S1. Demographics

A.

1.

| 0 | 25 | 50 | 75 | 100 % of participants |

| INMA | GINIplus | BAMSE |
| pre-school children | adolescents |

2.

| any allergic disease (n=355) | no allergic disease (n=431) |

| 0 | 25 | 50 | 75 | 100 % of cases |

| any single disease | | | any multimorbidity | | | |
| asthma alone (A) | dermatitis alone (D) | rhinitis alone (R) | A+D | D+R | A+R | ADR |

3.

asthma multim.	(A+D or A+R or A+D+R)
dermatitis multim.	(A+D or D+R or A+D+R)
rhinitis multim.	(A+R or D+R or A+D+R)

| 0 | 25 | 50 | 75 | 100 % of cases |

B.

ALL ALLERGIC PARTICIPANTS (355 cases)

A	65
D	76
R	91
A+D	34
A+R	50
D+R	21
A+D+R	18

BAMSE (156 cases)

A	32
D	22
R	23
A+D	17
A+R	33
D+R	13
A+D+R	16

GINIplus (107 cases)

A	15
D	6
R	64
A+D	1
A+R	15
D+R	4
A+D+R	2

INMA (92 cases)

A	18
D	48
R	4
A+D	16
A+R	2
D+R	4
A+D+R	0

S2. Variables adjustment

A. Any multimorbidity versus controls

ComBat → SVA

Residuals
Min -0.16
1Q -0.025
Median -0.0011
3Q 0.030
Max 0.099

Residual standard error
0.043 on 549 degrees of freedom
Multiple R-squared: 0.0016
Adjusted R-squared: -0.0056
F-statistic: 0.022 on 4 and 549 DF
0-value: 0.92

B. Surrogate variables in other contrasts

Number of surrogate variables found after ComBat adjustment

asthma multimorbidity	0
dermatitis multimorbidity	0
rhinitis multimorbidity	0
asthma alone	0
dermatitis alone	**1**
rhinitis alone	**10**
A+D+R	0
any multimorbidity in adolescents	0
any multimorbidity in children	**1**

dermatitis alone
p-value: 0.95

rhinitis alone
p-values

sv1: 0.92 sv2: 0.61 sv3: 0.48 sv4: 0.61
sv5: 0.97 sv6: 0.79 sv7: 0.97 sv8: 0.30
sv9: 0.83 sv10: 0.93

sv2   sv3   sv8

any multimorbidity in children
p-value: 0.95

S3. Circos plot of 50 DEGs

S4.1. DEGs in multimorbidities

A. Any multimorbidity

Any multimorbidity

B. Asthma multimorbidity

Asthma multimorbidity

C. Dermatitis multimorbidity

Dermatitis multimorbidity

D. Rhinitis multimorbidity

Rhinitis multimorbidity

S4.2. DEGs in single diseases

A. Asthma alone

Asthma alone

B. Dermatitis alone

Dermatitis alone

C. Rhinitis alone

Rhinitis alone

Fold Change variation

S6. RT-qPCR validation

A. RT-qPCR

B. HTA 2.0

C.

Difference asthma - control
Reference gene: CPB

Gene	asthma alone	asthma multimorbidity
ACSM3	0.24	0.37
CLC	1.61	1.58
HRH4	0.50	0.58
IL1RL1	1.20	1.46
LGALS12	0.37	0.58
PIK3R6	0.53	0.71
SIGLEC8	0.95	0.93
SLC29A1	0.68	1.27

Difference dermatitis - control
Reference gene: CPB

Gene	dermatitis alone	dermatitis multimorbidity
ACSM3	-0.08	0.31
CLC	0.33	0.71
HRH4	0.00	0.60
IL1RL1	0.18	1.38
LGALS12	-0.20	0.58
PIK3R6	-0.04	0.71
SIGLEC8	0.16	0.87
SLC29A1	0.14	1.23

Difference rhinitis - control
Reference gene: CPB

Gene	rhinitis alone	rhinitis multimorbidity
ACSM3	0.39	0.32
CLC	0.53	1.28
HRH4	0.62	0.64
IL1RL1	1.42	1.29
LGALS12	0.48	0.47
PIK3R6	0.48	0.61
SIGLEC8	0.96	0.84
SLC29A1	0.77	1.23

S7.1. Replication in any multimorbidity

S7.2. Replication in rhinitis alone

S7.3. Replication in asthma alone

S8. Gene Ontology in any multimorbidity

MULTIMORBIDITY – Gene Ontology ... Biological Process

signal transduction by protein phosphorylation · phosphorylation · phosphatidylinositol phosphorylation · regulation of MAPK cascade · interleukin–5 production · regulation of interleukin–5 production · regulation of multicellular organismal process · pyrimidine nucleoside transport · positive regulation of chemokine secretion · regulation of protein secretion · secretion · SA node cell action potential · regulation of membrane potential · cellular chemical homeostasis · membrane repolarization

regulation of intracellular signal transduction · regulation of signal transduction · negative regulation of adenylate cyclase · regulation of protein modification process · cellular protein modification process · regulation of cytokine production · positive regulation of multicellular organismal · negative regulation of interferon–gamma production · regulation of multicellular organismal development · protein secretion · regulation of secretion · calcium ion import · carbohydrate derivative transport · atrial cardiac muscle cell membrane repolarization · regulation of membrane potential · cardiac muscle cell contraction · regulation of heart rate by cardiac conduction · body fluid levels · cellular homeostasis · membrane depolarization

