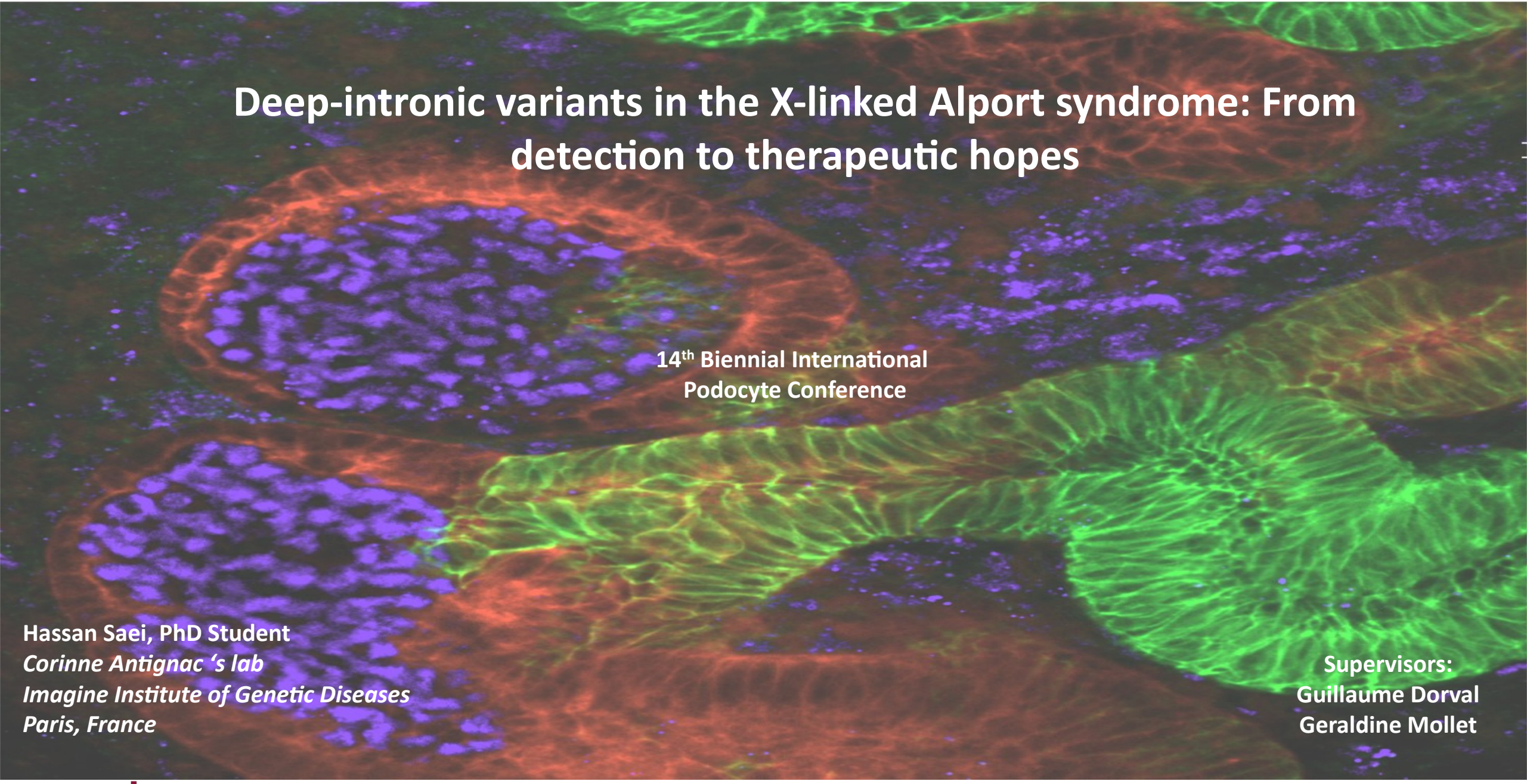
Deep-intronic variants in the X-linked Alport syndrome: From detection to therapeutic hopes



14th Biennial International
Podocyte Conference

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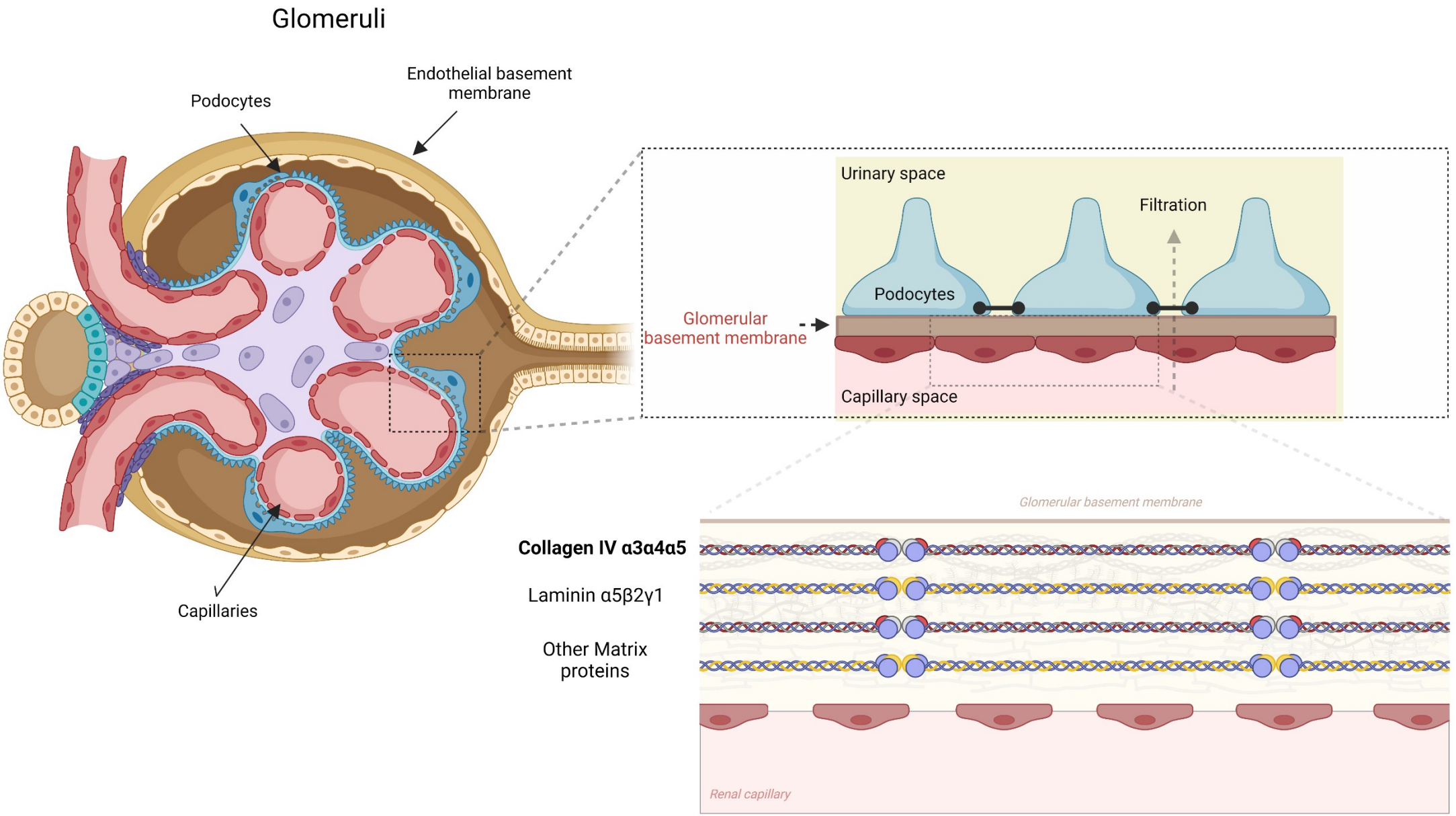
Supervisors:
Guillaume Dorval
Geraldine Mollet

