellular process, signaling, single-organism process, regulation of biological process, response to stimulus, localization, biological regulation
P01871	Ig mu chain C region	*IGHM*	49.28	14q32.33	0.232	0.799	immune system process, metabolic process, cellular process, signaling, single-organism process, regulation of biological process, response to stimulus, localization, multi-organism process, biological regulation, cellular component organization or biogenesis
P02746	Complement C1q subcomponent subunit B	*C1QB*	26.70	1p36.12	0.177	0.847	immune system process, metabolic process, multicellular organismal process, developmental process, single-organism process, regulation of biological process, response to stimulus, biological regulation
P02774	Vitamin D-binding protein	*GC*	52.93	4q13.3	0.176	0.804	metabolic process, single-organism process, localization
P05156	Complement factor I	*CFI*	65.71	4q25	0.174	0.821	immune system process, metabolic process, regulation of biological process, response to stimulus, localization, biological regulation
P03952	Plasma kallikrein	*KLKB1*	71.32	4q35.2	0.173	0.846	metabolic process, cellular process, multicellular organismal process, single-organism process, regulation of biological process, response to stimulus, biological regulation, cellular component organization or biogenesis
P0C0L4	Complement C4-A	*C4A*	192.66	6p21.33	0.168	0.878	immune system process, metabolic process, cellular process, single-organism process, regulation of biological process, response to stimulus, localization,

							biological regulation, cellular component organization or biogenesis
P0C0L5	Complement C4-B	*C4B_2*	192.63	6p21.33	0.168	0.878	immune system process, metabolic process, cellular process, single-organism process, regulation of biological process, response to stimulus, localization, multi-organism process, biological regulation, cellular component organization or biogenesis
Q9NZP8	Complement C1r subcomponent-like protein	*C1RL*	53.46	12q13.31	0.165	0.866	immune system process, metabolic process, regulation of biological process, response to stimulus, biological regulation
P05090	Apolipoprotein D	*APOD*	21.26	3q29	0.148	0.867	immune system process, metabolic process, cellular process, biological adhesion, signaling, multicellular organismal process, developmental process, growth, locomotion, single-organism process, regulation of biological process, response to stimulus, localization, biological regulation, cellular component organization or biogenesis
Q14624	Inter-alpha-trypsin inhibitor heavy chain H4	*ITIH4*	103.29	3p21.1	0.144	0.899	metabolic process, cellular process, single-organism process, regulation of biological process, response to stimulus, localization, biological regulation
P01764	Ig heavy chain V-III region 23	*IGHV3-23*	12.57	14q32.33	0.139	0.921	immune system process, metabolic process, cellular process, signaling, single-organism process, regulation of biological process, response to stimulus, localization, multi-organism process, biological regulation, cellular component organization or biogenesis
Q06033	Inter-alpha-trypsin inhibitor heavy chain H3	*ITIH3*	99.79	3p21.1	0.136	0.941	metabolic process, cellular process, single-organism process, regulation of biological process, localization, biological regulation
P01602	Ig heavy chain V-I region 5 (Fragment)	*IGKV1-5*	12.77	2p11.2	0.134	0.972	immune system process, metabolic process, cellular process, signaling, single-organism process, regulation of biological process, response to stimulus, localization, biological regulation
P09871	Complement C1s subcomponent	*C1S*	76.63	12p13.31	0.131	0.941	immune system process, metabolic process, regulation of biological process, response to stimulus, biological regulation