protein phosphorylation · glycerolipid metabolic process · negative regulation of I–kappaB kinase/NF–kappaB signaling · positive regulation of response to stimulus · regulation of lipid kinase activity · cytokine production · sleep · regulation of developmental process · tube morphogenesis · lactation · protein localization · organic substance transport · regulation of protein localization · phosphorus metabolic process · primary metabolic process · macromolecule modification · nitrogen compound metabolic process

lipid modification · regulation of phosphorus metabolic process · regulation of phosphatidylinositol 3–kinase activity · cellular protein metabolic process · positive regulation of intracellular signal transduction · positive regulation of angiogenesis · system development · multicellular organism development · regulation of anatomical structure morphogenesis · tube development · nitrogen compound transport · positive regulation of transport · regulation of potassium ion transmembrane transport · body fluid secretion · macromolecule localization · cellular metabolic process · organic substance metabolic process · regulation of protein metabolic process · cellular macromolecule metabolic process · phosphorus metabolism

immune response · regulation of leukocyte mediated immunity · lymphocyte anergy · regulation of cellular process · regulation of biological process · signal transduction · defense response · inflammatory response to antigenic stimulus · regulation of cyclase activity · regulation of cyclase activity · regulation of lyase activity · biological regulation · cellular process · response to stimulus

regulation of adaptive immune response based on somatic recombination of immune receptors built from immunoglobulin superfamily domains · lymphocyte mediated immunity · T cell activation · tolerance induction · regulation of leukocyte activation · G–protein coupled receptor signaling pathway · cellular response to stimulus · regulation of cellular process · response to stress · inflammatory response · regulation of response · natural killer cell mediated immunity · inflammatory response · biological_process · cell communication · immune system process · multicellular organismal process

regulation of leukocyte activation · regulation of immune effector process · adaptive immune response · regulation of macrophage activation · immune system development · intracellular signal transduction · regulation of cell communication · regulation of response to stimulus · regulation of biological quality · interleukin–5–mediated signaling pathway · cytokine–mediated signaling pathway · interleukin–5–mediated signaling pathway · lymphocyte apoptotic process · leukocyte apoptotic process · metabolism · cell activation

regulation of cell activation · regulation of immune system process · T cell cytokine production · macrophage activation · regulation of signaling · cell surface receptor signaling pathway · interleukin–33–mediated signaling pathway · cellular response to organic substance · leukocyte apoptotic process · signaling · leukotriene signaling pathway · regulation of leukocyte mediated cytotoxicity