Université Paris Cité

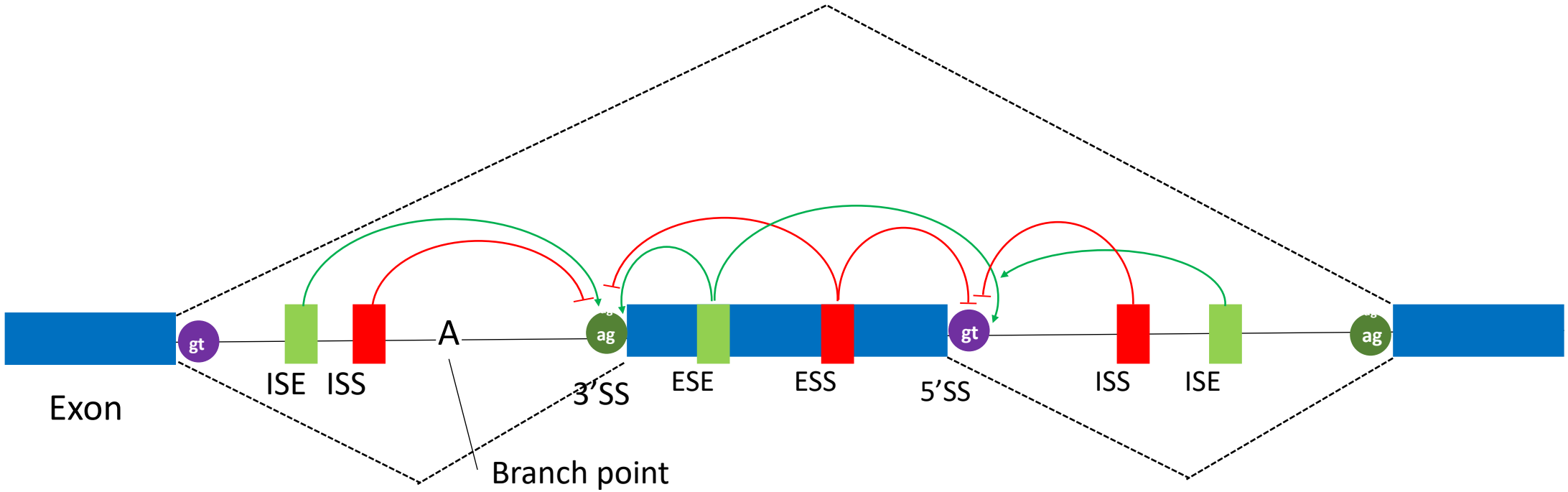
institut imagine
GUÉRIR LES MALADIES GÉNÉTIQUES

