Statistical inference of immunogenetic parameters reveals HLA-DRB1*11:01 allele associated with pediatric FSGS

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FOCAL SEGMENTAL GLOMERULOSCLEROSIS

FSGS

- Pediatric Nephrotic syndrome
- ~4-5x risk in African Americans (AA) Genetic factors
- Edema, Massive proteinuria
- Dialysis, Transplantation

First genomic study of renal failure in 140 AA children with Chronic Kidney Disease (CKD)

CKD Chronic Kidney Disease in Children

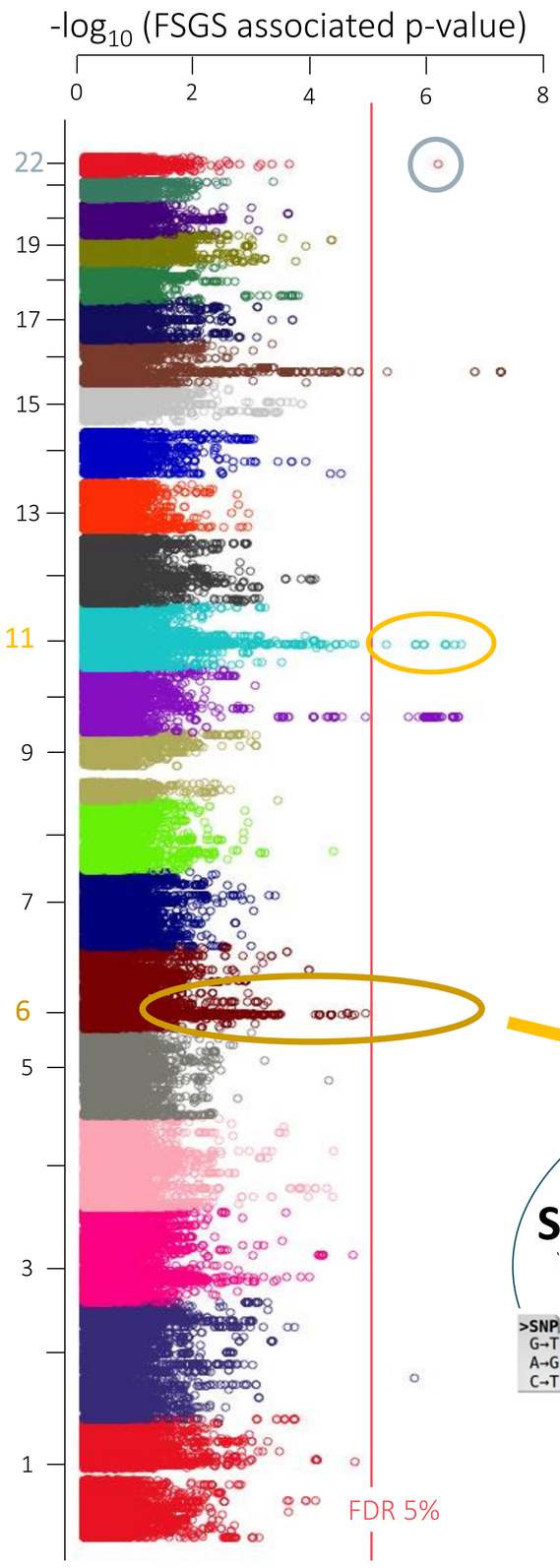
➡ Identify underlying genetic determinants in FSGS (29 cases)

METHODS

- ✓ **Genotyping arrays:** 254,000 SNPs on Illumina® Exome Chips
- ✓ **Quality Control and HRC imputation:** 934,000 common SNPs with Minor Allele Frequency ≥ 0.3% for statistical analysis
- ✓ **Association analysis with FSGS phenotype** using regression model
- ✓ **Gene-set enrichment analysis (GSEA)** using GSA-SNP2
- ✓ **Investigation of HLA:**
  - Imputation of 108 *HLA* alleles using HIBAG[1]
  - Inference of immunogenetic parameters (*e.g. HLA* 5-gene haplotypes, amino-acids) using Easy-HLA[2]