P01008	Antithrombin-III	*SERPINC1*	52.57	1q25.1	0.116	0.982	immune system process, metabolic process, cellular process, multicellular organismal process, developmental process, single-organism process, regulation of biological process, response to stimulus, localization, biological regulation
P05546	Heparin cofactor 2	*SERPIND1*	57.03	22q11.21	0.075	0.825	metabolic process, cellular process, multicellular organismal process, locomotion, single-organism process, regulation of biological process, response to stimulus, biological regulation
P22792	Carboxypeptidase N subunit 2	*CPN2*	60.52	3q29	0.069	0.896	biological regulation
P05155	Plasma protease C1 inhibitor	*SERPING1*	55.12	11q12.1	0.065	0.864	immune system process, metabolic process, cellular process, multicellular organismal process, developmental process, single-organism process, regulation of biological process, response to stimulus, localization, biological regulation

O75636	Ficolin-3	*FCN3*	32.88	1p36.11	0.054	0.893	immune system process, metabolic process, cellular process, single-organism process, regulation of biological process, response to stimulus, localization, multi-organism process, biological regulation
P02747	Complement C1q subcomponent subunit C	*C1QC*	25.76	1p36.12	0.037	0.822	immune system process, metabolic process, cellular process, multicellular organismal process, developmental process, single-organism process, regulation of biological process, response to stimulus, biological regulation
P35527	Keratin, type I cytoskeletal 9	*KRT9*	62.03	17q21.2	0.031	0.910	reproduction, cellular process, reproductive process, multicellular organismal process, developmental process, single-organism process, multi-organism process, cellular component organization or biogenesis
P02790	Hemopexin	*HPX*	51.64	11p15.4	0.029	0.845	immune system process, metabolic process, cellular process, signaling, single-organism process, regulation of biological process, response to stimulus, localization, multi-organism process, biological regulation
P13671	Complement component C6	*C6*	104.72	5p13.1	0.028	0.852	immune system process, metabolic process, cellular process, multicellular organismal process, developmental process, single-organism process, regulation of biological process, response to stimulus, biological regulation
P05543	Thyroxine-binding globulin	*SERPINA7*	46.29	Xq22.3	0.007	0.681	metabolic process, cellular process, single-organism process, regulation of biological process, localization, biological regulation
P02743	Serum amyloid P-component	*APCS*	25.37	1q23.2	-0.007	0.889	immune system process, metabolic process, cellular process, multicellular organismal process, developmental process, single-organism process, regulation of biological process, response to stimulus, multi-organism process, biological regulation, cellular component organization or biogenesis
P02656	Apolipoprotein C-III	*APOC3*	10.85	11q23.3	-0.036	0.749	metabolic process, cellular process, signaling, multicellular organismal process, single-organism process, regulation of biological process, response to stimulus, localization, biological regulation, cellular component organization or biogenesis
A0A075B6P5	Immunoglobulin kappa variable 2-28	*IGKV2-28*	12.95	2p11.2	-0.052	0.736	immune system process, response to stimulus
A0A0A0MS15	Immunoglobulin heavy variable 3-49	*IGHV3-49*	13.05	14q32.33	-0.089	0.638	(not available)
P02647	Apolipoprotein A-I	*APOA1*	30.76	11q23.3	-0.093	0.531	immune system process, metabolic process, cellular process, biological adhesion, signaling, multicellular organismal process, developmental process, locomotion, single-organism process, regulation of biological process, response to stimulus, localization, biological regulation, cellular component organization or biogenesis
Q06136	3-ketodihydrosphingosine reductase	*KDSR*	36.16	18q21.33	-0.102	0.557	metabolic process, cellular process, single-organism process