Inserm

Glomerular filtration barrier and basement membrane



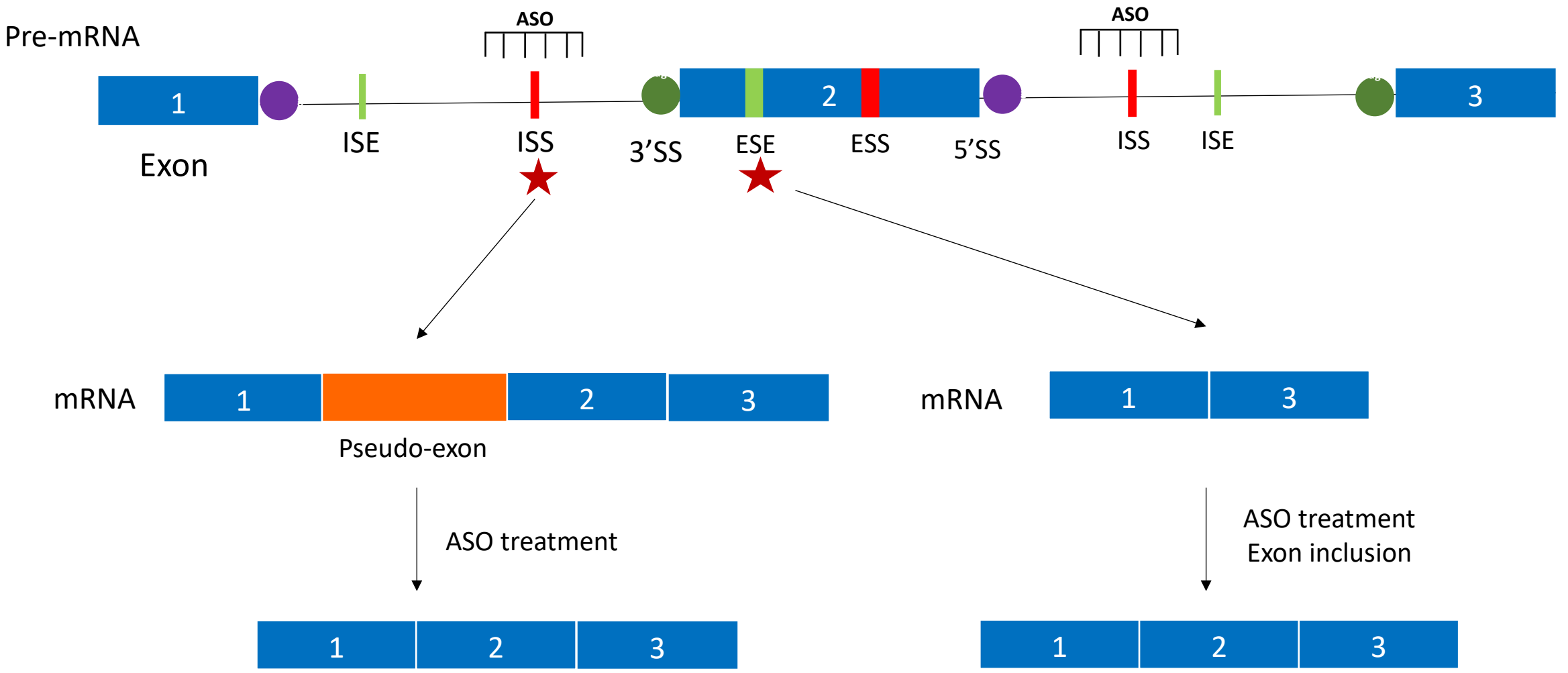
Cis regulation of mRNA splicing



ISE : Intronic splice Enhancer
ISS : Intronic splice Silencer
ESE : Exonic splice Enhancer
ESS : Exonic splice Silencer
: Acceptor splice site
: Donor splice site
: Inhibition
: Activation

Boisson et al. Accepted Kidney International

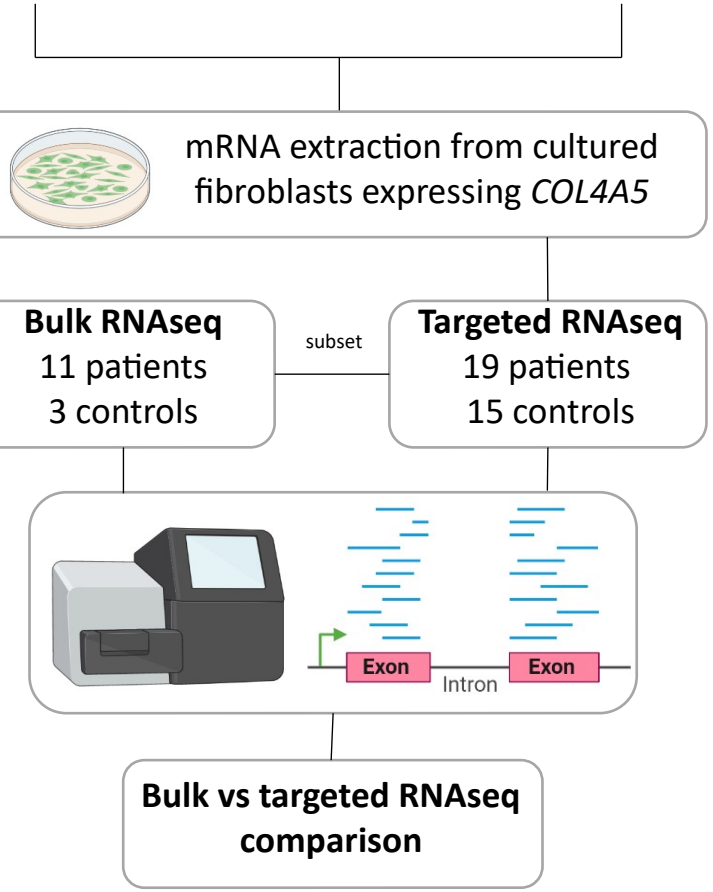
Antisense oligonucleotide (ASO) treatment



Deep intronic variants responsible for the disease

19 patients
Clinically proven AS
No pathogenic variant

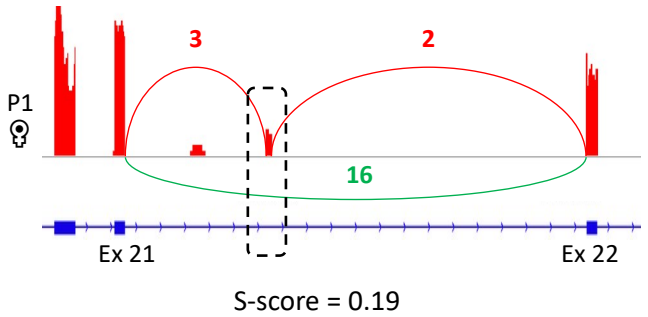
15 controls



Priorization of filtered alternative splicing events

S-score adapted from Cummings *et al*.

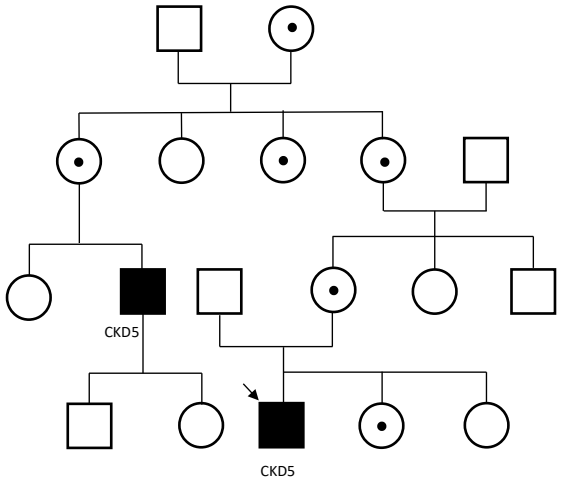
$$\textbf{S-Score} = \frac{\text{Nmax alternative reads}}{\text{Nmax canonical reads}}$$

