61ST ERA CONGRESS
STOCKHOLM & VIRTUAL
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Clinically boosted exome-sequencing is necessary for accurate and highly sensitive genetic diagnosis of ADTKD-MUC1

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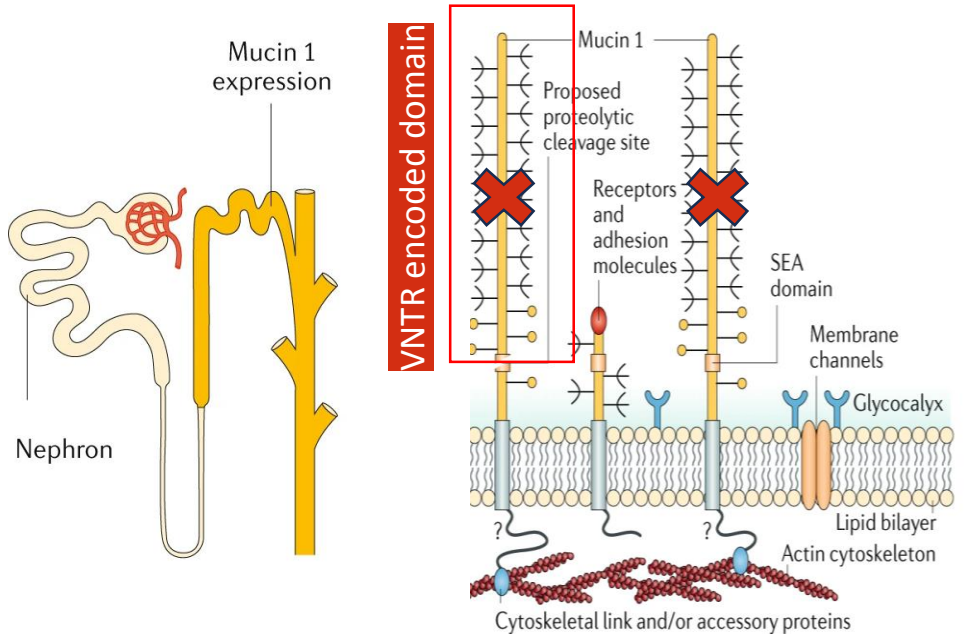
Challenges in ADTKD-MUC1 genetic diagnosis

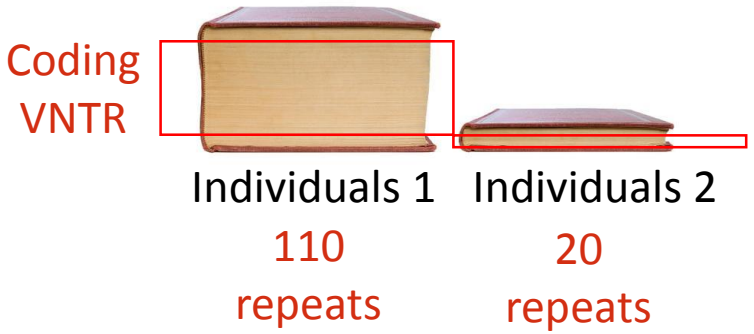
Human genome as library and Chromosomes as bookshelves



Cellular stress And cell death

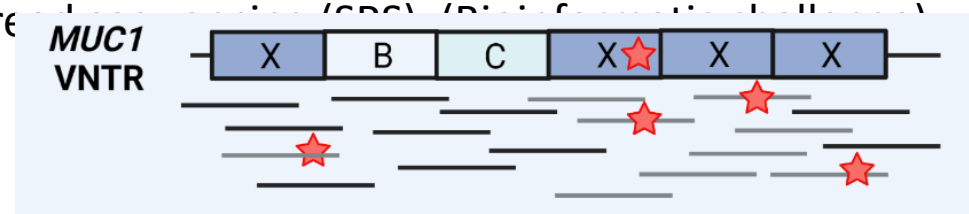
Devuyst, O. et al. *Nat Rev Dis Primer* (2019)