Q96PD5	N-acetylmuramoyl-L-alanine amidase	*PGLYRP2*	62.18	19p13.12	-0.107	0.609	immune system process, metabolic process, cellular process, signaling, multicellular organismal process, developmental process, growth, single-organism process, regulation of biological process, response to stimulus, multi-

							organism process, biological regulation
O95445	Apolipoprotein M	*APOM*	21.24	6p21.33	-0.109	0.341	metabolic process, cellular process, multicellular organismal process, single-organism process, regulation of biological process, response to stimulus, localization, biological regulation, cellular component organization or biogenesis, detoxification
P01742	Immunoglobulin heavy variable 1-69	*IGHV1-69*	12.65	14q32.33	-0.117	0.578	immune system process, metabolic process, cellular process, signaling, single-organism process, regulation of biological process, response to stimulus, localization, biological regulation
P07996	Thrombospondin-1	*THBS1*	129.30	15q14	-0.124	0.710	immune system process, behavior, metabolic process, cellular process, biological adhesion, signaling, multicellular organismal process, developmental process, locomotion, single-organism process, regulation of biological process, response to stimulus, localization, biological regulation, cellular component organization or biogenesis
P01709	Immunoglobulin lambda variable 2-8	*IGLV2-8*	12.37	22q11.22	-0.144	0.724	immune system process, metabolic process, cellular process, signaling, single-organism process, regulation of biological process, response to stimulus, localization, biological regulation
P01721	Immunoglobulin lambda variable 6-57	*IGLV6-57*	12.56	22q11.22	-0.147	0.605	immune system process, metabolic process, cellular process, signaling, single-organism process, regulation of biological process, response to stimulus, localization, biological regulation
P10909	Clusterin	*CLU*	52.46	8p21.1	-0.186	0.424	immune system process, metabolic process, cellular process, signaling, multicellular organismal process, developmental process, single-organism process, regulation of biological process, response to stimulus, localization, multi-organism process, biological regulation, cellular component organization or biogenesis
P04114	Apolipoprotein B-100	*APOB*	515.28	2p24.1	-0.194	0.334	reproduction, immune system process, metabolic process, cellular process, reproductive process, multicellular organismal process, developmental process, locomotion, single-organism process, regulation of biological process, response to stimulus, localization, multi-organism process, biological regulation, cellular component organization or biogenesis
P02751	Fibronectin	*FN1*	262.46	2q35	-0.232	0.345	immune system process, metabolic process, cellular process, biological adhesion, signaling, multicellular organismal process, developmental process, growth, locomotion, single-organism process, regulation of biological process, response to stimulus, localization, biological regulation, cellular component organization or biogenesis
P29622	Kallistatin	*SERPINA4*	48.51	14q32.13	-0.233	0.025	metabolic process, cellular process, single-organism process, regulation of biological process, localization, biological regulation
P69905	Hemoglobin subunit alpha	*HBA1*	15.25	16p13.3	-0.235	0.351	metabolic process, cellular process, single-organism process, regulation of biological process, response to stimulus, localization, biological regulation, cellular component organization or biogenesis, detoxification
P01701	Immunoglobulin	*IGLV1-51*	12.24	22q11.22	-0.269	0.385	immune system process, metabolic process, cellular process, signaling,

	lambda variable 1-51						single-organism process, regulation of biological process, response to stimulus, localization, biological regulation
P01699	Immunoglobulin lambda variable 1-44	*IGLV1-44*	12.19	22q11.22	-0.305	0.190	immune system process, metabolic process, cellular process, signaling, single-organism process, regulation of biological process, response to stimulus, localization, biological regulation