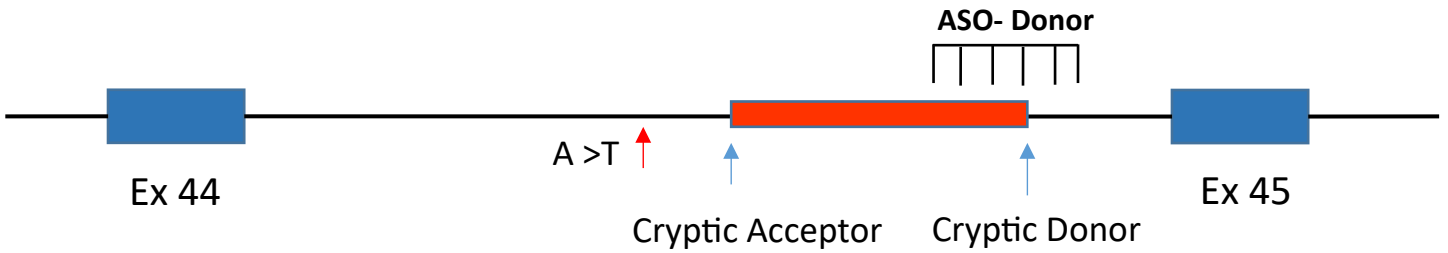


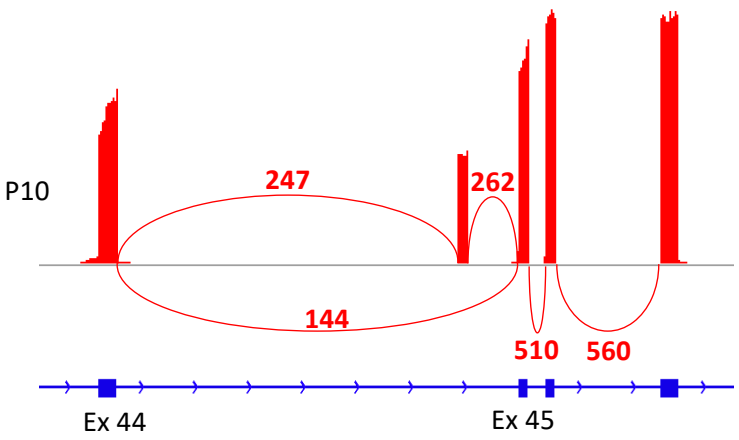
✓ Gene coverage was assessed by the total number of junctional reads aligning on *COL4A5*.

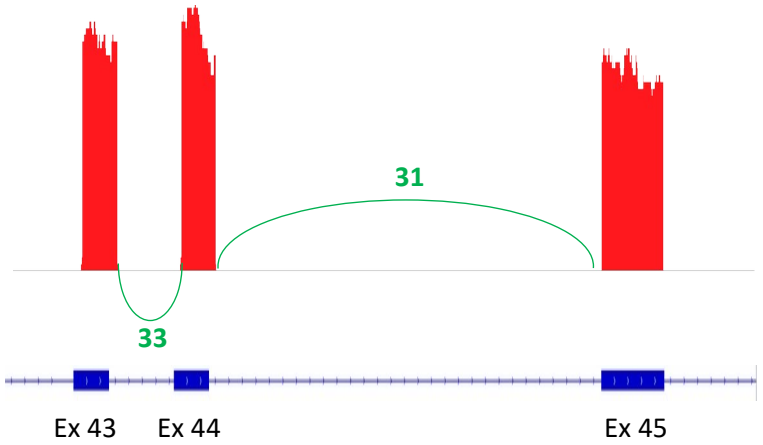
Boisson et al. Accepted Kidney International