MULTIMORBIDITY – Gene Ontology ... Cellular Component

plasma membrane · intrinsic component of membrane · phosphatidylinositol 3–kinase complex, class I · cell periphery · membrane
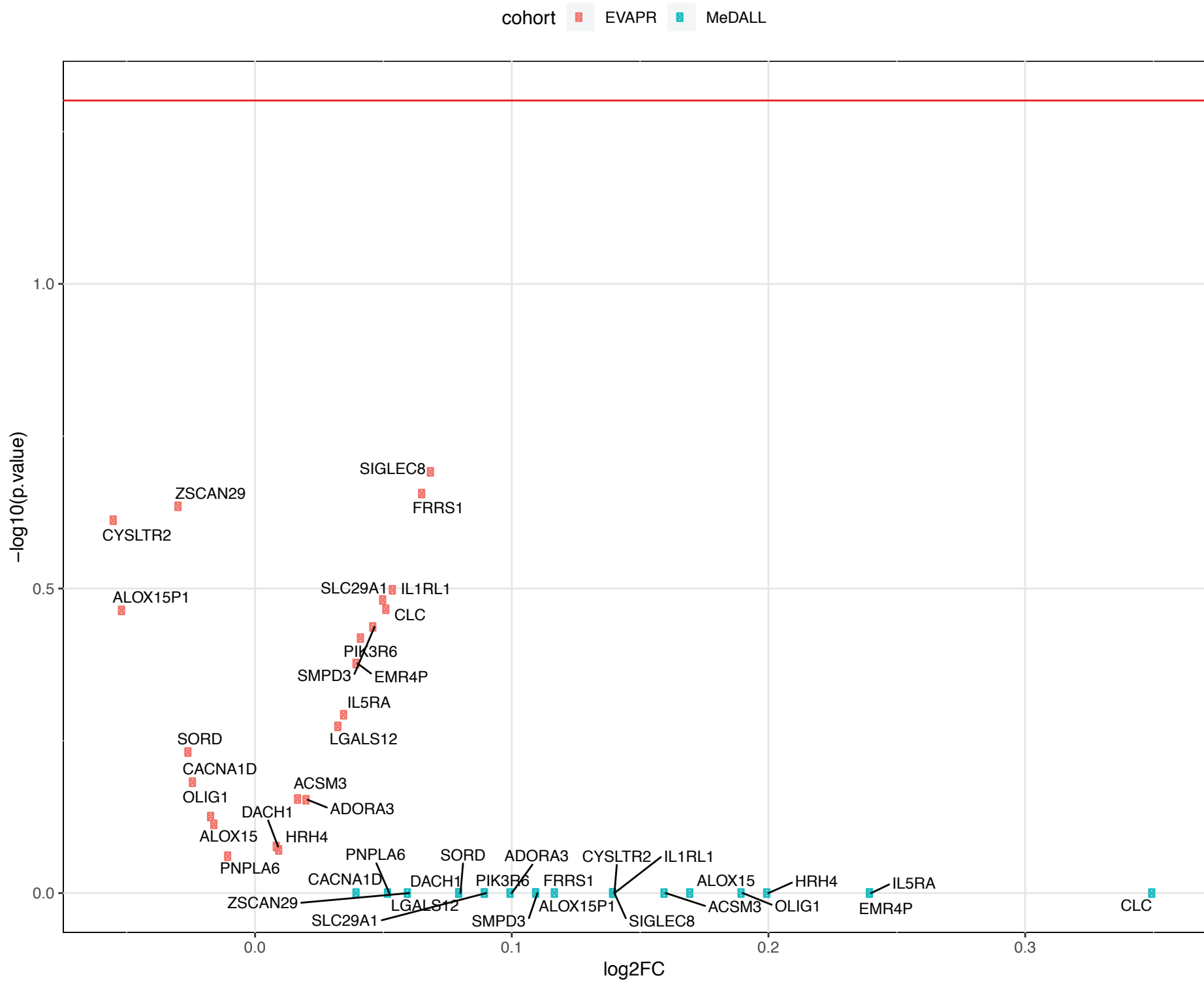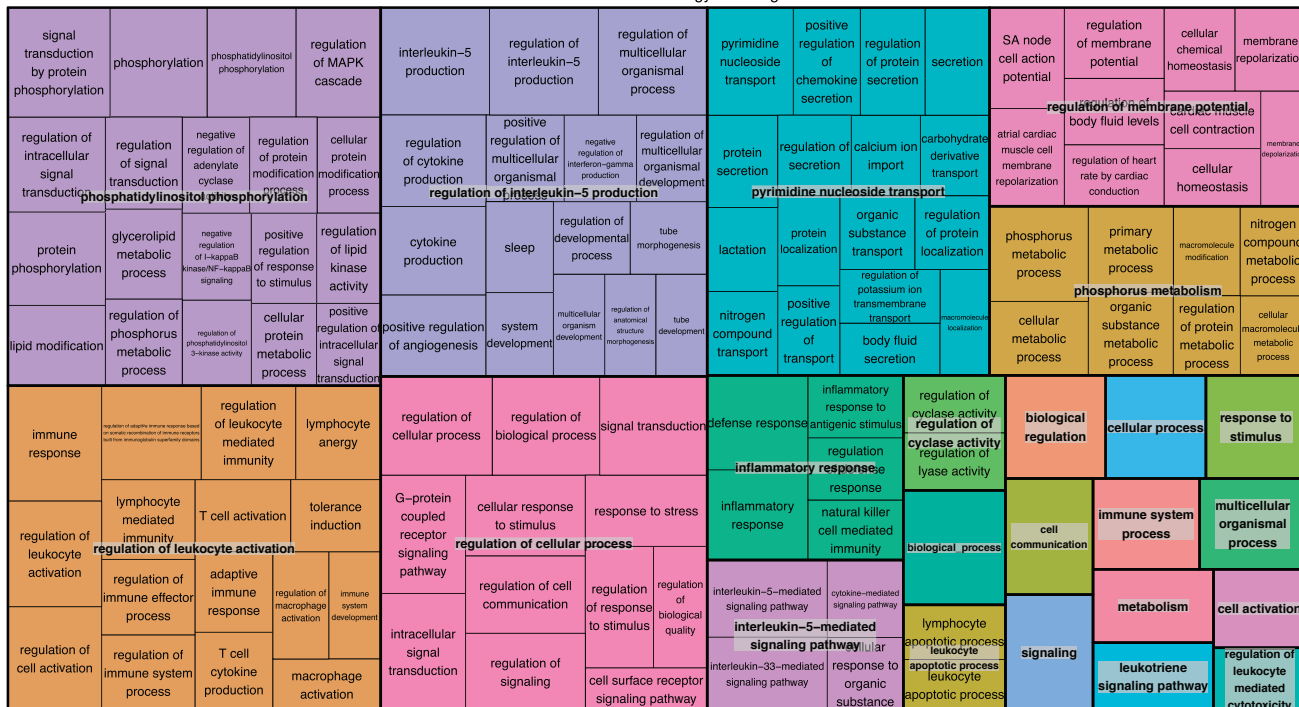