P01700	Immunoglobulin lambda variable 1-47	*IGLV1-47*	12.28	22q11.22	-0.325	0.309	immune system process, metabolic process, cellular process, signaling, single-organism process, regulation of biological process, response to stimulus, localization, biological regulation
P10643	Complement component C7	*C7*	93.46	5p13.1	-0.345	0.313	immune system process, metabolic process, cellular process, regulation of biological process, response to stimulus, biological regulation
P69892	Hemoglobin subunit gamma-2	*HBG2*	16.12	11p15.4	-0.353	0.158	multicellular organismal process, single-organism process, response to stimulus, localization, biological regulation
P69891	Hemoglobin subunit gamma-1	*HBG1*	16.13	11p15.4	-0.381	0.142	multicellular organismal process, single-organism process, response to stimulus, localization, biological regulation
P02042	Hemoglobin subunit delta	*HBD*	16.05	11p15.4	-0.395	0.156	multicellular organismal process, single-organism process, response to stimulus, localization, biological regulation
P68871	Hemoglobin subunit beta	*HBB*	15.99	11p15.4	-0.395	0.151	metabolic process, cellular process, biological adhesion, multicellular organismal process, single-organism process, regulation of biological process, response to stimulus, localization, biological regulation, cellular component organization or biogenesis, detoxification
P02771	Alpha-fetoprotein	*AFP*	68.63	4q13.3	-0.658	0.351	reproduction, metabolic process, cellular process, reproductive process, signaling, multicellular organismal process, developmental process, single-organism process, rhythmic process, regulation of biological process, response to stimulus, localization, multi-organism process, biological regulation

Log_2R is shown as average of binary logarithm of fold change of protein expression. *P* values were calculated by Student's *t*-test. MW, Molecular weight.

Supplementary Table 3 Differentially expressed proteins associated with complement and coagulation cascades.

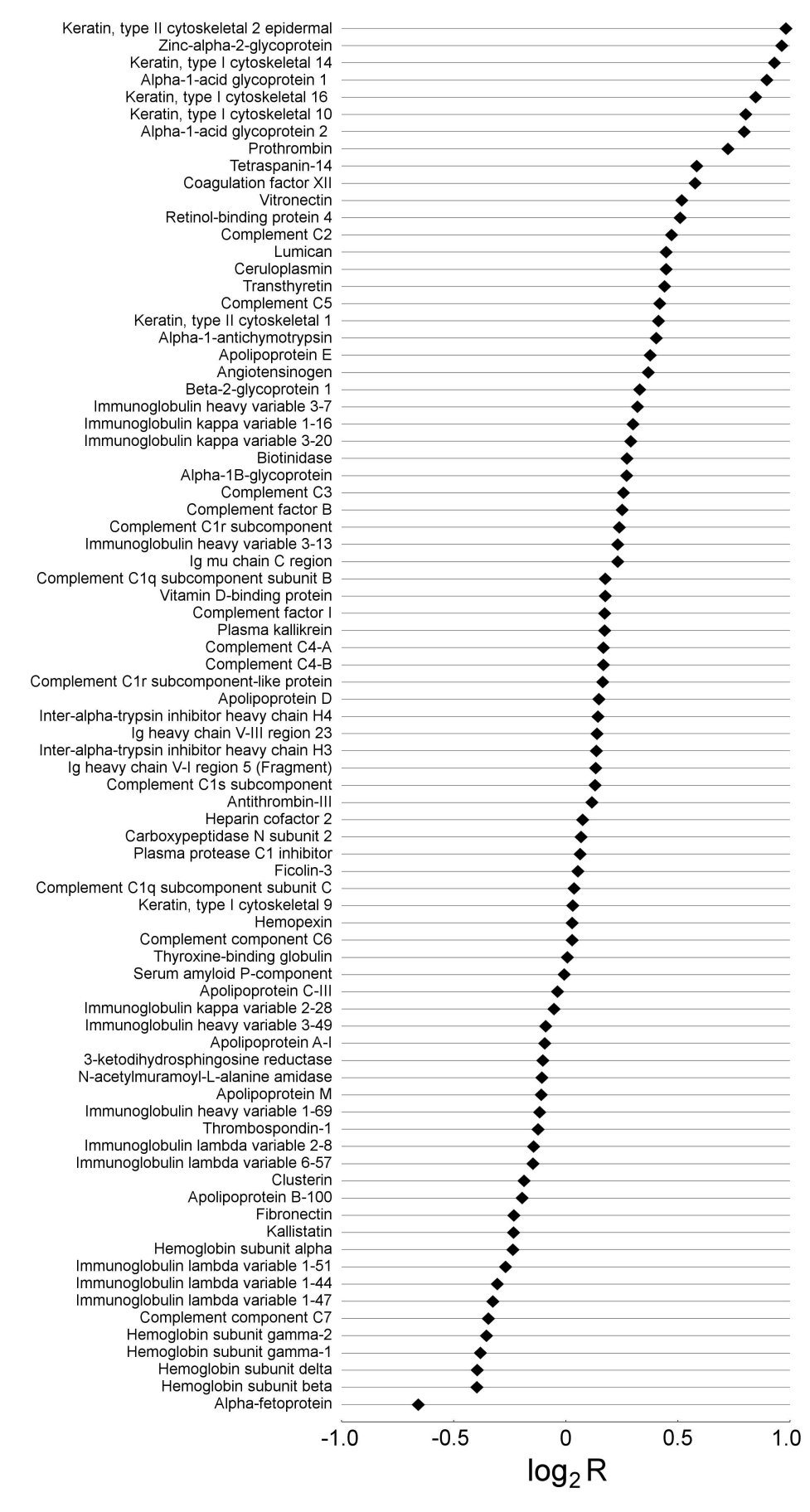
UniProt Accession Number	Protein name	Gene symbol	Log_2R (UA)	Log_2R (MS)
P00734	Prothrombin	*F2*	0.723	N/A
P00736	Complement C1r subcomponent	*C1R*	0.240	N/A
P00742	Coagulation factor X	*F10*	N/A	0.346
P00748	Coagulation factor XII	*F12*	0.577	0.529
P00751	Complement factor B	*CFB*	0.251	N/A
P01008	Antithrombin-III	*SERPINC1*	0.116	N/A
P01024	Complement C3	*C3*	0.258	0.010
P01031	Complement C5	*C5*	0.420	0.345
P02746	Complement C1q subcomponent subunit B	*C1QB*	0.177	N/A
P02747	Complement C1q subcomponent subunit C	*C1QC*	0.037	N/A
P02748	Complement component C9	*C9*	N/A	0.383
P03952	Plasma kallikrein	*KLKB1*	0.173	0.152
P05154	Plasma serine protease inhibitor	*SERPINA5*	N/A	0.331
P05155	Plasma protease C1 inhibitor	*SERPING1*	0.065	N/A
P05156	Complement factor I	*CFI*	0.174	0.064
P05160	Coagulation factor XIII B chain	*F13B*	N/A	0.089
P05546	Heparin cofactor 2	*SERPIND1*	0.075	N/A
P06681	Complement C2	*C2*	0.471	N/A
P08697	Alpha-2-antiplasmin	*SERPINF2*	N/A	0.133
P09871	Complement C1s subcomponent	*C1S*	0.131	N/A
P10643	Complement component C7	*C7*	-0.345	N/A
P13671	Complement component C6	*C6*	0.028	N/A
P0C0L4	Complement C4-A	*C4A*	0.168	0.351
P0C0L5	Complement C4-B	*C4B_2*	0.168	0.353

Log_2R is shown as average of binary logarithm of fold change of protein expression. UA, Umbilical arterial serum; MS, Maternal serum; N/A, Not available.

Supplementary Table 4 Drug therapy of subjects at delivery.

Case #	Antipsychotic	Other psychotropic
1	Blonanserin (SDA)	
2	Aripiprazole (DSS)	
3		Yokukansan (KMP)
4		Mianserin (TetraCA)
5	Risperidone (SDA)	
6	Quetiapine (MARTA), Aripiprazole (DSS)	Clonazepam (BZD), Estazolam (BZD)

SDA, Serotonin-Dopamine antagonist; DSS, Dopamine-Serotonin system stabilizer; MARTA, Multi-acting receptor-targeted antipsychotic; KMP, Kampo medicine; TetraCA, Tetracyclic antidepressant; BZD, Benzodiazepine.