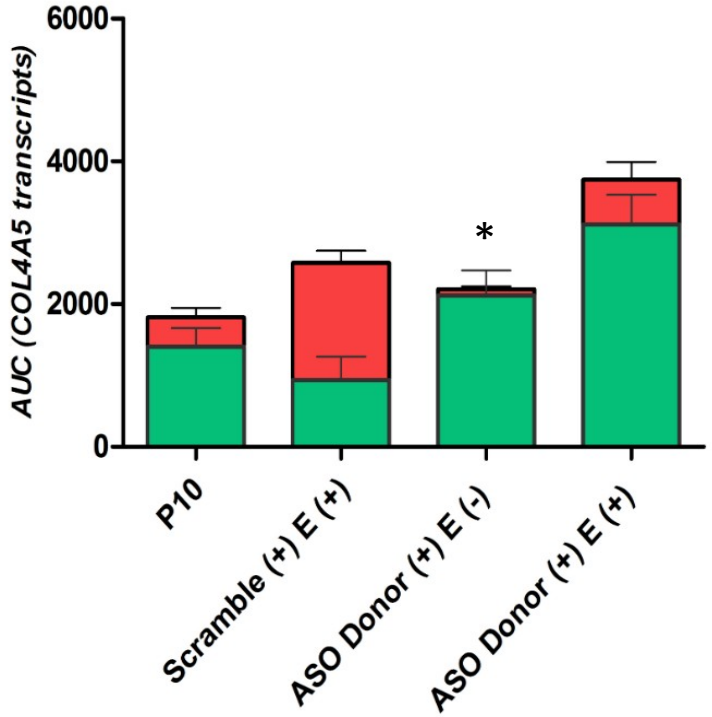
Patient 1







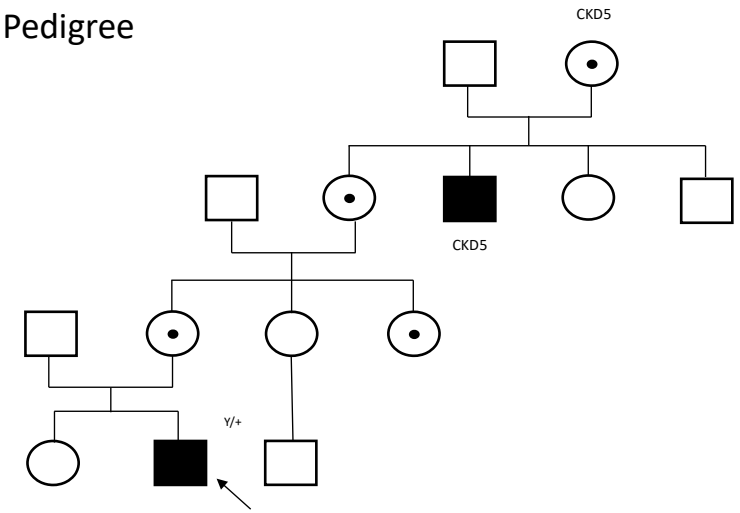




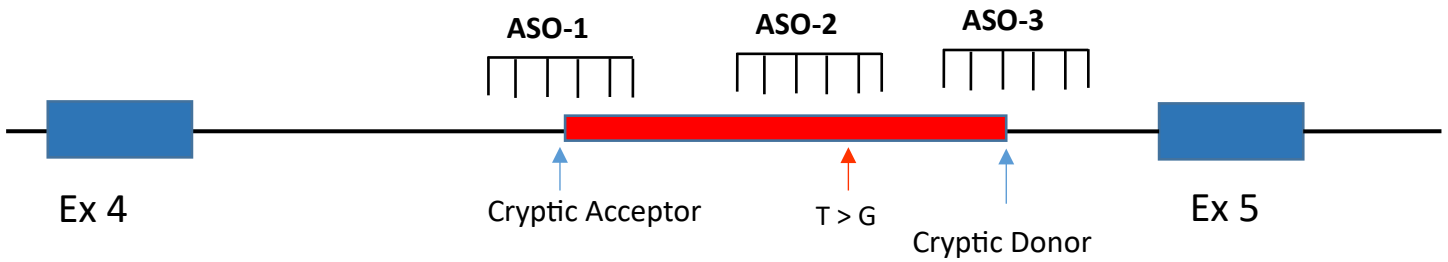
Unpublished results

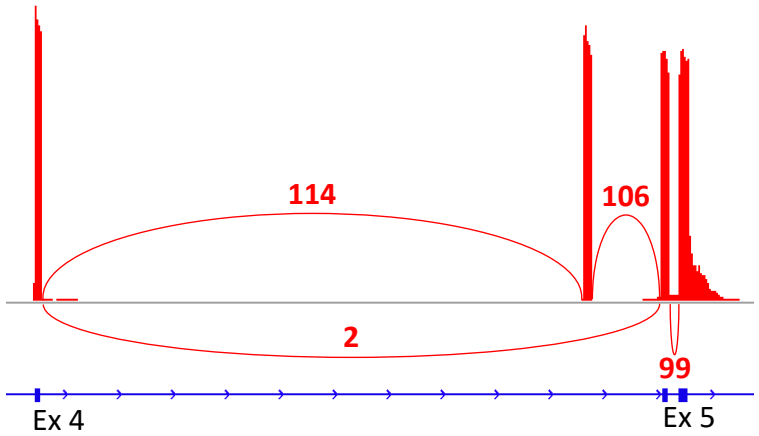
Patient 2

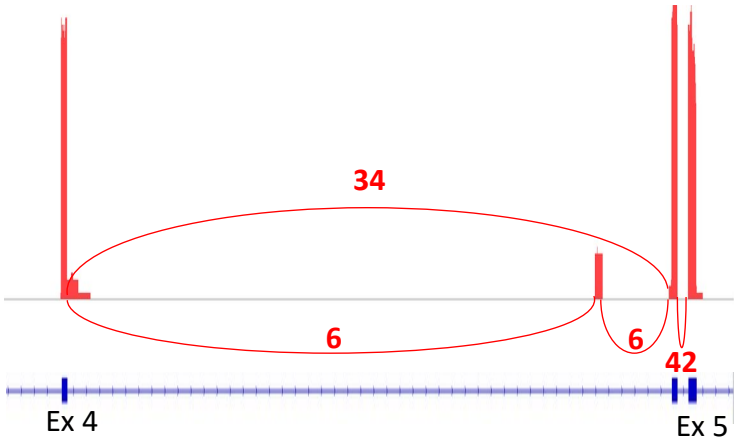
Pedigree

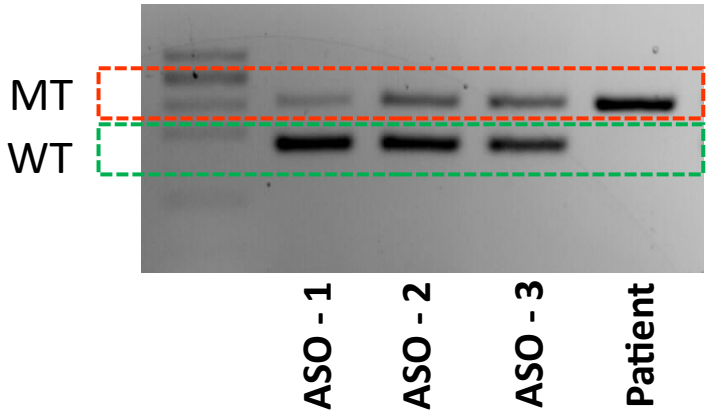


COL4A5 mRNA





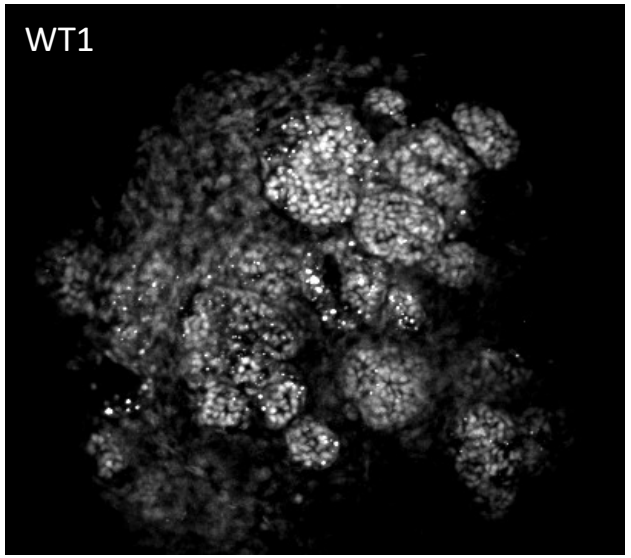


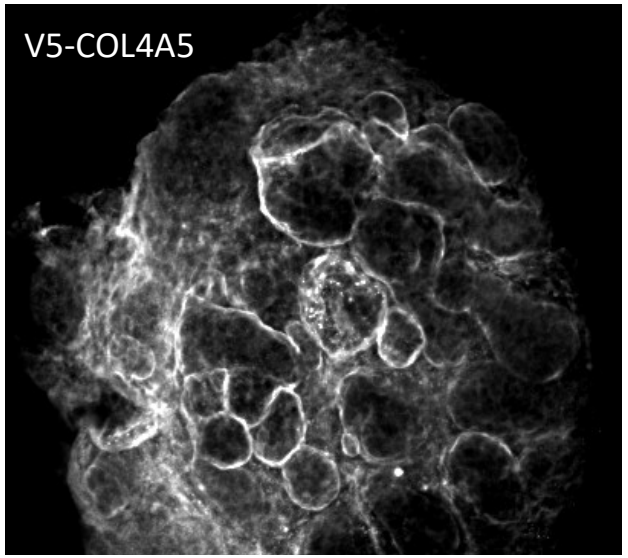


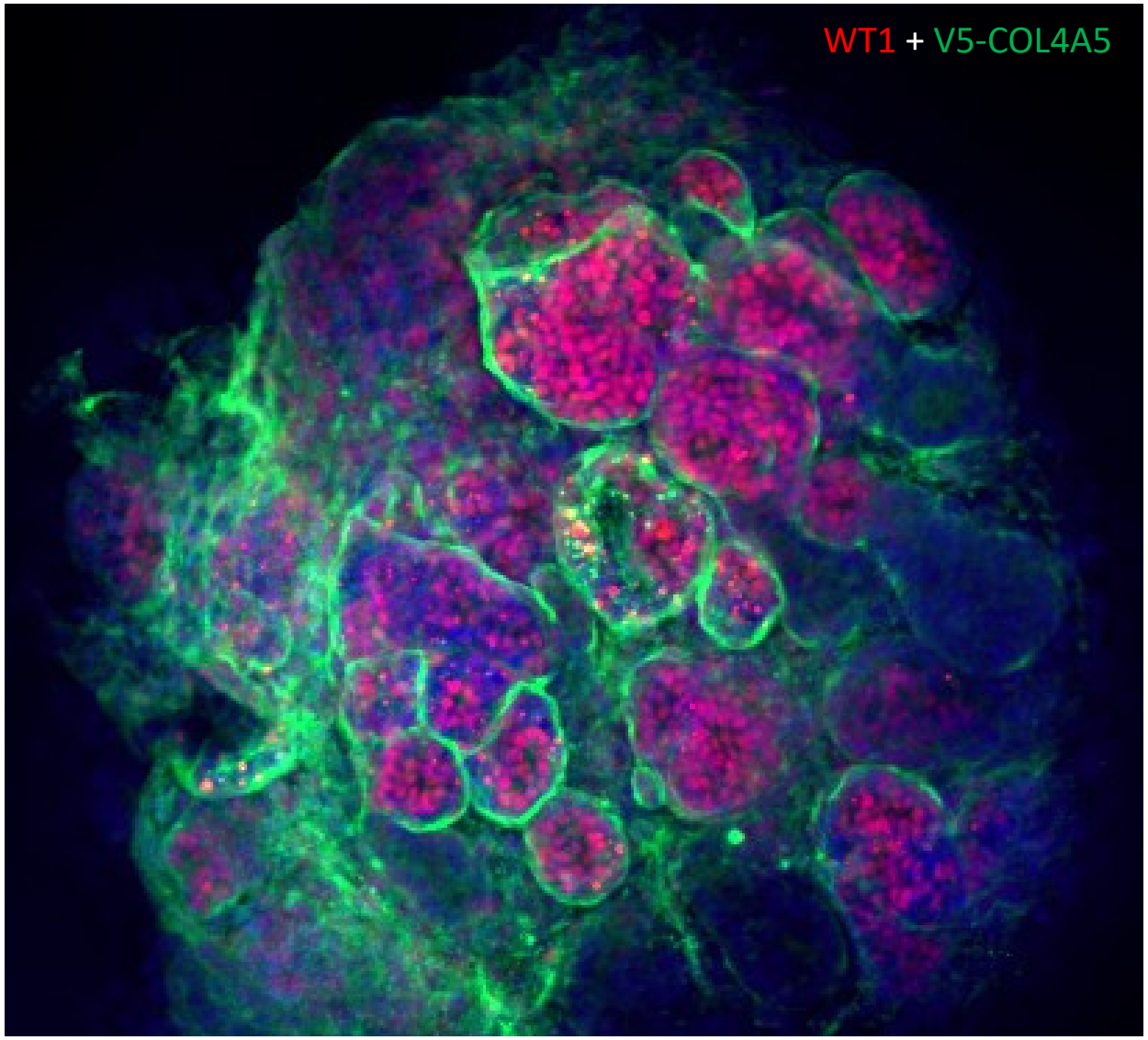
Unpublished results