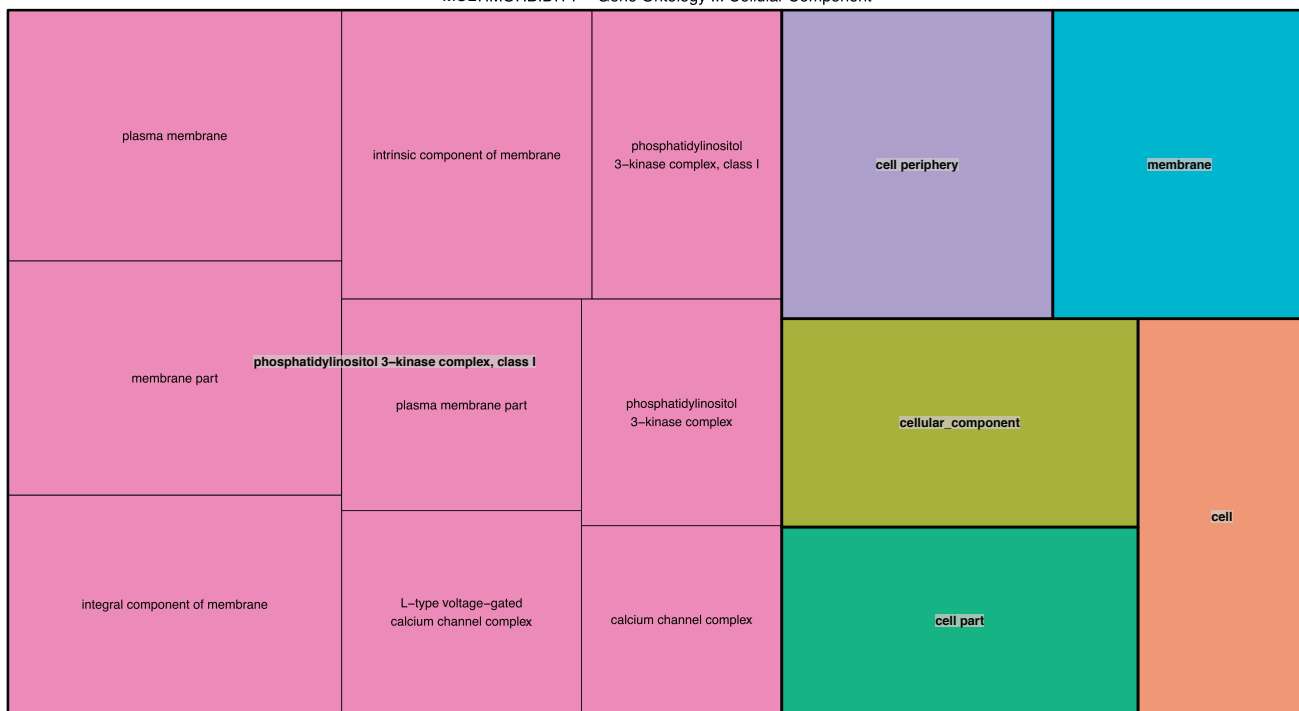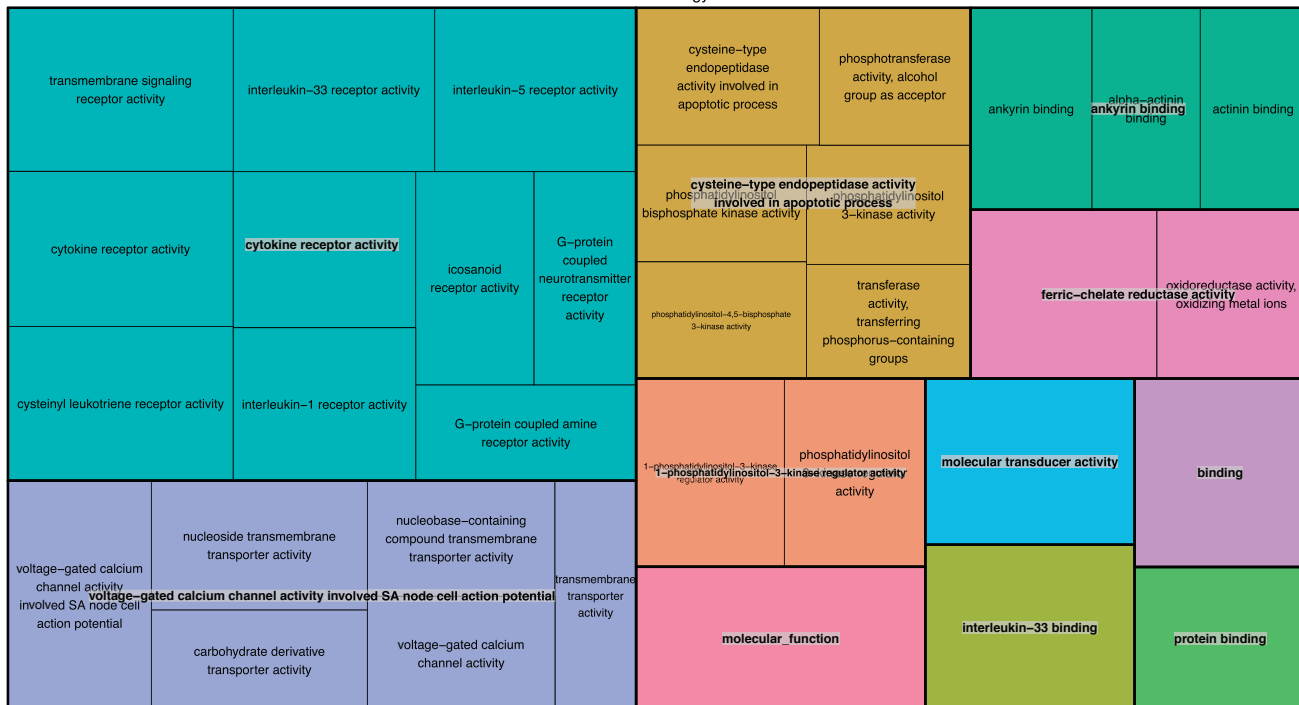
membrane part · phosphatidylinositol 3–kinase complex, class I · plasma membrane part · phosphatidylinositol 3–kinase complex · cellular_component · cell