Keratin, type II cytoskeletal 2 epidermal
Zinc-alpha-2-glycoprotein
Keratin, type I cytoskeletal 14
Alpha-1-acid glycoprotein 1
Keratin, type I cytoskeletal 16
Keratin, type I cytoskeletal 10
Alpha-1-acid glycoprotein 2
Prothrombin
Tetraspanin-14
Coagulation factor XII
Vitronectin
Retinol-binding protein 4
Complement C2
Lumican
Ceruloplasmin
Transthyretin
Complement C5
Keratin, type II cytoskeletal 1
Alpha-1-antichymotrypsin
Apolipoprotein E
Angiotensinogen
Beta-2-glycoprotein 1
Immunoglobulin heavy variable 3-7
Immunoglobulin kappa variable 1-16
Immunoglobulin kappa variable 3-20
Biotinidase
Alpha-1B-glycoprotein
Complement C3
Complement factor B
Complement C1r subcomponent
Immunoglobulin heavy variable 3-13
Ig mu chain C region
Complement C1q subcomponent subunit B
Vitamin D-binding protein
Complement factor I
Plasma kallikrein
Complement C4-A
Complement C4-B
Complement C1r subcomponent-like protein
Apolipoprotein D
Inter-alpha-trypsin inhibitor heavy chain H4
Ig heavy chain V-III region 23
Inter-alpha-trypsin inhibitor heavy chain H3
Ig heavy chain V-I region 5 (Fragment)
Complement C1s subcomponent
Antithrombin-III
Heparin cofactor 2
Carboxypeptidase N subunit 2
Plasma protease C1 inhibitor
Ficolin-3
Complement C1q subcomponent subunit C
Keratin, type I cytoskeletal 9