iPS-derived kidney organoids – healthy organoid

Healthy organoid



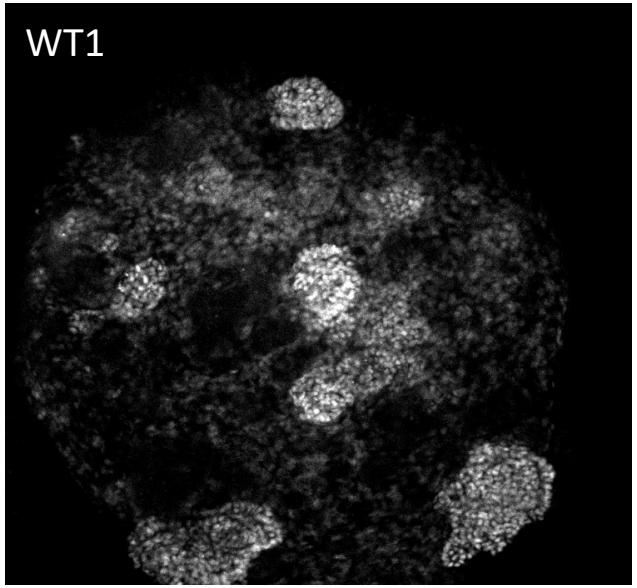


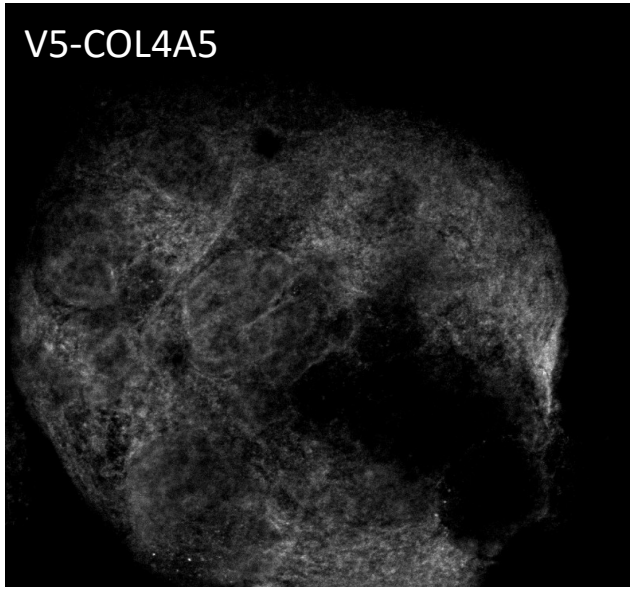


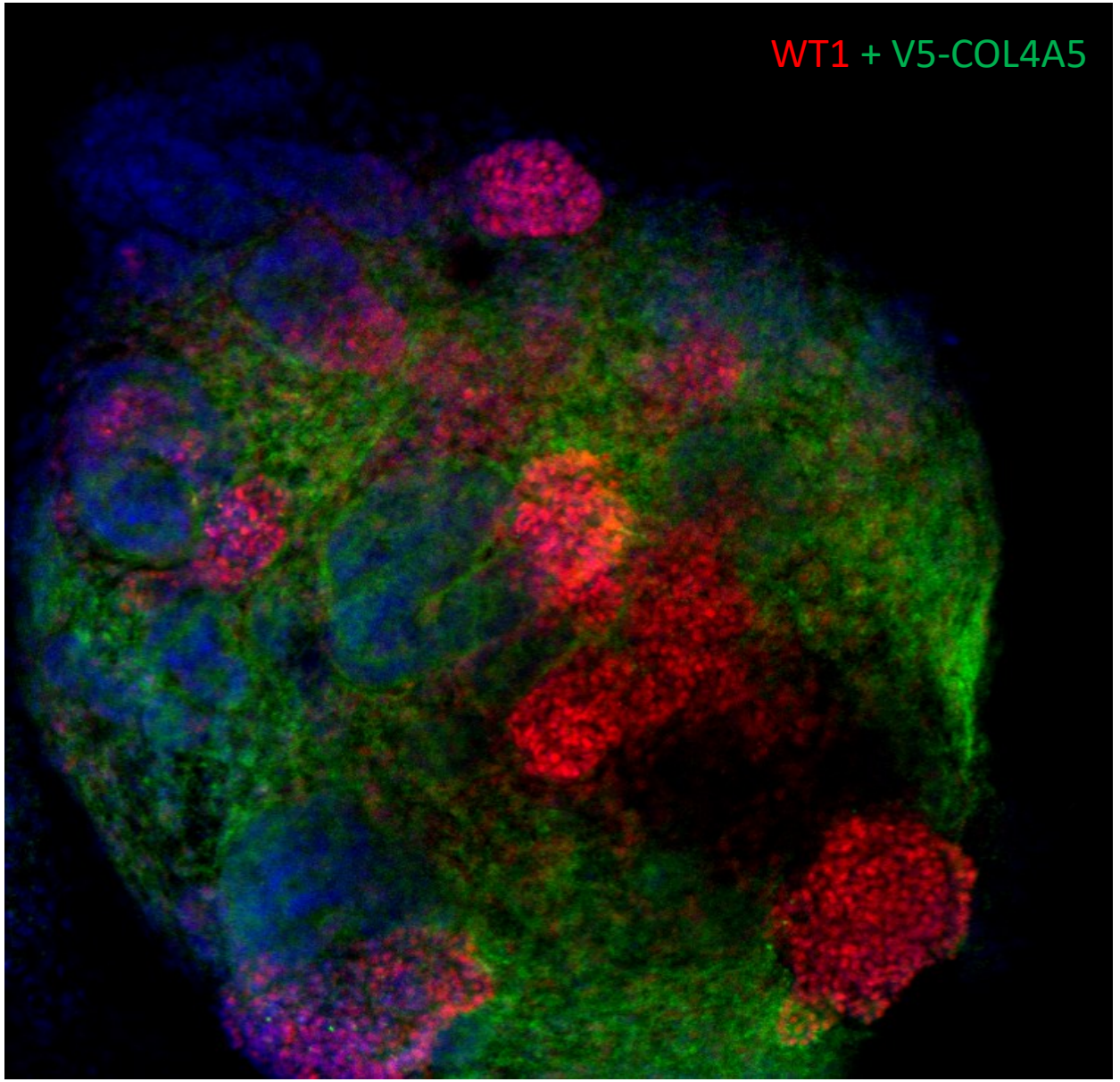
Unpublished results

Alport organoid model

Alport organoid model







Unpublished results

Summary

- Targeted RNASeq: rapid and robust method to identify aberrant splicing in patients.
- ASOs are the good treatment candidate in patients with splice modulation events.
- Genome and RNASeq data integration could be used to improve the genetic diagnosis.

Ongoing:

- Reverse splicing in organoid model of Alport syndrome.

Future work:

- Develop X-linked Alport mice model with intronic variation to study ASO treatment.

Labratory of hereditary kidney diseases

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Genomics Plateforme

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Thank you for your attention!

