

Supplemental Information for: Identification of Circulating Gene Expression Signatures of Intracranial Aneurysm in Peripheral Blood Mononuclear Cells

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Supplemental Tables

Table S1: Aneurysm Characteristics of the Discovery Cohort.*

| Characteristic | Value |
|---|--------------|
| Family history of IA (n/n_{total}) | 3/18 (16.7%) |
| Patients with Multiple IAs (n/n_{total}) | 1/18 (5.6%) |
| Size (mm) [mean (min/max)] | 6.2 (2/18) |
| IA Location (n/n_{total}) | |
| <i>ACom</i> | 1/19 (5.3%) |
| <i>BA</i> | 1/19 (5.3%) |
| <i>Cavernous ICA</i> | 2/19 (10.5%) |
| <i>ICA</i> | 6/19 (31.6%) |
| <i>MCA</i> | 5/19 (26.3%) |
| <i>PCom/PCA</i> | 4/19 (21.1%) |

*Aneurysm size ranged from 2 mm to 18 mm. The aneurysms were situated at various locations in the Circle of Willis, with most being around the internal carotid artery and its branches. Three patients with IAs had a family history of the disease. (Abbreviations: ACom=anterior communicating artery, BA=basilar Artery, IA=intracranial aneurysm, ICA=internal carotid artery, MCA=middle cerebral artery, n=number, PCA=posterior cerebellar artery, PCom=posterior communicating artery)

Table S2: RNA Quality.*

| ID | Class | 260/280 | RQN |
|-------------|--------------|----------------|------------|
| Control 1 | Discovery | 2.07 | 8.7 |
| Control 2 | Discovery | 2.06 | 8.0 |
| Control 3 | Discovery | 2.09 | 9.9 |
| Control 4 | Discovery | 2.07 | 9.6 |
| Control 5 | Discovery | 2.09 | 8.5 |
| Control 6 | Discovery | 2.11 | 9.2 |
| Control 7 | Discovery | 2.09 | 10.0 |
| Control 8 | Discovery | 2.05 | 10.0 |
| Control 9 | Discovery | 1.97 | 10.0 |
| Control 10 | Discovery | 2.07 | 10.0 |
| Control 11 | Discovery | 2.08 | 10.0 |
| Control 12 | Discovery | 2.09 | 10.0 |
| Control 13 | Discovery | 2.13 | 9.2 |
| Control 14 | Discovery | 2.07 | 9.9 |
| Control 15 | Discovery | 2.10 | 9.3 |
| Control 16 | Discovery | 2.10 | 8.4 |
| Control 17 | Discovery | 2.10 | 9.1 |
| Control 18 | Discovery | 2.11 | 9.3 |
| Control 19 | Discovery | 2.09 | 9.2 |
| Control 20 | Discovery | 2.11 | 10.0 |
| Control 21 | Discovery | 2.07 | 9.3 |
| Control 22 | Validation | 2.06 | 9.5 |
| Control 23 | Validation | 2.09 | 9.3 |
| Control 24 | Validation | 2.05 | 9.6 |
| Control 25 | Validation | 2.08 | 9.7 |
| Control 26 | Validation | 2.05 | 9.6 |
| Control 27 | Validation | 2.05 | 9.2 |
| Control 28 | Validation | 2.07 | 9.1 |
| Aneurysm 1 | Discovery | 2.09 | 8.8 |
| Aneurysm 2 | Discovery | 2.08 | 9.7 |
| Aneurysm 3 | Discovery | 2.08 | 9.9 |
| Aneurysm 4 | Discovery | 2.08 | 8.9 |
| Aneurysm 5 | Discovery | 2.04 | 9.7 |
| Aneurysm 6 | Discovery | 2.09 | 8.1 |
| Aneurysm 7 | Discovery | 2.06 | 8.9 |
| Aneurysm 8 | Discovery | 2.07 | 8.2 |
| Aneurysm 9 | Discovery | 2.01 | 9.7 |
| Aneurysm 10 | Discovery | 2.06 | 9.0 |
| Aneurysm 11 | Discovery | 2.08 | 9.7 |
| Aneurysm 12 | Discovery | 2.10 | 9.7 |
| Aneurysm 13 | Discovery | 2.09 | 9.8 |
| Aneurysm 14 | Discovery | 2.05 | 9.5 |
| Aneurysm 15 | Discovery | 2.09 | 9.6 |
| Aneurysm 16 | Discovery | 2.09 | 10.0 |
| Aneurysm 17 | Discovery | 2.08 | 9.9 |
| Aneurysm 18 | Discovery | 2.07 | 8.7 |
| Aneurysm 19 | Validation | 2.08 | 10.0 |
| Aneurysm 20 | Validation | 2.06 | 10.0 |

| | | | |
|-------------|------------|------|-----|
| Aneurysm 21 | Validation | 2.06 | 9.4 |
| Aneurysm 22 | Validation | 2.94 | 8.7 |
| Aneurysm 23 | Validation | 2.09 | 9.9 |
| Aneurysm 24 | Validation | 2.08 | 9.6 |

* The quality of the RNA samples was assessed by the 260/280 ratio and the RQN. (Abbreviations: RQN=RNA quality number)