Hemopexin
Complement component C6
Thyroxine-binding globulin
Serum amyloid P-component
Apolipoprotein C-III
Immunoglobulin kappa variable 2-28
Immunoglobulin heavy variable 3-49
Apolipoprotein A-I
3-ketodihydrosphingosine reductase
N-acetylmuramoyl-L-alanine amidase
Apolipoprotein M
Immunoglobulin heavy variable 1-69
Thrombospondin-1
Immunoglobulin lambda variable 2-8
Immunoglobulin lambda variable 6-57
Clusterin
Apolipoprotein B-100
Fibronectin
Kallistatin
Hemoglobin subunit alpha
Immunoglobulin lambda variable 1-51
Immunoglobulin lambda variable 1-44
Immunoglobulin lambda variable 1-47
Complement component C7
Hemoglobin subunit gamma-2
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Hemoglobin subunit delta
Hemoglobin subunit beta
Alpha-fetoprotein
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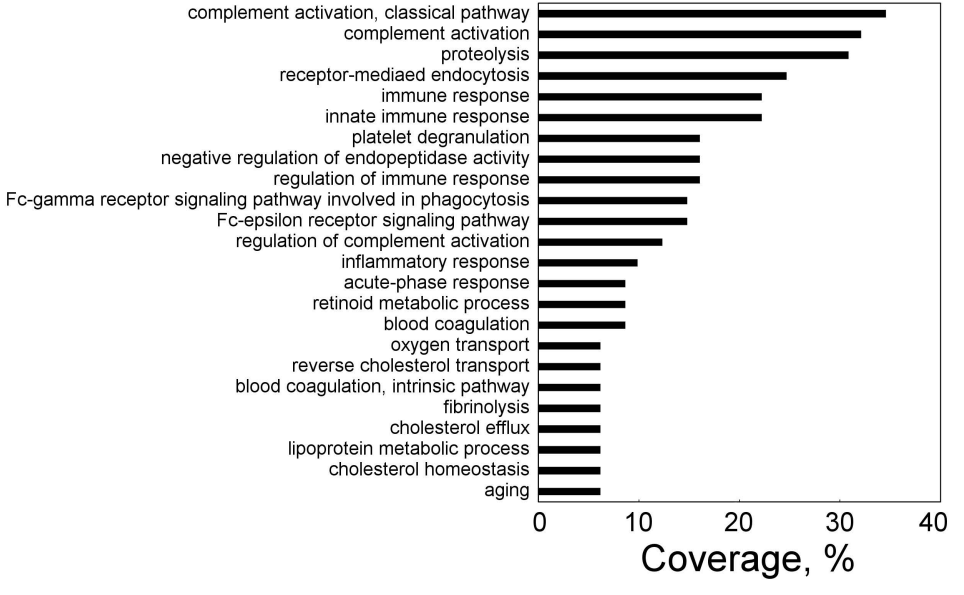
log2 R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complement activation
proteolysis
receptor-mediaed endocytosis
immune response
innate immune response
platelet degranulation
negative regulation of endopeptidase activity
regulation of immune response
Fc-gamma receptor signaling pathway involved in phagocytosis
Fc-epsilon receptor signaling pathway
regulation of complement activation
inflammatory response
acute-phase response