integral component of membrane · L–type voltage–gated calcium channel complex · calcium channel complex · cell part · cell

MULTIMORBIDITY – Gene Ontology ... Molecular Function

transmembrane signaling receptor activity · interleukin–33 receptor activity · interleukin–5 receptor activity · cysteine–type endopeptidase activity involved in apoptotic process · phosphotransferase activity, alcohol group as acceptor · ankyrin binding · ankyrin binding · alpha–actinin binding · actinin binding

cytokine receptor activity · cytokine receptor activity · icosanoid receptor activity · G–protein coupled neurotransmitter receptor activity · cysteine–type endopeptidase activity involved in apoptotic process · phosphatidylinositol bisphosphate kinase activity · phosphatidylinositol 3–kinase activity · transferase activity, transferring phosphorus–containing groups · ferric–chelate reductase activity · oxidoreductase activity, oxidizing metal ions

cysteinyl leukotriene receptor activity · interleukin–1 receptor activity · G–protein coupled amine receptor activity · phosphatidylinositol–4,5–bisphosphate 3–kinase activity · 1–phosphatidylinositol–3–kinase regulator activity · phosphatidylinositol–3–kinase regulator activity · phosphatidylinositol 3–kinase regulator activity · molecular transducer activity · binding

voltage–gated calcium channel activity involved SA node cell action potential · nucleoside transmembrane transporter activity · nucleobase–containing compound transmembrane transporter activity · transmembrane transporter activity · voltage–gated calcium channel activity involved SA node cell action potential · carbohydrate derivative transporter activity · voltage–gated calcium channel activity · molecular_function · interleukin–33 binding · protein binding

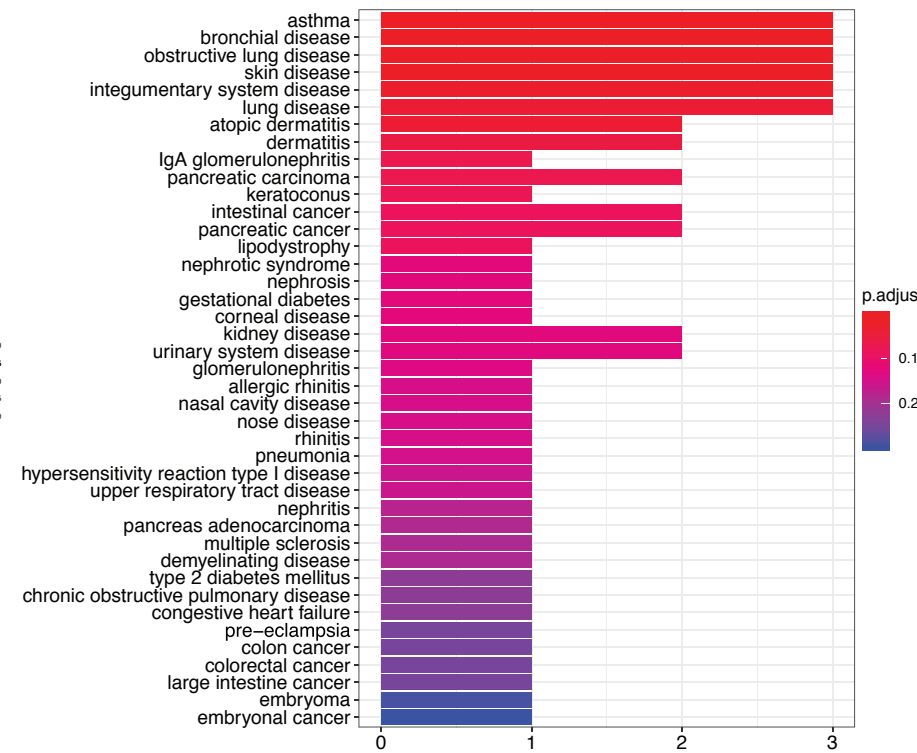# S9. Disease Ontology in any multimorbidity
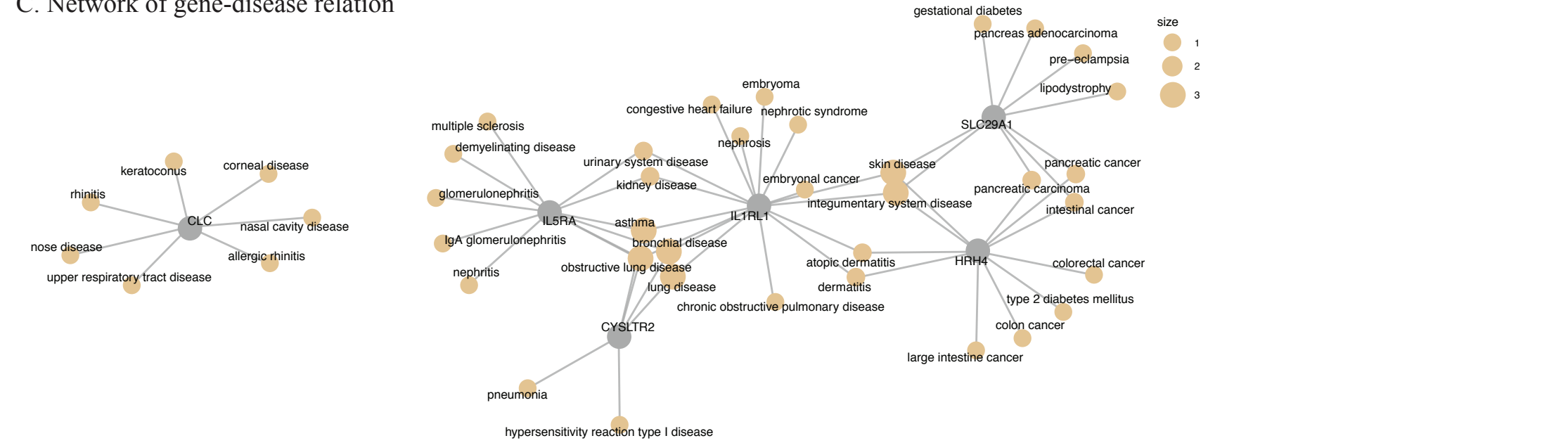
A. Semantical similarity of disease terms