Table S3: Sequencing Quality.*

| ID | Class | M Seqs | % Aligned |
|-------------|--------------|---------------|------------------|
| Control 1 | Discovery | 25.7 | 95.7% |
| Control 2 | Discovery | 33.7 | 92.3% |
| Control 3 | Discovery | 25.7 | 96.2% |
| Control 4 | Discovery | 30.1 | 95.7% |
| Control 5 | Discovery | 26.4 | 96.8% |
| Control 6 | Discovery | 26.6 | 96.6% |
| Control 7 | Discovery | 43.2 | 96.8% |
| Control 8 | Discovery | 43.6 | 97.0% |
| Control 9 | Discovery | 38.7 | 96.9% |
| Control 10 | Discovery | 51.3 | 97.1% |
| Control 11 | Discovery | 32.1 | 96.4% |
| Control 12 | Discovery | 29.1 | 96.3% |
| Control 13 | Discovery | 30.4 | 96.2% |
| Control 14 | Discovery | 27.2 | 97.0% |
| Control 15 | Discovery | 29.9 | 96.7% |
| Control 16 | Discovery | 25.2 | 97.1% |
| Control 17 | Discovery | 26.0 | 97.1% |
| Control 18 | Discovery | 26.7 | 97.0% |
| Control 19 | Discovery | 33.8 | 94.2% |
| Control 20 | Discovery | 30.4 | 97.3% |
| Control 21 | Discovery | 24.4 | 96.8% |
| Control 22 | Validation | 39.4 | 95.7% |
| Control 23 | Validation | 34.2 | 94.6% |
| Control 24 | Validation | 44.4 | 95.6% |
| Control 25 | Validation | 34.1 | 93.6% |
| Control 26 | Validation | 37.3 | 96.5% |
| Control 27 | Validation | 26.5 | 96.5% |
| Control 28 | Validation | 30.0 | 96.2% |
| Aneurysm 1 | Discovery | 36.2 | 95.3% |
| Aneurysm 2 | Discovery | 28.9 | 96.3% |
| Aneurysm 3 | Discovery | 27.5 | 96.4% |
| Aneurysm 4 | Discovery | 28.9 | 94.7% |
| Aneurysm 5 | Discovery | 31.6 | 97.2% |
| Aneurysm 6 | Discovery | 28.6 | 96.9% |
| Aneurysm 7 | Discovery | 36.8 | 96.9% |
| Aneurysm 8 | Discovery | 41.3 | 96.9% |
| Aneurysm 9 | Discovery | 29.7 | 97.2% |
| Aneurysm 10 | Discovery | 33.9 | 97.0% |
| Aneurysm 11 | Discovery | 30.7 | 96.5% |
| Aneurysm 12 | Discovery | 28.8 | 97.0% |
| Aneurysm 13 | Discovery | 27.1 | 96.8% |
| Aneurysm 14 | Discovery | 32.6 | 97.2% |
| Aneurysm 15 | Discovery | 23.4 | 95.1% |
| Aneurysm 16 | Discovery | 25.1 | 95.9% |
| Aneurysm 17 | Discovery | 32.1 | 95.6% |
| Aneurysm 18 | Discovery | 29.9 | 96.9% |
| Aneurysm 19 | Validation | 37.8 | 96.2% |
| Aneurysm 20 | Validation | 29.3 | 95.8% |

| | | | |
|-------------|------------|------|-------|
| Aneurysm 21 | Validation | 36.2 | 97.1% |
| Aneurysm 22 | Validation | 36.6 | 97.2% |
| Aneurysm 23 | Validation | 35.5 | 96.9% |
| Aneurysm 24 | Validation | 38.9 | 97.0% |

* The quality of the RNA sequencing experiments was measure post-alignment via MultiQC. The report showed that the sequencing experiments had an average of 32.2 million mapped reads with a 96.3% aligned rate. (Abbreviations: M=million, Seqs=sequences)

Table S4: Significantly Enriched Gene Ontologies.*

| Category | GO ID | GO Name | q-value | Focus Molecules |
|---|------------|----------------------------------|----------|---|
| <i>Genes with Increased Expression in IA</i> | | | | |
| Biological Process | GO:0008150 | biological process | 2.47E-07 | SSTR3, CACNA1I, SCARF2, RAVR2, FMN1, ANO5, HSPA2, SHISA8, TRIM7, MEOX1, SDC3, KCNG1, TRPV4, MKRN3, SYNPO, FAM83D, ADAMTS17, PTGS2, CNTNAP1, OMG, ZNF135, G0S2, EGR2, CCR8, SORCS3, COCH, SLC7A8, PHOSPHO1, OR2AK2, HLA-DQB2 |
| Biological Process | GO:0009987 | cellular process | 5.85E-07 | SSTR3, CACNA1I, SCARF2, RAVR2, FMN1, ANO5, HSPA2, SHISA8, TRIM7, MEOX1, SDC3, KCNG1, TRPV4, MKRN3, SYNPO, FAM83D, ADAMTS17, PTGS2, CNTNAP1, OMG, ZNF135, G0S2, EGR2, CCR8, SORCS3, SLC7A8, PHOSPHO1, OR2AK2, HLA-DQB2 |
| Biological Process | GO:0065007 | biological regulation | 0.000116 | SSTR3, CACNA1I, FMN1, HSPA2, SHISA8, MEOX1, KCNG1, TRPV4, SYNPO, FAM83D, PTGS2, CNTNAP1, OMG, ZNF135, G0S2, EGR2, CCR8, SORCS3, COCH, SLC7A8, PHOSPHO1, OR2AK2, HLA-DQB2 |
| Biological Process | GO:0050789 | regulation of biological process | 0.000235 | SSTR3, CACNA1I, FMN1, HSPA2, SHISA8, MEOX1, KCNG1, TRPV4, SYNPO, FAM83D, PTGS2, CNTNAP1, OMG, ZNF135, G0S2, EGR2, CCR8, SORCS3, COCH, PHOSPHO1, OR2AK2, HLA-DQB2 |
| Biological Process | GO:0032501 | multicellular organismal process | 0.000282 | SSTR3, CACNA1I, FMN1, HSPA2, MEOX1, TRPV4, FAM83D, PTGS2, CNTNAP1, OMG, G0S2, EGR2, SORCS3, COCH, SLC7A8, PHOSPHO1, OR2AK2, HLA-DQB2 |
| Biological Process | GO:0050794 | regulation of cellular process | 0.002889 | SSTR3, CACNA1I, FMN1, HSPA2, SHISA8, MEOX1, KCNG1, TRPV4, SYNPO, FAM83D, PTGS2, CNTNAP1, |