MUC1 gene in different individuals

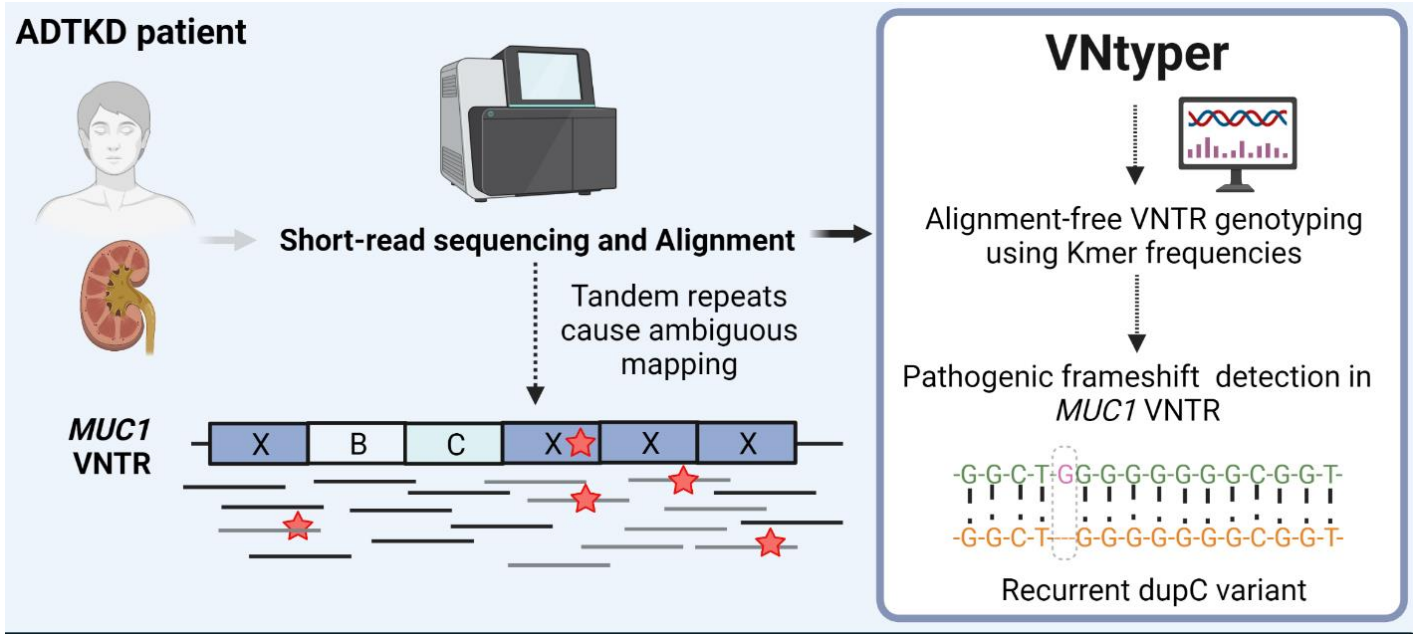


Genetic Diagnosis?

1. SNaPshot minisequencing assay (Know recurrent variation)
2. Long-read sequencing (Pacbio) (Expensive and research-only)
3. Short-re



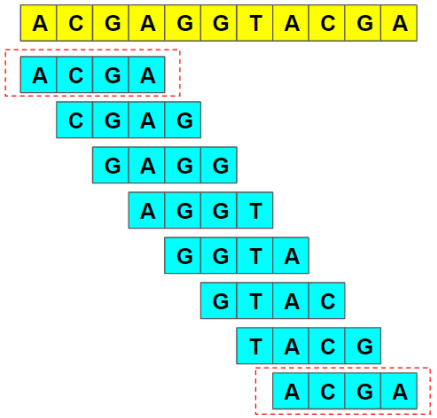
MUC1 gene coding-VNTR genotyping with VNtyper



K-mer frequency?

	Total	Distinct	Unique
ACGA	2	1	0
CGAG	1	1	1
GAGG	1	1	1
AGGT	1	1	1
GGTA	1	1	1
GTAC	1	1	1
TACG	1	1	1

Patient read



VNtyper validation On **targeted sequencing data**

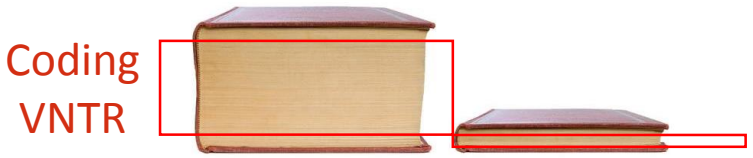
- **ADTKD cohort** N=237 → Re-identified ADTKD patients (n= 96)
- **Hereditary kidney disease cohort** N= ~4000 → **Diagnosed 40 new ADTKD patients**

Can we adapt VNtyper for WES data?