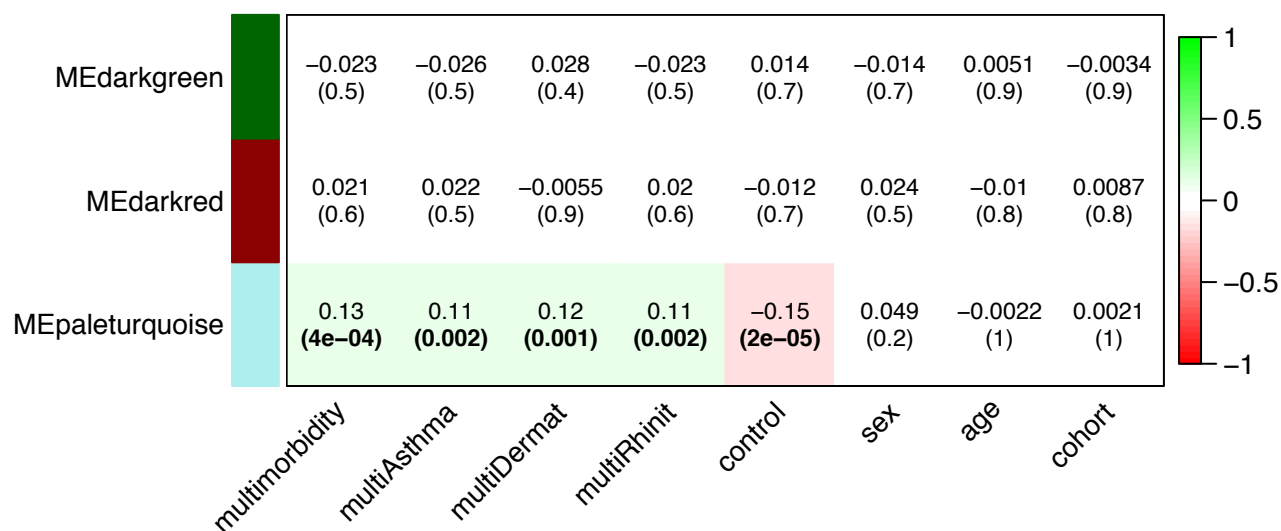## B. Number of query genes in each terms and significance

C. Network of gene-disease relation

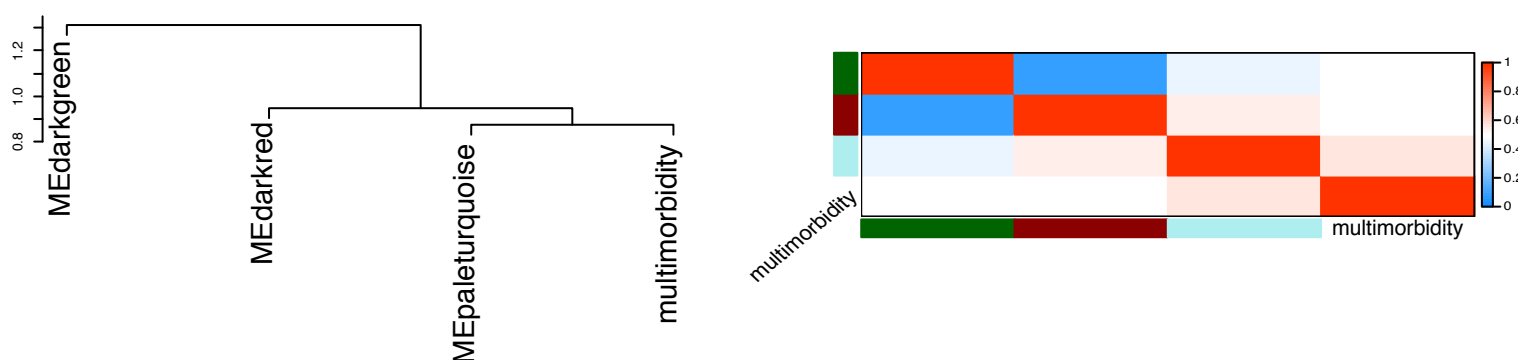# S10.1. Weighted Gene Co-expression Network Analysis