| | | | | |
|--------------------|------------|------------------------------------|----------|---|
| Biological Process | GO:0065008 | regulation of biological quality | 0.005548 | OMG, ZNF135, G0S2, EGR2, CCR8, SORCS3, OR2AK2, HLA-DQB2 CACNA1I, FMN1, SHISA8, TRPV4, PTGS2, CNTNAP1, G0S2, EGR2, CCR8, SORCS3, COCH, SLC7A8 |
| Biological Process | GO:0009653 | anatomical structure morphogenesis | 0.007229 | FMN1, MEOX1, TRPV4, PTGS2, CNTNAP1, OMG, ZNF135, EGR2, COCH, PHOSPHO1 |
| Biological Process | GO:0048856 | anatomical structure development | 0.010642 | SSTR3, FMN1, HSPA2, MEOX1, TRPV4, FAM83D, PTGS2, CNTNAP1, OMG, ZNF135, EGR2, COCH, PHOSPHO1, HLA-DQB2 |
| Biological Process | GO:0006812 | cation transport | 0.010708 | CACNA1I, HSPA2, SHISA8, KCNG1, TRPV4, PTGS2, SLC7A8 |
| Biological Process | GO:0003008 | system process | 0.011273 | CACNA1I, TRPV4, PTGS2, CNTNAP1, EGR2, SORCS3, COCH, SLC7A8, OR2AK2 |
| Biological Process | GO:0050896 | response to stimulus | 0.01803 | SSTR3, CACNA1I, HSPA2, SHISA8, TRPV4, FAM83D, PTGS2, CNTNAP1, OMG, G0S2, EGR2, CCR8, SORCS3, COCH, SLC7A8, OR2AK2, HLA-DQB2 |
| Biological Process | GO:0098655 | cation transmembrane transport | 0.027353 | CACNA1I, HSPA2, SHISA8, KCNG1, TRPV4, SLC7A8 |
| Biological Process | GO:0032502 | developmental process | 0.027443 | SSTR3, FMN1, HSPA2, MEOX1, TRPV4, FAM83D, PTGS2, CNTNAP1, OMG, ZNF135, EGR2, COCH, PHOSPHO1, HLA-DQB2 |
| Biological Process | GO:0034220 | ion transmembrane transport | 0.029008 | CACNA1I, ANO5, HSPA2, SHISA8, KCNG1, TRPV4, SLC7A8 |
| Biological Process | GO:0050877 | nervous system process | 0.033083 | CACNA1I, PTGS2, CNTNAP1, EGR2, SORCS3, COCH, OR2AK2 |
| Biological Process | GO:0051716 | cellular response to stimulus | 0.036248 | SSTR3, CACNA1I, HSPA2, SHISA8, TRPV4, FAM83D, PTGS2, CNTNAP1, OMG, G0S2, EGR2, CCR8, SORCS3, OR2AK2, HLA-DQB2 |
| Biological Process | GO:0040011 | locomotion | 0.038102 | CACNA1I, SDC3, TRPV4, FAM83D, PTGS2, EGR2, CCR8, SLC7A8 |

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|--------------------|------------|---------------------------------|----------|--|
| Biological Process | GO:0051179 | localization | 0.043439 | CACNA1I, SCARF2, ANO5, HSPA2, SHISA8, SDC3, KCNG1, TRPV4, FAM83D, PTGS2, CNTNAP1, EGR2, CCR8, SLC7A8 |
| Biological Process | GO:0007155 | cell adhesion | 0.044145 | SCARF2, FMN1, TRPV4, CNTNAP1, OMG, CCR8, HLA-DQB2 |
| Biological Process | GO:0022610 | biological adhesion | 0.045479 | SCARF2, FMN1, TRPV4, CNTNAP1, OMG, CCR8, HLA-DQB2 |
| Cellular Component | GO:0005575 | cellular component | 2.31E-12 | SSTR3, CACNA1I, SCARF2, ANKRD34B, RAVR2, FMN1, ANO5, C7ORF61, HSPA2, SHISA8, ODF3B, TRIM7, TIMD4, MEOX1, SDC3, KCNG1, TRPV4, MKRN3, SYNPO, FAM83D, ADAMTS17, PTGS2, CNTNAP1, OMG, ZNF135, G0S2, EGR2, CCR8, SORCS3, COCH, SLC7A8, PHOSPHO1, OR2AK2, HLA-DQB2 |
| Cellular Component | GO:0110165 | cellular anatomical entity | 3.42E-11 | SSTR3, CACNA1I, SCARF2, ANKRD34B, RAVR2, FMN1, ANO5, C7ORF61, HSPA2, SHISA8, ODF3B, TRIM7, TIMD4, MEOX1, SDC3, KCNG1, TRPV4, SYNPO, FAM83D, ADAMTS17, PTGS2, CNTNAP1, OMG, ZNF135, G0S2, EGR2, CCR8, SORCS3, COCH, SLC7A8, PHOSPHO1, OR2AK2, HLA-DQB2 |
| Cellular Component | GO:0071944 | cell periphery | 5.09E-09 | SSTR3, CACNA1I, FMN1, ANO5, HSPA2, SHISA8, SDC3, KCNG1, TRPV4, ADAMTS17, PTGS2, CNTNAP1, OMG, CCR8, SORCS3, COCH, SLC7A8, PHOSPHO1, OR2AK2, HLA-DQB2 |
| Cellular Component | GO:0005886 | plasma membrane | 1.06E-06 | SSTR3, CACNA1I, FMN1, ANO5, HSPA2, SHISA8, SDC3, KCNG1, TRPV4, PTGS2, CNTNAP1, OMG, CCR8, SORCS3, SLC7A8, OR2AK2, HLA-DQB2 |
| Cellular Component | GO:0031224 | intrinsic component of membrane | 1.73E-06 | SSTR3, CACNA1I, SCARF2, ANO5, HSPA2, SHISA8, TIMD4, SDC3, KCNG1, TRPV4, CNTNAP1, OMG, CCR8, |

