Research Article

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2026.65.010193

# Supplemental Text

## Supplemental Materials

### Supplemental Discussions

ADCY6 expression was shown to be negatively correlated with the activation of immune signaling pathways, immune checkpoint receptors, and ligands in breast cancer [21], it is possible that ADCY6 down-regulation in kidney diseases is associated with immune activation. ADCYAP1 is a ADCY stimulating hormone and plays a protective role for neurons and nerves for infection responses [22] and in peripheral nerve injury [23], ADCYAP1 down-regulation might suggest a diminished protective role in kidney injury. ADCY1 is an important regulator of cAMP [24] which affects various pathways such as DNA repair, apoptosis, proliferation and etc., promoting cancers [25] or inducing chemo-resistance [26], and causing CNS related problems [27], and so on. ADCY1 down- regulation might reduce cAMP levels in kidneys. A study has shown that lower urine cAMP is an independent predictor of renal deterioration and cardiovascular death in patients with CKD [24]. GNAO1 is highly expressed in the CNS and plays essential roles in neural circuit formation, its mutations are associated with a spectrum of hyperkinetic movement disorders and/or epilepsy, and typically with global developmental delay and intellectual disability [28,29]. More discussion was left in the supplemental sections. GNAO1 regulates Rho signaling pathway as a molecular switch in differentiating neurons [30], and it is intriguing to uncover how GNAO1 down-regulation is related to most kidney diseases. On the other hand, GNAI1 and GNAI3, originally identified as ADCY inhibitors, are highly expressed in immune cells.

They were shown to regulate macrophage polarization [31], to reduce colitis-associated tumorigenesis by blocking IL6 and GNAI2 [32], and to activate EGF-mediated Akt-mTORC1 pathway [33]. It would be an important research topic to address the exact mechanism of their up-regulations over many types of kidney diseases. At last, for single kidney disease, first, OR1F2P, OR2W1, and OR7C1 were down-regulated s.s. solely for SLE. Since Olfr19 is listed as a mice ortholog of OR1F2P and of OR7A17 with high protein sequence similarity, the sequences between OR1F2P and OR7A17 were aligned with about 51% similarity, hence we guessed that OR1F2P and OR7A17 might play similar function in kidneys. OR7A17 was demonstrated to be expressed in human keratinocytes and a popular skin medication, all-trans retinoic acid, suppressed OR7A17 and keratinocyte proliferation [34], it is interesting to study whether OR1F2P played a similar role in kidney and is down-regulated in SLE. OR2W1 is a widely tuned receptor and can be activated by a large number of chemicals/ordants [35]. OR7C1 was shown to be expressed in colon and oral cancer stem cells and is a potential immunotherapy target [36,37]. Second, OR2B2, OR2B6 and OR6A2 were down-regulated s.s. only for RPGN. OR2B6 was expressed in healthy platelet [38], and was highly expressed in breast carcinoma tissue [39], moreover it was correlated with proliferation genes and luminal A subtypes [40]. OR6A2 shares 87.32% sequence similarity with mouse ortholog Olfr2. OR6A2/Olfr2 was shown to induce inflammasome activation in conjunction with TLR4 ligation [41].

In addition, OR12D3, OR3A2, OR3A3, OR7C2 and GNAT2 were down-regulated s.s. only for SLE and RPGN. OR12D3/Olfr109 is a sensor of insulin peptides and modulates glucose metabolism [42]. No published results were found for OR3A2, OR3A3 and OR7C2. GNAT2 is associated with achromatopsia and cone dystrophy [43]. Finally, a more interesting result is that GNA12, GNAQ, GNAS and GNAZ were up-regulated s.s. only for DN and RPGN, in contrast to the down-regulation scenarios as in the above. GNA12 and GNA13 play central and integrative roles in the regulation of signal transduction cascades within various cell types in the kidney, and coupled GNA12/13 proteins are deeply involved in renal epithelial injury events. GNA12 activation mediates heat shock protein 90 (Hsp90)/tyrosine protein kinase cSrc (Src)- induced zonula occludens-1 (ZO-1) phosphorylation and disruption of the tubular epithelial barrier. GNA12 activation also leads to PP2A-mediated JNK1 stimulation of epithelial cell apoptosis via Bcl-2 proteins. Furthermore, GNA12 inhibits phagocytic clearance of apoptotic cells, and GNA12 blockade in the GDP-bound inactive state promotes tissue repair [44]. GNAQ mutation induces hyperactivated calcium signaling [20]. GNAS has a highly complex imprinted expression pattern and its mutations lead to a spectrum of disorders [45]. GNAS can activate ADCY leading to increased cAMP levels. GNAZ was shown to link the circadian and dopaminergic system to G protein-mediated signaling in a mouse model [46]. It would be fascinating to find why these four genes were particularly activated in DN and RPGN but less active in other kidney diseases [47-49].

### Supplemental Tables

(Supplemental Tables 1-4).