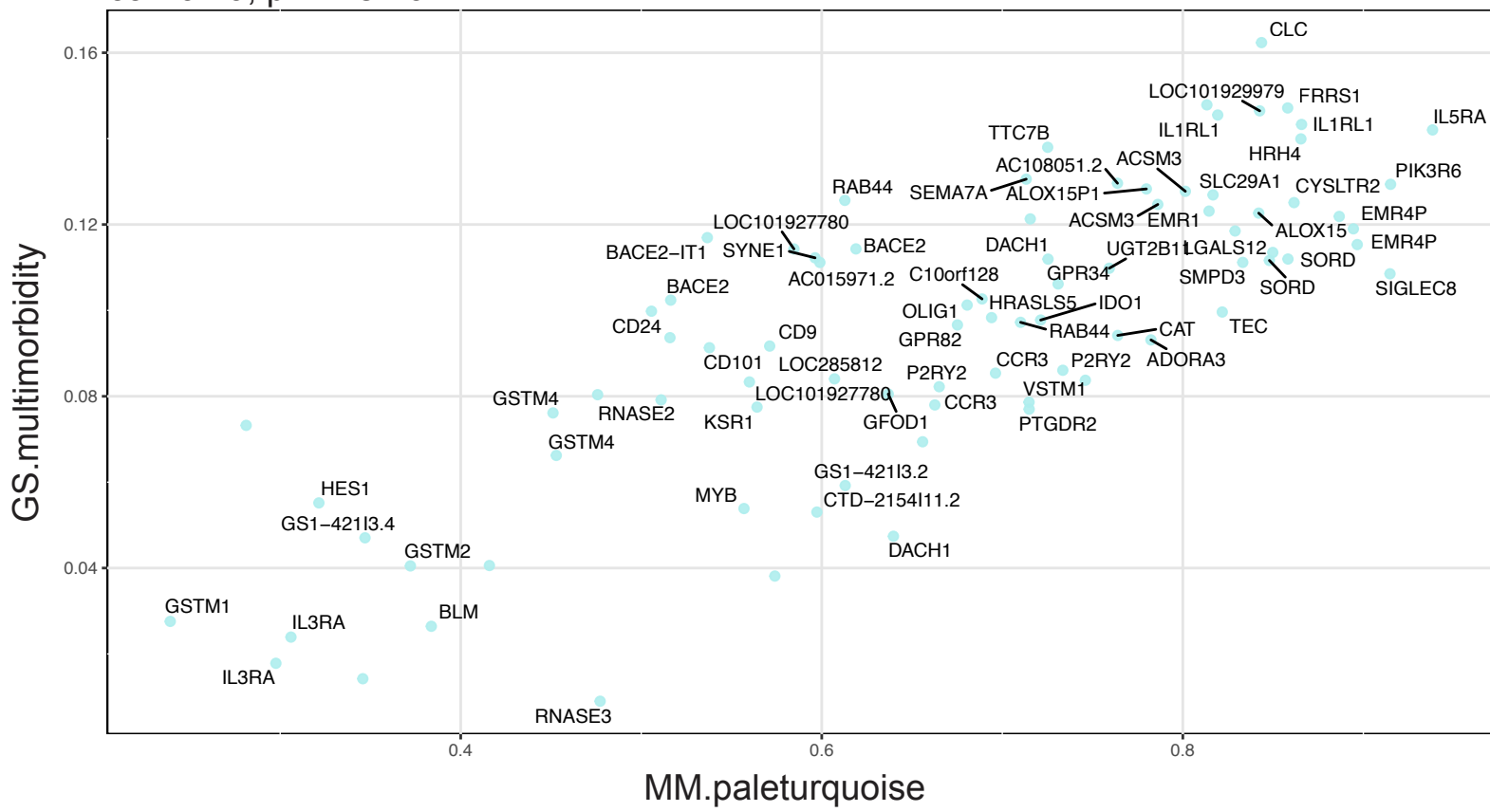## A. Correlation of modules with allergic phenotypes