| | | | | |
|--------------------|------------|---|----------|--|
| Cellular Component | GO:0016021 | integral component of membrane | 9.1E-06 | SORCS3, SLC7A8, OR2AK2, HLA-DQB2 SSTR3, CACNA1I, SCARF2, ANO5, HSPA2, SHISA8, TIMD4, SDC3, KCNG1, TRPV4, CNTNAP1, CCR8, SORCS3, SLC7A8, OR2AK2, HLA-DQB2 |
| Cellular Component | GO:0005887 | integral component of plasma membrane | 6.35E-05 | SSTR3, CACNA1I, SHISA8, KCNG1, TRPV4, CNTNAP1, CCR8, SORCS3, SLC7A8 |
| Cellular Component | GO:0031226 | intrinsic component of plasma membrane | 9.46E-05 | SSTR3, CACNA1I, SHISA8, KCNG1, TRPV4, CNTNAP1, CCR8, SORCS3, SLC7A8 |
| Cellular Component | GO:0016020 | membrane | 0.000112 | SSTR3, CACNA1I, SCARF2, FMN1, ANO5, HSPA2, SHISA8, TIMD4, SDC3, KCNG1, TRPV4, PTGS2, CNTNAP1, OMG, CCR8, SORCS3, SLC7A8, OR2AK2, HLA-DQB2 |
| Cellular Component | GO:0043226 | organelle | 0.000292 | SSTR3, ANKRD34B, RAVR2, FMN1, ANO5, C7ORF61, HSPA2, SHISA8, ODF3B, TRIM7, MEOX1, SDC3, TRPV4, SYNPO, FAM83D, PTGS2, ZNF135, G0S2, EGR2, SORCS3, PHOSPHO1, HLA-DQB2 |
| Cellular Component | GO:0120025 | plasma membrane bounded cell projection | 0.000767 | SSTR3, CACNA1I, SHISA8, SDC3, TRPV4, SYNPO, PTGS2, CNTNAP1, SLC7A8 |
| Cellular Component | GO:0042995 | cell projection | 0.001096 | SSTR3, CACNA1I, SHISA8, SDC3, TRPV4, SYNPO, PTGS2, CNTNAP1, SLC7A8 |
| Cellular Component | GO:0098590 | plasma membrane region | 0.001151 | SSTR3, SHISA8, TRPV4, PTGS2, CNTNAP1, SORCS3, SLC7A8 |
| Cellular Component | GO:0043005 | neuron projection | 0.002293 | SSTR3, CACNA1I, SHISA8, TRPV4, SYNPO, PTGS2, CNTNAP1 |
| Cellular Component | GO:0005622 | intracellular anatomical structure | 0.003344 | SSTR3, ANKRD34B, RAVR2, FMN1, ANO5, C7ORF61, HSPA2, ODF3B, TRIM7, MEOX1, SDC3, TRPV4, SYNPO, FAM83D, PTGS2, ZNF135, G0S2, EGR2, SLC7A8, PHOSPHO1, HLA-DQB2 |

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|--------------------|------------|---------------------------------|----------|---|
| Cellular Component | GO:0098797 | plasma membrane protein complex | 0.008091 | CACNA1I, HSPA2, SHISA8, KCNG1, HLA-DQB2 |
| Cellular Component | GO:0005737 | cytoplasm | 0.008933 | SSTR3, ANKRD34B, RAVR2, FMN1, ANO5, HSPA2, TRIM7, MEOX1, SDC3, TRPV4, SYNPO, FAM83D, PTGS2, G0S2, EGR2, SLC7A8, PHOSPHO1, HLA-DQB2 |
| Cellular Component | GO:0043229 | intracellular organelle | 0.017065 | ANKRD34B, RAVR2, FMN1, ANO5, C7ORF61, HSPA2, ODF3B, TRIM7, MEOX1, SDC3, TRPV4, SYNPO, FAM83D, PTGS2, ZNF135, G0S2, EGR2, HLA-DQB2 |
| Cellular Component | GO:0070161 | anchoring junction | 0.019326 | SCARF2, FMN1, TRPV4, SYNPO, CNTNAP1 |
| Cellular Component | GO:0043227 | membrane-bounded organelle | 0.025159 | SSTR3, ANKRD34B, RAVR2, FMN1, ANO5, C7ORF61, HSPA2, TRIM7, MEOX1, SDC3, TRPV4, SYNPO, PTGS2, ZNF135, G0S2, EGR2, PHOSPHO1, HLA-DQB2 |
| Cellular Component | GO:0009986 | cell surface | 0.027053 | HSPA2, SDC3, TRPV4, CCR8, HLA-DQB2 |
| Cellular Component | GO:0030054 | cell junction | 0.032222 | SCARF2, FMN1, SHISA8, TRPV4, SYNPO, CNTNAP1, SORCS3 |
| Molecular Function | GO:0003674 | molecular function | 2.33E-12 | SSTR3, CACNA1I, SCARF2, ANKRD34B, RAVR2, FMN1, ANO5, HSPA2, ODF3B, TRIM7, FAM71F2, MEOX1, SDC3, KCNG1, TRPV4, MKRN3, SYNPO, FAM83D, ADAMTS17, PTGS2, CNTNAP1, OMG, ZNF135, G0S2, EGR2, CCR8, SORCS3, COCH, SLC7A8, ANKRD22, PHOSPHO1, OR2AK2, HLA-DQB2, ANKRD24 |
| Molecular Function | GO:0005488 | binding | 2.7E-12 | SSTR3, CACNA1I, SCARF2, ANKRD34B, RAVR2, FMN1, ANO5, HSPA2, ODF3B, TRIM7, FAM71F2, MEOX1, SDC3, KCNG1, TRPV4, MKRN3, SYNPO, FAM83D, ADAMTS17, PTGS2, CNTNAP1, OMG, ZNF135, G0S2, EGR2, CCR8, SORCS3, COCH, SLC7A8, ANKRD22, PHOSPHO1, HLA-DQB2, ANKRD24 |

| | | | | |
|--|------------|---|----------|--|
| Molecular Function | GO:0005515 | protein binding | 9.5E-12 | SSTR3, CACNA1I, SCARF2, ANKRD34B, FMN1, ANO5, HSPA2, ODF3B, TRIM7, FAM71F2, MEOX1, SDC3, KCNG1, TRPV4, MKRN3, SYNPO, FAM83D, PTGS2, CNTNAP1, OMG, ZNF135, G0S2, EGR2, CCR8, SORCS3, COCH, SLC7A8, ANKRD22, PHOSPHO1, HLA-DQB2, ANKRD24 |
| Molecular Function | GO:0019904 | protein domain specific binding | 0.000927 | FMN1, HSPA2, MEOX1, TRPV4, CNTNAP1, EGR2 |
| Molecular Function | GO:0060089 | molecular transducer activity | 0.005399 | SSTR3, TRPV4, CNTNAP1, CCR8, SORCS3, OR2AK2, HLA-DQB2 |
| Molecular Function | GO:0038023 | signaling receptor activity | 0.005399 | SSTR3, TRPV4, CNTNAP1, CCR8, SORCS3, OR2AK2, HLA-DQB2 |
| Molecular Function | GO:0004888 | transmembrane signaling receptor activity | 0.02384 | SSTR3, TRPV4, CCR8, SORCS3, OR2AK2, HLA-DQB2 |
| Molecular Function | GO:0015318 | inorganic molecular entity transmembrane transporter activity | 0.031136 | CACNA1I, ANO5, KCNG1, TRPV4, SLC7A8 |
| <hr/> | | | | |
| Genes with Decreased Expression in IA | | | | |
| Biological Process | GO:0032501 | multicellular organismal process | 0.010904 | UTS2, PRTN3, TNNT1, RETN, BOK, PHGDH, FOLR3, TRNP1, SAMD14 |
| Biological Process | GO:0009987 | cellular process | 0.011832 | UTS2, PRTN3, L1TD1, TNNT1, KIR3DL2, DEFA4, RETN, BOK, PHGDH, FOLR3, TRNP1, SAMD14 |
| Biological Process | GO:0008150 | biological process | 0.02115 | UTS2, PRTN3, L1TD1, TNNT1, KIR3DL2, DEFA4, RETN, BOK, PHGDH, FOLR3, TRNP1, SAMD14 |
| Biological Process | GO:0050896 | response to stimulus | 0.044048 | UTS2, PRTN3, TNNT1, KIR3DL2, DEFA4, RETN, BOK, FOLR3, SAMD14 |
| Cellular Component | GO:0110165 | cellular anatomical entity | 1.66E-05 | UTS2, PRTN3, L1TD1, TNNT1, KIR3DL2, DEFA4, RETN, BOK, PDZK1IP1, PHGDH, FOLR3, CDCP1, TRNP1, SAMD14 |
| Cellular Component | GO:0005575 | cellular component | 1.85E-05 | UTS2, PRTN3, L1TD1, TNNT1, KIR3DL2, DEFA4, RETN, BOK, PDZK1IP1, PHGDH, FOLR3, CDCP1, TRNP1, SAMD14 |