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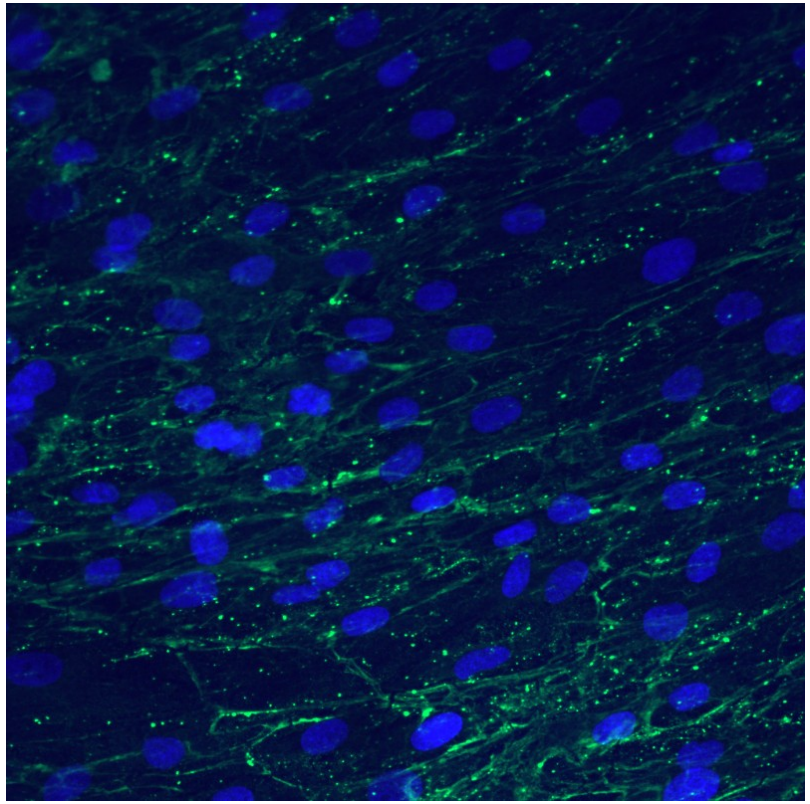
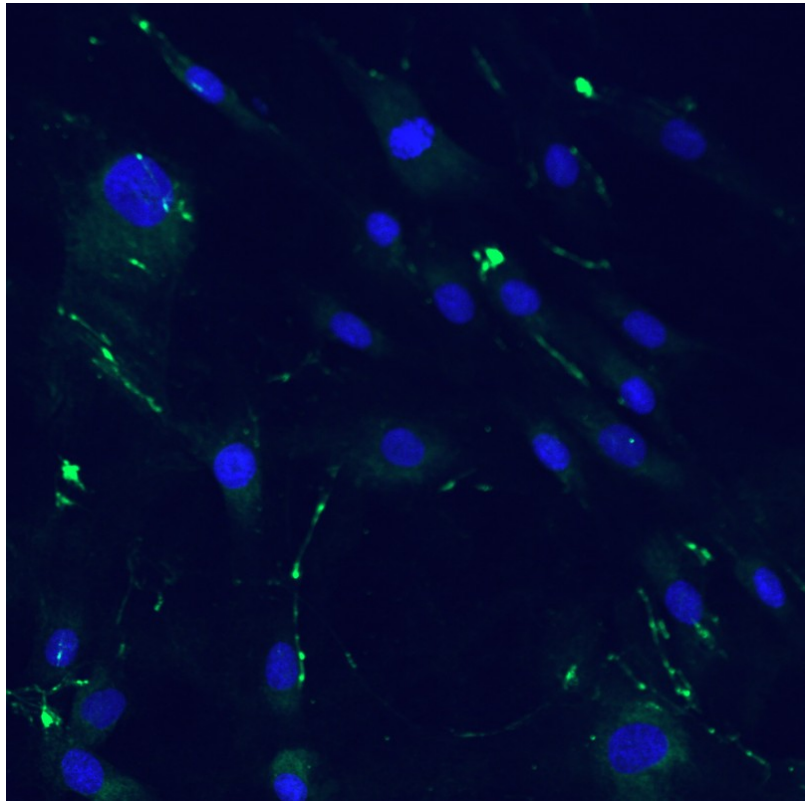
Poster number 002

Collagen 4 staining in patient-derived fibroblasts

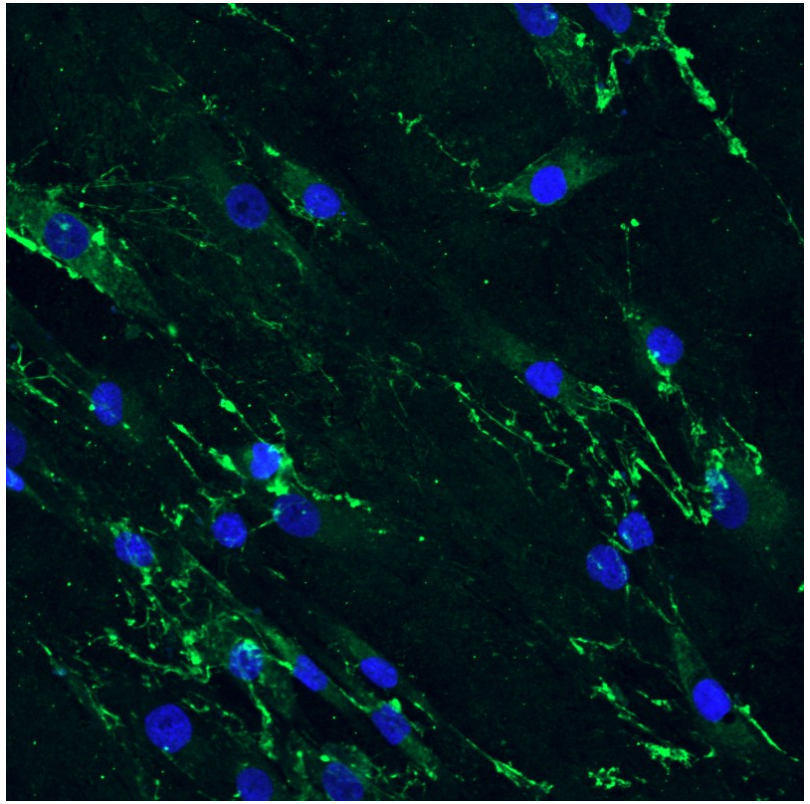
Healthy control



Patient



Fibroblast treated with ASO



Unpublished results