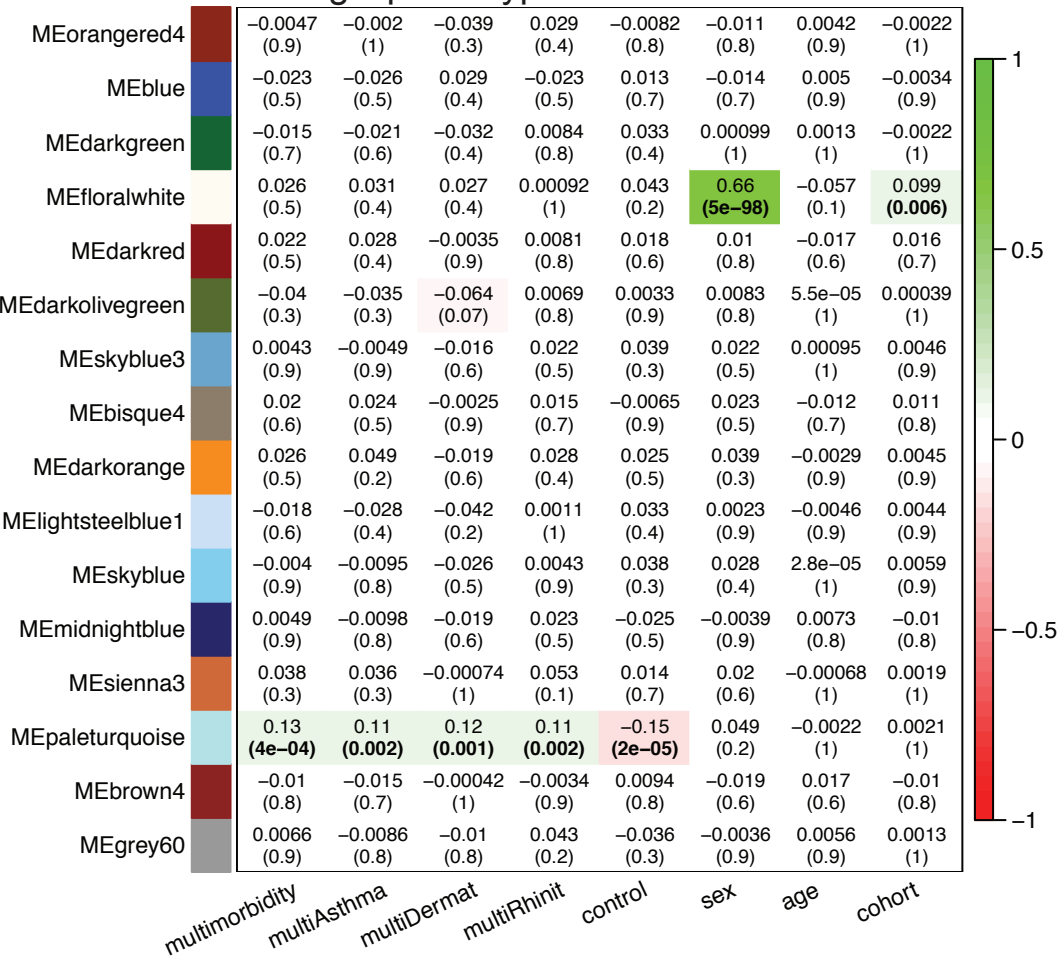## B. Visualization of eigengene network

D. Co-expressed genes in paleturquoise module

cor=0.79, p=4.2e-19

S10.2. Weighted Gene Co-expression Network Analysis

A. Correlation of modules with allergic phenotypes

	multimorbidity	multiAsthma	multiDermat	multiRhinit	control	sex	age	cohort
MEorangered4	−0.0047 (0.9)	−0.002 (1)	−0.039 (0.3)	0.029 (0.4)	−0.0082 (0.8)	−0.011 (0.8)	0.0042 (0.9)	−0.0022 (1)
MEblue	−0.023 (0.5)	−0.026 (0.5)	0.029 (0.4)	−0.023 (0.5)	0.013 (0.7)	−0.014 (0.7)	0.005 (0.9)	−0.0034 (0.9)
MEdarkgreen	−0.015 (0.7)	−0.021 (0.6)	−0.032 (0.4)	0.0084 (0.8)	0.033 (0.4)	0.00099 (1)	0.0013 (1)	−0.0022 (1)
MEfloralwhite	0.026 (0.5)	0.031 (0.4)	0.027 (0.4)	0.00092 (1)	0.043 (0.2)	0.66 (5e−98)	−0.057 (0.1)	0.099 (0.006)
MEdarkred	0.022 (0.5)	0.028 (0.4)	−0.0035 (0.9)	0.0081 (0.8)	0.018 (0.6)	0.01 (0.8)	−0.017 (0.6)	0.016 (0.7)
MEdarkolivegreen	−0.04 (0.3)	−0.035 (0.3)	−0.064 (0.07)	0.0069 (0.8)	0.0033 (0.9)	0.0083 (0.8)	5.5e−05 (1)	0.00039 (1)
MEskyblue3	0.0043 (0.9)	−0.0049 (0.9)	−0.016 (0.6)	0.022 (0.5)	0.039 (0.3)	0.022 (0.5)	0.00095 (1)	0.0046 (0.9)
MEbisque4	0.02 (0.6)	0.024 (0.5)	−0.0025 (0.9)	0.015 (0.7)	−0.0065 (0.9)	0.023 (0.5)	−0.012 (0.7)	0.011 (0.8)
MEdarkorange	0.026 (0.5)	0.049 (0.2)	−0.019 (0.6)	0.028 (0.4)	0.025 (0.5)	0.039 (0.3)	−0.0029 (0.9)	0.0045 (0.9)
MElightsteelblue1	−0.018 (0.6)	−0.028 (0.4)	−0.042 (0.2)	0.0011 (1)	0.033 (0.4)	0.0023 (0.9)	−0.0046 (0.9)	0.0044 (0.9)
MEskyblue	−0.004 (0.9)	−0.0095 (0.8)	−0.026 (0.5)	0.0043 (0.9)	0.038 (0.3)	0.028 (0.4)	2.8e−05 (1)	0.0059 (0.9)
MEmidnightblue	0.0049 (0.9)	−0.0098 (0.8)	−0.019 (0.6)	0.023 (0.5)	−0.025 (0.5)	−0.0039 (0.9)	0.0073 (0.8)	−0.01 (0.8)
MEsienna3	0.038 (0.3)	0.036 (0.3)	−0.00074 (1)	0.053 (0.1)	0.014 (0.7)	0.02 (0.6)	−0.00068 (1)	0.0019 (1)
MEpaleturquoise	0.13 (4e−04)	0.11 (0.002)	0.12 (0.001)	0.11 (0.002)	−0.15 (2e−05)	0.049 (0.2)	−0.0022 (1)	0.0021 (1)
MEbrown4	−0.01 (0.8)	−0.015 (0.7)	−0.00042 (1)	−0.0034 (0.9)	0.0094 (0.8)	−0.019 (0.6)	0.017 (0.6)	−0.01 (0.8)
MEgrey60	0.0066 (0.9)	−0.0086 (0.8)	−0.01 (0.8)	0.043 (0.2)	−0.036 (0.3)	−0.0036 (0.9)	0.0056 (0.9)	0.0013 (1)

B. Visualization of eigengene network