Are miR-548 family members potential genetic drivers of CAKUT?

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Introduction

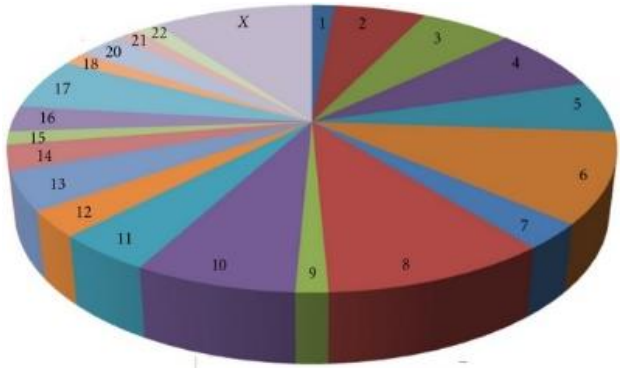
CAKUT - Congenital Anomalies of Kidney and Urinary Tract

- overall rate: **1: 500**, which makes them the most common congenital anomalies
- 41.3 % of children who undergo renal replacement therapy have CAKUT as underlying disease

Copy number variants (CNVs) are the common genetic cause of CAKUT

CNV regions harbor genes for miRNAs

- miR-548 family members regulate podocyte differentiation *in vitro*, which is important for kidney development
- There are 73 known precursors from the mir-548 family in the human genome annotated by miRBase, located on all human chromosomes except chr19 and chrY
- It is not known to which extent CNVs associated with CAKUT harbour miR-548 members



Distribution of all mir-548 family members across all human chromosomes

Materials and Methods

Verbitsky et al. 2019

- Verbitsky et al. 2015
- Westland et al. 2015
- Lopez-Rivera et al. 2017
- Sanna-Cherchi et al. 2012

+2000 CAKUT cases

Pathogenic and likely pathogenic CNVs in CAKUT patients

Mapping of miRNAs sequences onto CNV regions
UCSC genome browser- accessed Dec 2020.
Tool: *Table Browser*
track: sno/miRNA
assembly: GRCh37/ hg19
group: genes and gene predictiones

Set miRNA located in pathogenic and likely pathogenic CNVs associated with CAKUT

Descriptive statistical analysis- R

Identification of hsa-miR-548 family members in CNV regions associated with CAKUT

Bioinformatic enrichment analysis
miRPathDB 2.0
database: *KEGG*
evidence: *Predicted (intersection)*

List of pathways in which targets of a representative miRNA is enriched

gnomAD v2.1 database

Data extraction
Mammal, Human, GRCh37/ hg19

Set CNV regions in gnomAD Controls

Data filtering
SVtype: Deletion, Duplication
Af (alternative allele frequency): keep> = 0.2
Svlen (length of CNV): keep> = 1KB

Filtered set of CNV regions in gnomAD Controls

Mapping of miRNAs sequences onto CNV regions
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Tool: *Table Browser*
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assembly: GRCh37/ hg19
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Set miRNA located in CNVs in controls

Descriptive statistical analysis- R

Identification of hsa-miR-548 family members in CNV regions associated with controls

Bioinformatic enrichment analysis
miRPathDB 2.0
database: *KEGG*
evidence: *Predicted (intersection)*

List of pathways in which targets of a representative miRNA is enriched

Results

Table 1. Identified miR-548 family members in polymorphic CNVs and CNVs associated with CAKUT

miR-548 family members identified in CNV regions of CASES	miR-548 family members identified in CNV regions of CONTROLS
hsa-miR-548f-3	hsa-miR-548i-3
hsa-miR-548f-4	
hsa-miR-548f-5	
hsa-miR-548h-2	
hsa-miR-548i-1	
hsa-miR-548i-2	
hsa-miR-548i-4	
hsa-miR-548j	
hsa-miR-548l	
hsa-miR-548m	
hsa-miR-548p	
hsa-miR-548x	
hsa-miR-548f-2	

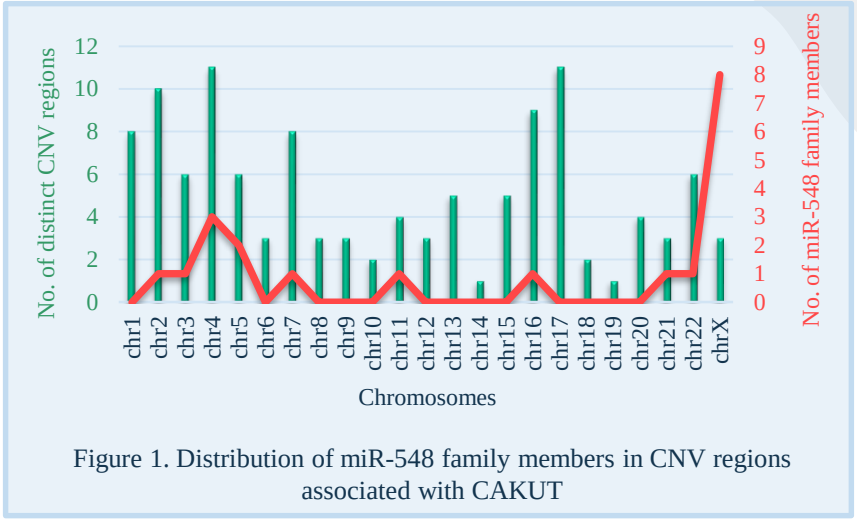
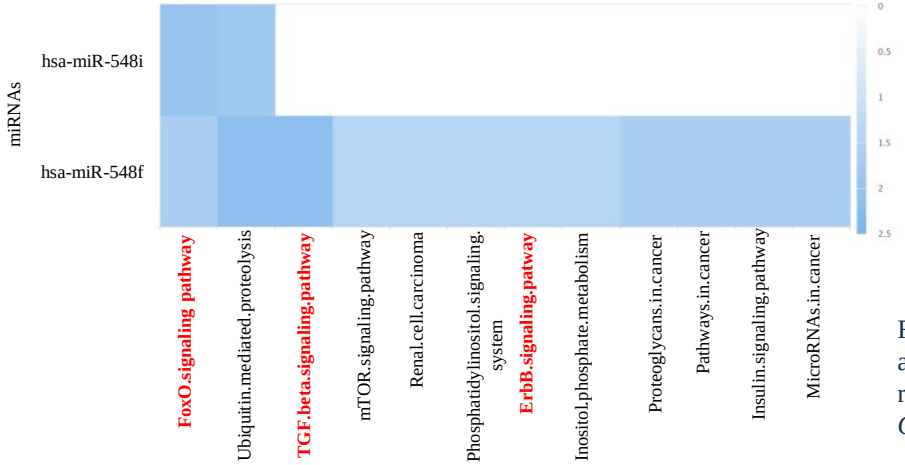


Figure 1. Distribution of miR-548 family members in CNV regions associated with CAKUT



TGF-beta and ErbB signaling patways

↓

Nephrogenesis

FOXOs signaling pathway

↓

Renal protection

Figure 2. Heatmap of KEGG enrichment analysis on genes which are targets for representative miRNAs.
Color intensity - higher p value

Conclusion

- miR-548 family members are often found in CNV regions associated with CAKUT, which is not the case with controls.
- Enrichment analysis has suggested that miR-548 family members regulate genes involved in nephrogenesis

The results reported in the current study can be helpful for more focused future confirmatory analysis, where **miR-548 family members** located in CNV regions associated with CAKUT should be investigated as **potential genetic drivers of CAKUT**

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