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|--------------------|------------|----------------------------|----------|--|
| Cellular Component | GO:0005576 | extracellular region | 0.000444 | UTS2, PRTN3, DEFA4, RETN, PDZK1IP1, PHGDH, FOLR3, CDCP1 |
| Cellular Component | GO:0031982 | vesicle | 0.002914 | PRTN3, DEFA4, RETN, BOK, PDZK1IP1, PHGDH, FOLR3 |
| Cellular Component | GO:0043226 | organelle | 0.003874 | PRTN3, L1TD1, TNNT1, DEFA4, RETN, BOK, PDZK1IP1, PHGDH, FOLR3, TRNP1, SAMD14 |
| Cellular Component | GO:0005615 | extracellular space | 0.018592 | UTS2, PRTN3, DEFA4, RETN, PDZK1IP1, PHGDH |
| Cellular Component | GO:0031410 | cytoplasmic vesicle | 0.032618 | PRTN3, DEFA4, RETN, BOK, FOLR3 |
| Cellular Component | GO:0097708 | intracellular vesicle | 0.032871 | PRTN3, DEFA4, RETN, BOK, FOLR3 |
| Molecular Function | GO:0005488 | binding | 4.28E-06 | UTS2, PRTN3, L1TD1, TNNT1, KIR3DL2, DEFA4, RETN, BOK, PDZK1IP1, PHGDH, FOLR3, CDCP1, TRNP1, SAMD14 |
| Molecular Function | GO:0003674 | molecular function | 1.5E-05 | UTS2, PRTN3, L1TD1, TNNT1, KIR3DL2, DEFA4, RETN, BOK, PDZK1IP1, PHGDH, FOLR3, CDCP1, TRNP1, SAMD14 |
| Molecular Function | GO:0005515 | protein binding | 0.000517 | UTS2, PRTN3, L1TD1, TNNT1, KIR3DL2, DEFA4, RETN, BOK, PDZK1IP1, FOLR3, CDCP1, SAMD14 |
| Molecular Function | GO:0005102 | signaling receptor binding | 0.005591 | UTS2, PRTN3, KIR3DL2, RETN, BOK |

* Significant ontologies with a q-value<0.05 and five or more focus molecules are reported.
(Abbreviations: GO=gene ontology)

Table S5: Additional Information on Significant Networks From IPA.*

| Network | Molecules in Network | P-score | Focus Molecules | Top Diseases and Functions |
|----------------|---|----------------|------------------------|--|
| 1 | 26s Proteasome, Actin, BOK, CDCP1, CG, cytokine, EGR2, ERK, ERK1/2, FMN1, G0S2, Histone h3, Ige, IgG, Immunoglobulin, Insulin, LDL, Mek, NFkB (complex), P38 MAPK, Pka, PRKAA, PRTN3, PTGS2, RETN, RNA polymerase II, SCARF2, SDC3, SMN1/SMN2, SORCS3, SSTR3, TIMD4, TRPV4, Ubiquitin, UTS2 | 36 | 16 | Behavior, Cell Death and Survival, Connective Tissue Disorders |
| 2 | ADAM19, ADAMTS17, ADAMTS4, AGR3, ANKRD22, ANO5, beta-glycerophosphoric acid, BOD1L1, CGB3 (includes others), COCH, COL11A1, COL1A1, Collagen type VII, CUL1, desoxycorticosterone, Ecm, EGFR, Endothelin, EZH2, HSPA2, L1TD1, LOC102724788/PRODH, MGAT5, MGP, mir-101, MYC, OMG, PDZK1IP1, PHGDH, SLC3A1, SLC7A8, TFRC, TGFB1, THSD4, ZFP42 | 20 | 10 | Amino Acid Metabolism, Cell Cycle, Cellular Development |
| 3 | ACBD4, ANTKMT, APEX2, AR, CNTNAP1, DDX5, DNA-methyltransferase, EGR4, EI24, HDAC2, HEPH, HPGD, KCNG1, MEOX1, mir-143, MKRN3, MYOZ2, NABP1, ODF3B, OR2AK2, PEX26, PLEKHF1, RAVR2, RBM41, SHISA8, SMARCA4, SRF, TBPL1, TNNI2, TNNT1, TNNT2, TP53, TRNP1, Troponin t, TSHZ3 | 20 | 10 | Cardiovascular System Development and Function, Cellular Assembly and Organization, Cellular Development |

* Significant networks with a P-score ≥ 20 are reported. (Abbreviations: IPA=Ingenuity Pathway Analysis)