SHLARC

Easy-HLA

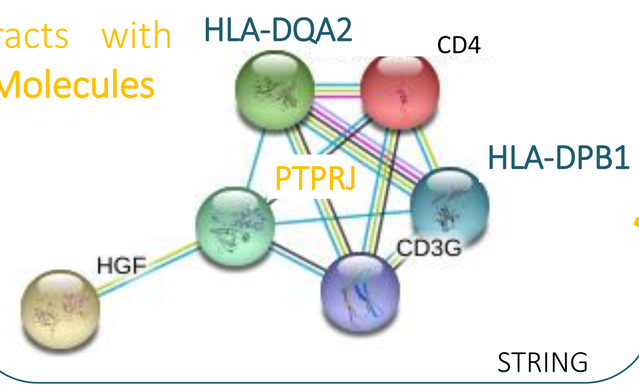


APOL1 - G1

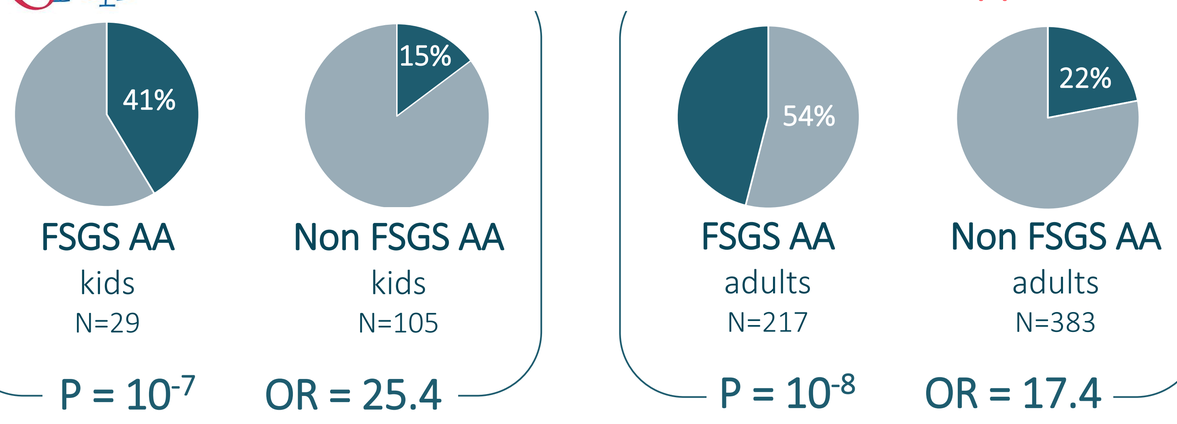
- ✓ Confirmation of previously major described signal in adult FSGS and CKD
- ✓ Validation of our analysis and cohort

PTPRJ

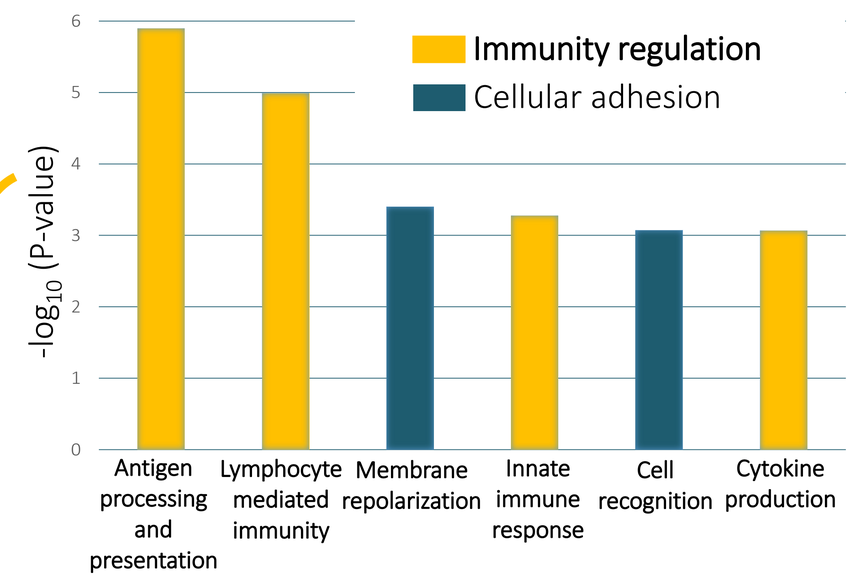
- 5 significant SNPs
- PTPRJ interacts with class II HLA Molecules



CKD — rs73885319 — Kopp2011[3]



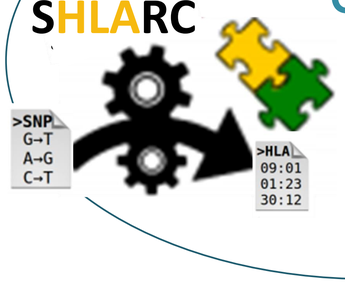
GSEA with Gene Ontology



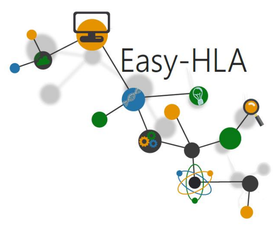
➡ Importance of **antigen processing and presentation** pathways in pediatric FSGS

Further investigation of HLA

SHLARC



Easy-HLA



HLA ASSOCIATION WITH FSGS

- 108 *HLA* alleles (=80 Class I alleles + 28 Class II alleles)
- 714 HLA amino acids and 17 *HLA* 5-gene haplotypes

	P-value	OR
*HLA-DRB1*11:01* N = 13/29 FSGS kids	5.6×10^{-3}	10.5
67F & 58E HLA-DRB1 N= 9/29 FSGS kids	5.0×10^{-3}	4.5

CONCLUSION

- ✓ Identification of 5 statistically significant and biologically-relevant loci with pediatric FSGS
- ✓ First demonstration of a role for class II HLA in FSGS
- ✓ Further genetic and functional analyses focusing on these loci will enhance our understanding of molecular pathogenicity mechanisms underlying pediatric FSGS.

1. SHLARC , JOBIM 2019, Poster session Wednesday July 3rd, Poster n°41, *Douillard et al.*
2. EasyMatch-R, JOBIM 2019, Demo session Wednesday July 3rd, Demo n°1, *Geffard et al*.
3. **Kopp. JB et al,** APOL1 genetics variant in FSGS and HIV-associated Nephropathy. JASN (2011) 22, 2129-37.

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