retinoid metabolic process
blood coagulation
oxygen transport
reverse cholesterol transport
blood coagulation, intrinsic pathway
fibrinolysis
cholesterol efflux
lipoprotein metabolic process
cholesterol homeostasis
aging
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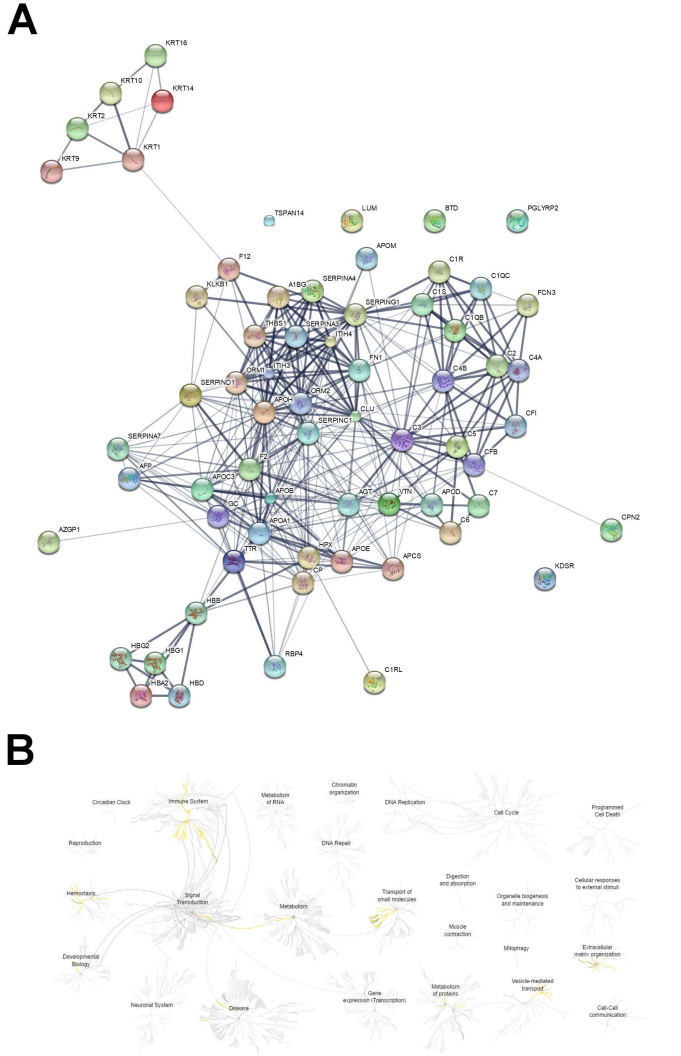
Coverage, %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C1QC
KLKB1
A1BG
SERPINA4
C1S
FCN3
SERPING1
C1QB
THBS1
SERPINA1
ITIH4
FN1
C2
C4A
C4B
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FGA
AFP
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AGT
VTN
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C6
CPN2
GC
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APOA1
TTR
HPX
APOE
APOC3
C9
KDSR
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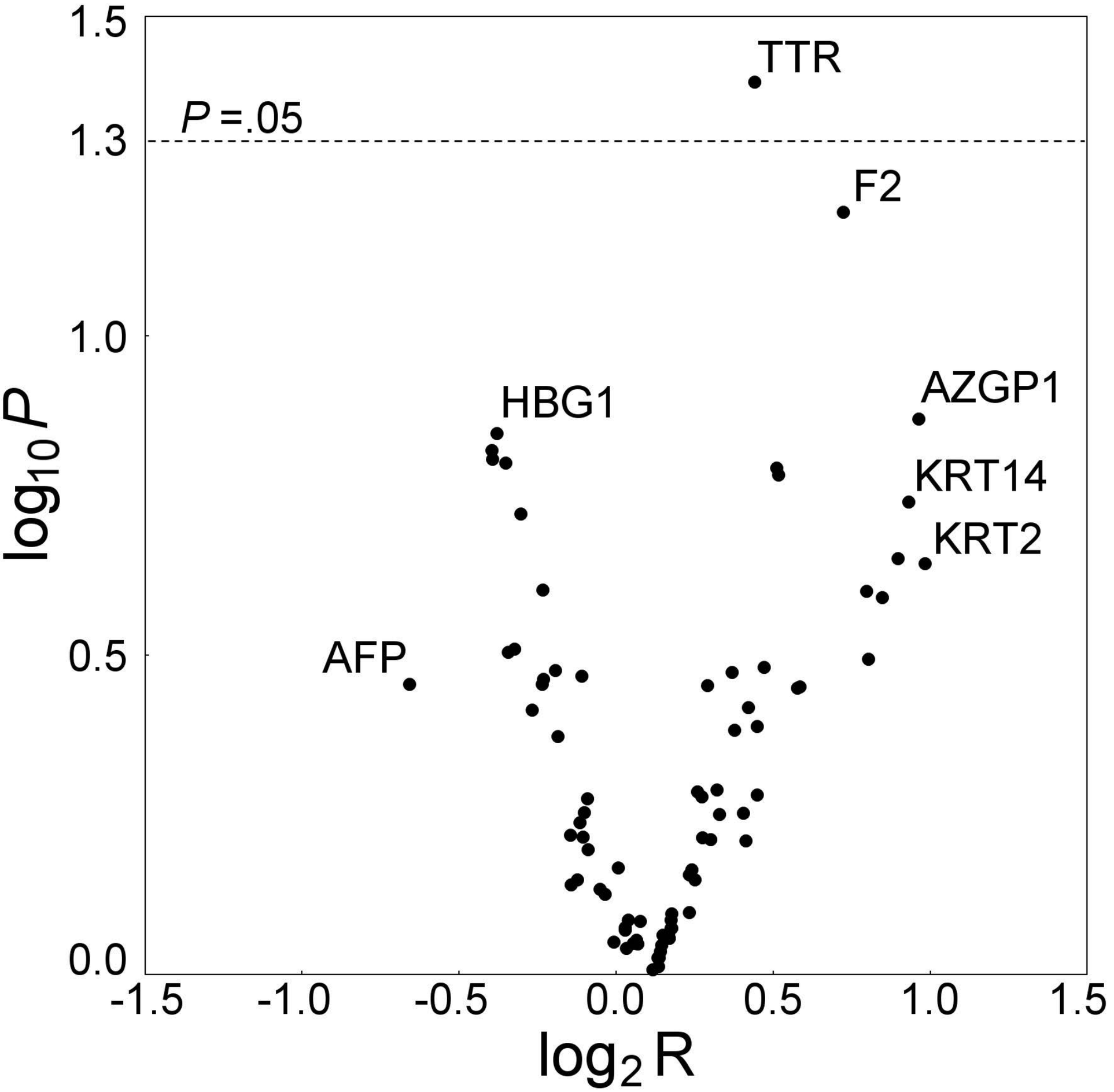
HBG2
HBG1
RBP4
HBA2
HBD
C1RL
B
Circadian Clock
Immune System
Metabolism of RNA
Chromatin organization
DNA Replication
Cell Cycle
Programmed Cell Death
Reproduction
DNA Repair
Digestion and absorption
Cellular responses to external stimuli
Hemostasis
Signal Transduction
Metabolism
Transport of small molecules
Organelle biogenesis and maintenance
Muscle contraction
Developmental Biology
Mitophagy
Extracellular matrix organization
Vesicle-mediated transport
Metabolism of proteins