**Supplemental Table 1:** Linear model weights with 4 OR genes. A negative weight indicates expression down- regulation.

| Disease | Intercept | OR2F1 | OR10H3 | OR1D2 | OR7A5 |
|---|---|---|---|---|---|
| *SLE* | 0.6309 | -0.0189 | -0.0519 | -0.1377 | -0.1522 |
| *IGAN* | 0.6178 | -0.0709 | -0.1543 | -0.055 | -0.0397 |
| *RPGN* | 0.5021 | -0.1025 | -0.0562 | -0.1587 | -0.1171 |
| *HN* | 0.5721 | -0.1056 | -0.0779 | -0.0947 | -0.022 |
| *MGN* | 0.5402 | -0.2328 | -0.1003 | 0.0276 | -0.0502 |
| *DN* | 0.48 | -0.2476 | 0.1016 | -0.2343 | -0.0315 |
| *MCD* | 0.5156 | 0.1215 | -0.1481 | -0.0303 | -0.1719 |
| *FSGS* | 0.4785 | -0.1975 | -0.2831 | 0.0617 | 0.0699 |

**Supplemental Table 2:** Linear model weights with 4 ADCY genes. A negative weight indicates expression down- regulation.

| Disease | Intercept | ADCY7 | ADCY1 | ADCYAP1 | ADCY6 |
|---|---|---|---|---|---|
| *SLE* | 0.6774 | 0.177 | -0.0446 | -0.1181 | -0.1679 |
| *IGAN* | 0.6645 | 0.1983 | -0.0546 | -0.0516 | -0.1704 |
| *RPGN* | 0.5691 | 0.1464 | 0.0473 | -0.1276 | -0.3726 |
| *HN* | 0.6471 | 0.1582 | -0.0328 | -0.0649 | -0.2208 |
| *MGN* | 0.6531 | 0.2283 | -0.1255 | -0.0235 | -0.1515 |
| *DN* | 0.5615 | 0.2788 | 0.0011 | -0.0534 | -0.2877 |
| *MCD* | 0.6302 | 0.128 | -0.0662 | -0.1973 | -0.1127 |
| *FSGS* | 0.4965 | -0.0497 | 0.0902 | -0.082 | -0.4451 |

**Supplemental Table 3:** Linear model weights with 4 OR genes. A negative weight indicates expression down- regulation.

| Disease | Intercept | GNAI3 | GNAI1 | GNAO1 | GNA11 |
|---|---|---|---|---|---|
| *SLE* | 0.7261 | 0.1629 | 0.0029 | -0.1968 | -0.2224 |
| *IGAN* | 0.7138 | 0.3065 | -0.1021 | -0.0793 | -0.3133 |
| *RPGN* | 0.5557 | 0.2841 | 0.1482 | 0.0404 | -0.2995 |
| *HN* | 0.7433 | 0.2496 | 0.0645 | -0.1179 | -0.3594 |
| *MGN* | 0.7939 | 0.3835 | 0.0801 | -0.0696 | -0.3502 |
| *DN* | 0.5709 | 0.2896 | 0.0077 | -0.135 | -0.2341 |
| *MCD* | 0.7922 | 0.5671 | -0.1595 | -0.0646 | -0.3522 |
| *FSGS* | 0.6124 | 0.1468 | 0.042 | -0.1343 | -0.3812 |

**Supplemental Table 4:** ROC results of 24 linear models. AUC: area under the curve; FPR: false positive rate; TPR: true positive rate; CUTOFF: score cutoff; N0: number of HC samples; N1: number of disease samples.

| CATEGORY | DISEASE | AUC | FPR | TPR | CUTOFF | N0 | N1 |
|---|---|---|---|---|---|---|---|
| *ADCY* | DN | 0.97 | 0.1 | 0.88 | 0.4756 | 21 | 17 |
| *GNA* | DN | 0.99 | 0 | 0.94 | 0.585 | 21 | 17 |
| *OR* | DN | 0.86 | 0.24 | 0.82 | 0.4726 | 21 | 17 |
| *ADCY* | FSGS | 0.95 | 0.1 | 0.92 | 0.53 | 21 | 13 |
| *GNA* | FSGS | 0.92 | 0.1 | 0.85 | 0.3904 | 21 | 13 |
| *OR* | FSGS | 0.86 | 0.14 | 0.77 | 0.4546 | 21 | 13 |
| *ADCY* | HN | 0.82 | 0.24 | 0.8 | 0.5086 | 21 | 20 |
| *GNA* | HN | 0.96 | 0.14 | 0.95 | 0.4164 | 21 | 20 |
| *OR* | HN | 0.75 | 0.05 | 0.6 | 0.5715 | 21 | 20 |
| *ADCY* | IGAN | 0.81 | 0.24 | 0.72 | 0.5094 | 21 | 25 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| *GNA* | IGAN | 0.9 | 0.14 | 0.84 | 0.4879 | 21 | 25 |
| *OR* | IGAN | 0.79 | 0.05 | 0.64 | 0.609 | 21 | 25 |
| *ADCY* | MCD | 0.79 | 0.14 | 0.65 | 0.5345 | 21 | 17 |
| *GNA* | MCD | 0.96 | 0.1 | 0.88 | 0.4466 | 21 | 17 |
| *OR* | MCD | 0.8 | 0.1 | 0.71 | 0.5598 | 21 | 17 |
| *ADCY* | MGN | 0.75 | 0.14 | 0.67 | 0.521 | 21 | 18 |
| *GNA* | MGN | 0.93 | 0.1 | 0.89 | 0.479 | 21 | 18 |
| *OR* | MGN | 0.8 | 0.19 | 0.67 | 0.507 | 21 | 18 |
| *ADCY* | RPGN | 0.99 | 0 | 0.9 | 0.6192 | 21 | 21 |
| *GNA* | RPGN | 1 | 0 | 1 | 0.4066 | 21 | 21 |
| *OR* | RPGN | 0.95 | 0.1 | 0.9 | 0.529 | 21 | 21 |
| *ADCY* | SLE | 0.89 | 0.14 | 0.78 | 0.5648 | 21 | 32 |
| *GNA* | SLE | 0.89 | 0.1 | 0.81 | 0.595 | 21 | 32 |
| *OR* | SLE | 0.85 | 0.19 | 0.72 | 0.5929 | 21 | 32 |

**ISSN: 2574-1241**

DOI: 10.26717/BJSTR.2026.65.010193

**Aibing Rao and Ying Tang.** Biomed J Sci & Tech Res