Table S6: Additional Information on Upstream Regulators From IPA.*

| Upstream Regulator | Molecule Type | z-score | p-value | Target Molecules |
|---------------------------|-------------------------|----------------|----------------|--|
| TNF | cytokine | 1.918 | 0.00442 | CCR8, EGR2, G0S2, MEOX1, PHGDH, PRTN3, PTGS2, RETN, SLC7A8, SYNPO, TIMD4 |
| CREB1 | transcription regulator | 1.397 | 0.0114 | COCH, EGR2, OMG, PTGS2, SORCS3 |
| PTEN | phosphatase | 0.206 | 0.00627 | EGR2, G0S2, MEOX1, PHGDH, PTGS2, SLC7A8 |
| MRTFB | transcription regulator | 0.152 | 0.000687 | G0S2, PRTN3, PTGS2, TRNP1 |

* Significant upstream regulators with a with a q-value<0.05 and an absolute z-score<0 are reported.
(Abbreviations: IPA=Ingenuity Pathway Analysis)

Table S7: Patient Characteristics of the Validation Cohort.*

| | Patients with IA (n=6) | Patients without IA (n=7) | p-value |
|--|-----------------------------------|--------------------------------------|----------------|
| Age (years) (mean±SE) [Q2 (Q1/Q3)] | 42.7±5.28 40 (34/50.5) | 56.7±4.89 62 (50.5/62.5) | 0.078 |
| Sex | | | |
| <i>Female</i> | 66.67% | 57.14% | 1 |
| Current Smoker | | | |
| <i>Yes</i> | 50.00% | 28.57% | 0.592 |
| Comorbidities | | | |
| <i>Osteoarthritis</i> | 16.67% | 42.86% | 0.559 |
| <i>Diabetes mellitus</i> | 0.00% | 14.29% | 1 |
| <i>Heart disease</i> | 0.00% | 28.57% | 0.462 |
| <i>Hyperlipidemia</i> | 33.33% | 28.57% | 1 |
| <i>Hypertension</i> | 16.67% | 28.57% | 1 |
| <i>Stroke history</i> | 16.67% | 28.57% | 1 |

*Clinical characteristics of the randomly-assigned validation cohort. These clinical factors were retrieved from patients' medical records. With the exception of age, these datapoints were quantified as binary data points. Significant differences between each group were evaluated with a Student's t-test for continuous data (age) and a Fisher's exact test for categorical data ($\alpha=0.05$). There was no statistically significant difference in age, sex, smoking, or comorbidities between the IA and control groups. (Abbreviations: IA=intracranial aneurysm, n=number, Q=quartile, SE=standard error)

Table S8: Aneurysm Characteristics of the Validation Cohort.*

| Characteristic | Value |
|--|-------------|
| Family history of IA (n/n _{total}) | 0/6 (0%) |
| Patients with Multiple IAs (n/n _{total}) | 1/6 (16.7%) |
| Size (mm) [mean (min/max)] | 6.4 (3/10) |
| IA Location (n/n _{total}) | |
| <i>ACom</i> | 1/7 (14.3%) |
| <i>BA</i> | 1/7 (14.3%) |
| <i>Cavernous ICA</i> | 1/7 (14.3%) |
| <i>ICA</i> | 2/7 (28.6%) |
| <i>MCA</i> | 1/7 (14.3%) |
| <i>PCom/PCA</i> | 1/7 (14.3%) |

*Aneurysm size ranged from 3 mm to 10 mm. The aneurysms were situated at various locations in the Circle of Willis, with most residing again at the internal carotid artery and its branches. None of the patients had a family history of the disease. (Abbreviations: ACom=anterior communicating artery, BA=basilar Artery, IA=intracranial aneurysm, ICA=internal carotid artery, MCA=middle cerebral artery, n=number, PCA=posterior cerebellar artery, PCom=posterior communicating artery)