Gene expression (Transcription)
Neuronal System
Disease
Cell-Cell communication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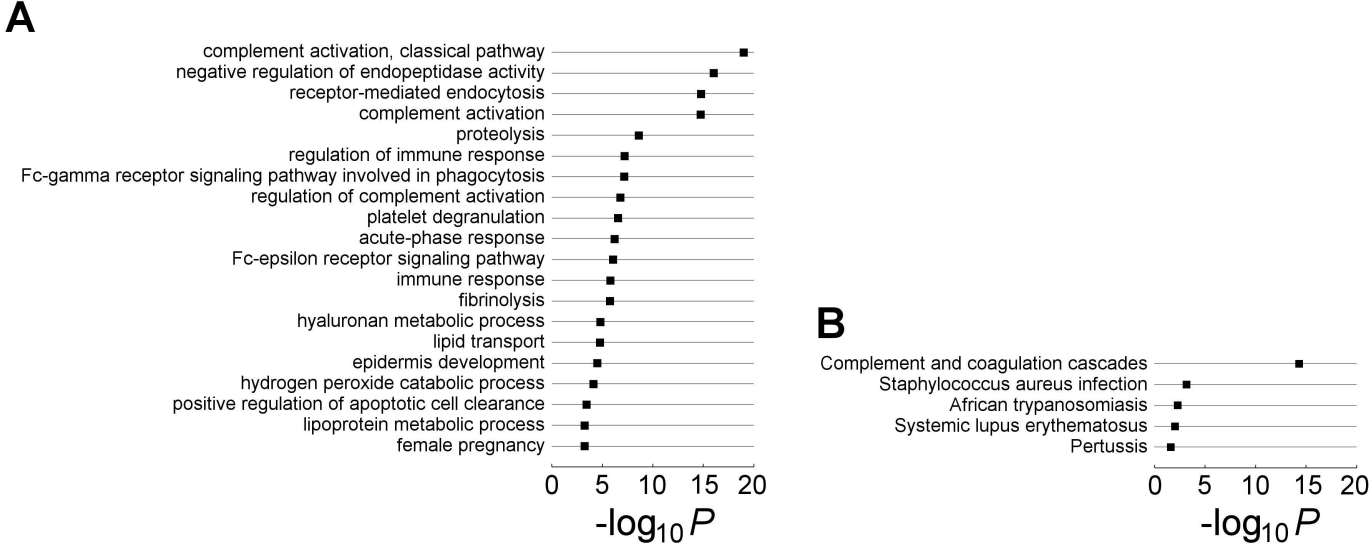
log2 R


A
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negative regulation of endopeptidase activity
receptor-mediated endocytosis
complement activation
proteolysis
regulation of immune response
Fc-gamma receptor signaling pathway involved in phagocytosis
regulation of complement activation
platelet degranulation
acute-phase response
Fc-epsilon receptor signaling pathway
immune response
fibrinolysis
hyaluronan metabolic process
lipid transport
epidermis development
hydrogen peroxide catabolic process
positive regulation of apoptotic cell clearance
lipoprotein metabolic process
female pregnancy
0 5 10 15 20
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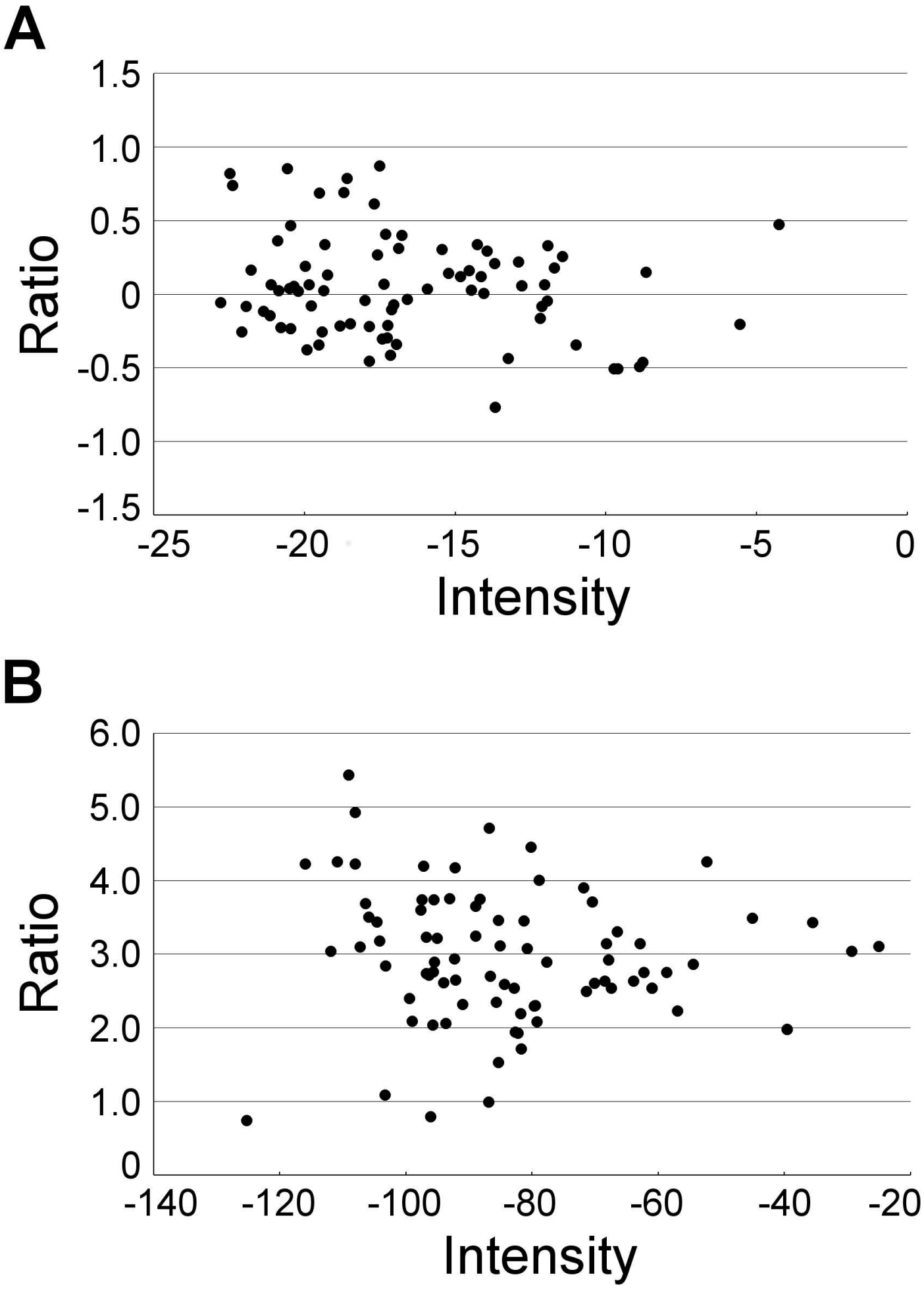
Complement and coagulation cascades
Staphylococcus aureus infection
African trypanosomiasis
Systemic lupus erythematosus
Pertussis
0 5 10 15 20
-log10 P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Ratio
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-5
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Intensity
B
6.0
5.0
4.0
3.0
2.0
1.0
0
Ratio
-140
-120
-100
-80
-60
-40
-20
Intensity