Table S9: All Correlation Analysis Results.*

| Gene | Correlation with IA Size | | | Correlation with ISUIA | | |
|--------------------------|--------------------------|----------------|----------|------------------------|-----------------|----------|
| | PCC | 95% CI | p-val | PCC | 95% CI | p-val |
| <i>ADAMTS17</i> | 0.429859 | [0.05 – 0.7] | 0.028398 | -0.10813 | [-0.48 – 0.29] | 0.59903 |
| <i>ANKRD22</i> | 0.029435 | [-0.36 – 0.41] | 0.886498 | -0.02247 | [-0.41 – 0.37] | 0.913244 |
| <i>ANKRD24</i> | -0.16438 | [-0.52 – 0.24] | 0.422298 | -0.14132 | [-0.5 – 0.26] | 0.491069 |
| <i>ANKRD34B</i> | 0.096854 | [-0.3 – 0.47] | 0.637868 | 0.468448 | [0.1 – 0.72] | 0.015792 |
| <i>ANO5</i> | 0.120798 | [-0.28 – 0.49] | 0.556653 | 0.297858 | [-0.1 – 0.61] | 0.139442 |
| <i>BOK</i> | -0.23607 | [-0.57 – 0.17] | 0.245637 | -0.29368 | [-0.61 – 0.11] | 0.14535 |
| <i>C7orf61</i> | -0.0607 | [-0.44 – 0.33] | 0.768326 | -0.14516 | [-0.5 – 0.26] | 0.479229 |
| <i>CACNA1I</i> | 0.063152 | [-0.33 – 0.44] | 0.759238 | -0.29149 | [-0.61 – 0.11] | 0.148505 |
| <i>CCR8</i> | 0.460603 | [0.09 – 0.72] | 0.017886 | 0.186343 | [-0.22 – 0.54] | 0.362054 |
| <i>CDCP1</i> | 0.128491 | [-0.27 – 0.49] | 0.531606 | -0.08465 | [-0.46 – 0.31] | 0.680977 |
| <i>CNTNAP1</i> | 0.059704 | [-0.34 – 0.44] | 0.772033 | -0.17284 | [-0.53 – 0.23] | 0.398471 |
| <i>COCH</i> | 0.171721 | [-0.23 – 0.52] | 0.401581 | 0.03634 | [-0.36 – 0.42] | 0.860102 |
| <i>CXorf67</i> | 0.092204 | [-0.31 – 0.46] | 0.654164 | -0.21743 | [-0.56 – 0.19] | 0.285985 |
| <i>DEFA4</i> | -0.12537 | [-0.49 – 0.28] | 0.541692 | -0.08517 | [-0.46 – 0.31] | 0.679126 |
| <i>EGR2</i> | -0.11761 | [-0.48 – 0.28] | 0.567178 | -0.08241 | [-0.46 – 0.32] | 0.689002 |
| <i>FAM71F2</i> | -0.16984 | [-0.52 – 0.23] | 0.406836 | -0.15872 | [-0.51 – 0.24] | 0.438662 |
| <i>FAM83D</i> | 0.021499 | [-0.37 – 0.41] | 0.916977 | -0.13054 | [-0.49 – 0.27] | 0.525038 |
| <i>FMN1</i> | 0.007483 | [-0.38 – 0.39] | 0.971058 | -0.14359 | [-0.5 – 0.26] | 0.484066 |
| <i>FOLR3</i> | -0.05162 | [-0.43 – 0.34] | 0.802258 | -0.14316 | [-0.5 – 0.26] | 0.485367 |
| <i>G0S2</i> | -0.25827 | [-0.59 – 0.14] | 0.202695 | -0.24751 | [-0.58 – 0.15] | 0.222825 |
| <i>HLA-DQB2</i> | -0.05005 | [-0.43 – 0.34] | 0.808169 | -0.33953 | [-0.64 – 0.06] | 0.0897 |
| <i>HSPA2</i> | 0.234463 | [-0.17 – 0.57] | 0.248953 | 0.210915 | [-0.19 – 0.55] | 0.301013 |
| <i>KCNG1</i> | -0.0234 | [-0.41 – 0.37] | 0.909645 | -0.20007 | [-0.55 – 0.2] | 0.327109 |
| <i>KIR3DL2</i> | 0.052643 | [-0.34 – 0.43] | 0.798413 | 0.197909 | [-0.21 – 0.54] | 0.332473 |
| <i>L1TD1</i> | 0.012884 | [-0.38 – 0.4] | 0.95019 | 0.354834 | [-0.04 – 0.65] | 0.075286 |
| <i>MEOX1</i> | -0.06837 | [-0.44 – 0.33] | 0.739985 | -0.291 | [-0.61 – 0.11] | 0.149225 |
| <i>MKRN3[†]</i> | 0.558093 | [0.22 – 0.78] | 0.003049 | 0.301667 | [-0.1 – 0.62] | 0.134212 |
| <i>ODF3B</i> | 0.147954 | [-0.25 – 0.51] | 0.470724 | 0.408777 | [0.03 – 0.69] | 0.038133 |
| <i>OMG</i> | -0.12107 | [-0.49 – 0.28] | 0.555759 | -0.2099 | [-0.55 – 0.19] | 0.303409 |
| <i>OR2AK2</i> | -0.13769 | [-0.5 – 0.26] | 0.502385 | -0.01057 | [-0.4 – 0.38] | 0.959122 |
| <i>PDZK1IP1</i> | 0.330016 | [-0.07 – 0.64] | 0.099661 | 0.12498 | [-0.28 – 0.49] | 0.542971 |
| <i>PHGDH[†]</i> | -0.38706 | [-0.67 – 0.] | 0.050763 | -0.45808 | [-0.72 – -0.09] | 0.018606 |
| <i>PHOSPHO1</i> | -0.25931 | [-0.59 – 0.14] | 0.200831 | -0.25582 | [-0.59 – 0.15] | 0.207172 |
| <i>PRTN3</i> | -0.05629 | [-0.43 – 0.34] | 0.784752 | 0.103089 | [-0.3 – 0.47] | 0.616272 |
| <i>PTGS2</i> | -0.20343 | [-0.55 – 0.2] | 0.318883 | -0.14647 | [-0.51 – 0.26] | 0.475244 |
| <i>RAVER2</i> | -0.12503 | [-0.49 – 0.28] | 0.542809 | -0.06533 | [-0.44 – 0.33] | 0.751195 |
| <i>RETN</i> | -0.16844 | [-0.52 – 0.23] | 0.410778 | -0.10162 | [-0.47 – 0.3] | 0.62132 |
| <i>RP11-231C14.4</i> | 0.006594 | [-0.38 – 0.39] | 0.974496 | -0.01111 | [-0.4 – 0.38] | 0.957034 |
| <i>SAMD14</i> | 0.264546 | [-0.14 – 0.59] | 0.191554 | 0.269657 | [-0.13 – 0.59] | 0.182795 |

| | | | | | | |
|---------------------------|----------|----------------|----------|----------|-----------------|----------|
| <i>SCARF2</i> | -0.07195 | [-0.45 – 0.32] | 0.726883 | -0.07383 | [-0.45 – 0.32] | 0.720014 |
| <i>SDC3</i> | 0.162637 | [-0.24 – 0.52] | 0.427306 | 0.328102 | [-0.07 – 0.63] | 0.101759 |
| <i>SHISA8</i> | 0.283847 | [-0.12 – 0.6] | 0.159944 | 0.371597 | [-0.02 – 0.66] | 0.061601 |
| <i>SLC7A8</i> | -0.25557 | [-0.59 – 0.15] | 0.207618 | -0.1871 | [-0.54 – 0.22] | 0.360073 |
| <i>SMN1</i> | -0.02562 | [-0.41 – 0.37] | 0.90113 | -0.26629 | [-0.59 – 0.13] | 0.188534 |
| <i>SORCS3</i> | -0.09719 | [-0.47 – 0.3] | 0.636709 | -0.25039 | [-0.58 – 0.15] | 0.217303 |
| <i>SSTR3</i> | 0.020817 | [-0.37 – 0.4] | 0.919603 | -0.25508 | [-0.58 – 0.15] | 0.208524 |
| <i>SYNPO</i> | 0.119444 | [-0.28 – 0.48] | 0.561119 | -0.21102 | [-0.55 – 0.19] | 0.300774 |
| <i>TIMD4</i> [†] | -0.28971 | [-0.61 – 0.11] | 0.151117 | -0.49403 | [-0.74 – -0.13] | 0.010313 |
| <i>TNNT1</i> | 0.157598 | [-0.24 – 0.51] | 0.441954 | 0.027172 | [-0.36 – 0.41] | 0.895176 |
| <i>TRIM7</i> [†] | 0.265114 | [-0.14 – 0.59] | 0.190567 | 0.399163 | [0.01 – 0.68] | 0.043374 |
| <i>TRNP1</i> | -0.22145 | [-0.56 – 0.18] | 0.276947 | -0.04795 | [-0.43 – 0.35] | 0.816073 |
| <i>TRPV4</i> | 0.036878 | [-0.36 – 0.42] | 0.858054 | 0.497969 | [0.14 – 0.74] | 0.009631 |
| <i>UTS2</i> | 0.237144 | [-0.17 – 0.57] | 0.243427 | -0.01688 | [-0.4 – 0.37] | 0.934775 |
| <i>ZNF135</i> | -0.08776 | [-0.46 – 0.31] | 0.669886 | -0.36532 | [-0.66 – 0.03] | 0.066479 |

* Genes with an absolute PCC>0.25 in both groups are indicated by “†”. (Abbreviations: CI=confidence interval, PCC=Pearson correlation coefficient)

Supplemental Figures

Figure S1

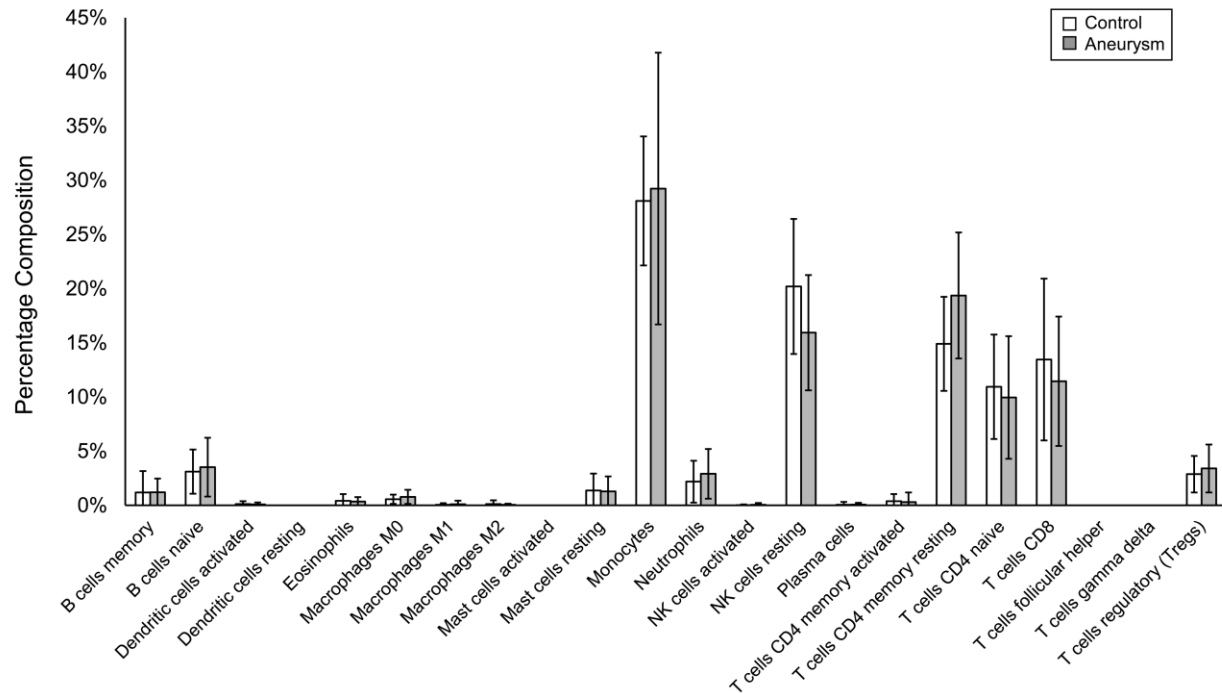


Figure S1: Distribution of cell types in isolated PBMCs of both groups computed by CIBERSORT. In the discovery cohort, there were no statistically significant differences between cell type proportions in the aneurysm (grey) and control groups (white). All comparisons had a false discovery rate-corrected q -value > 0.05 . In both groups, monocytes comprise majority of cells, followed by NK cells and several T cell populations.

Figure S2

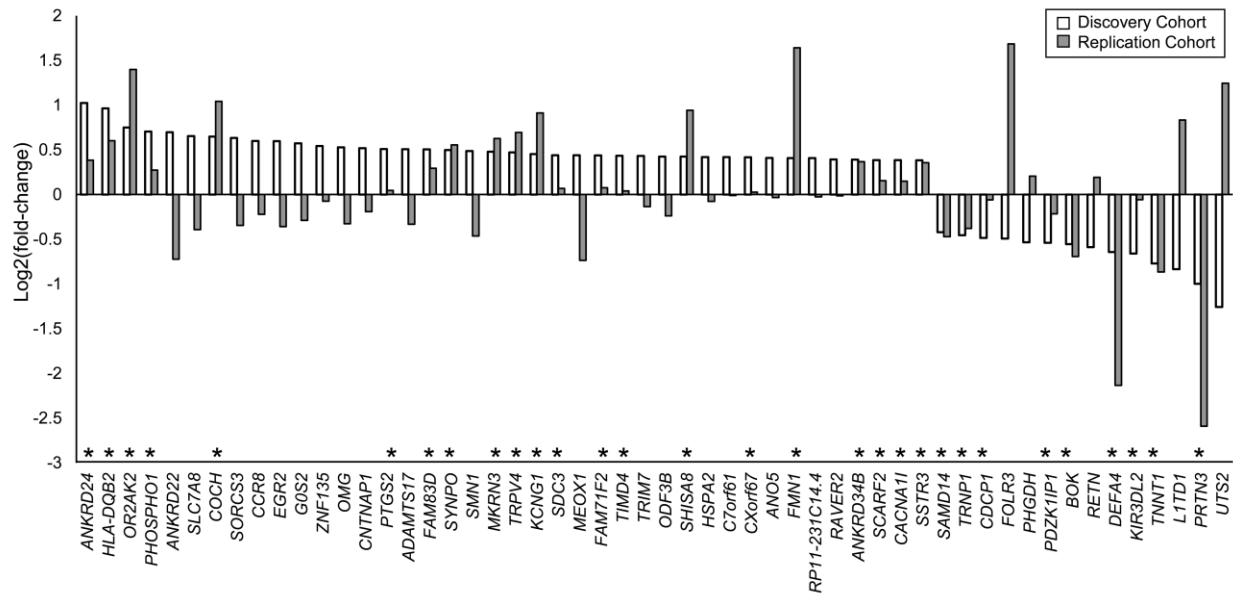


Figure S2: Comparison in fold-change of differentially expressed gene in the discovery cohort compared to the validation cohort. The 54 genes are presented in order of decreasing fold-change in the in the discovery cohort (white). A majority of the genes (30/54) have the same direction change in expression in the replication cohort (grey). These genes are indicated by the “*”.