Saei et al. *iScience* (2023)

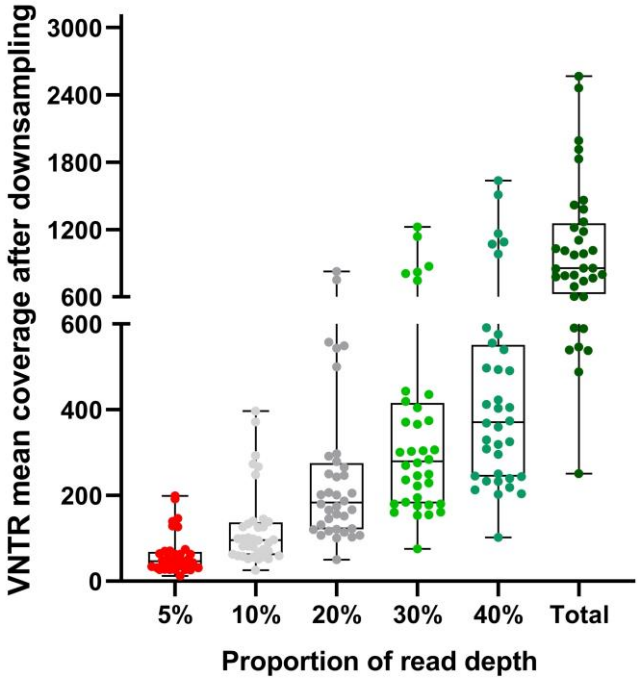
Clinically boosted exome sequencing for ADTKD

Dilution effect and **enrichment issues**



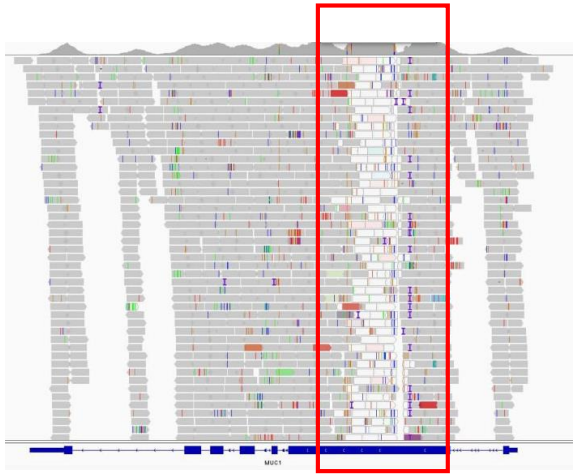
Individuals 1
110
repeats

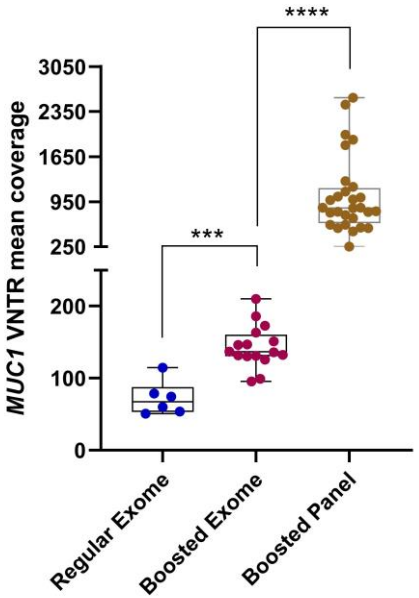
Individuals 2
20
repeats

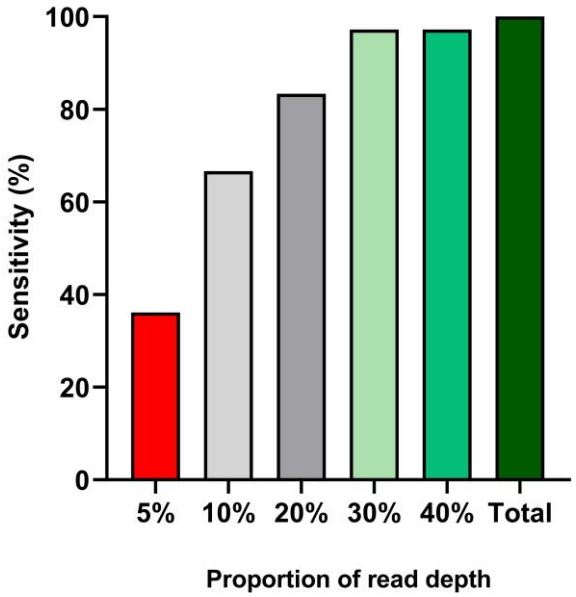


Regular exome VNTR region

Boosted exome VNTR region







We can apply VNtyper on WES data obtained from ADTKD patients only if we boost the enrichment step in the library preparation!

Unpublished

Take home messages

- VNtyper is a powerful and specialized tool developed for genotype *MUC1* gene coding-VNTR in ADTKD.
- This tool utilizes short-read data obtained from targeted and boosted panel sequencing (290 genes responsible for hereditary kidney diseases)
- With applying our tool on ~4000 patients we diagnosed new patients which were overlooked before.
- As VNtyper is very sensitive to sequencing coverage, it should not be applied on regular exome sequencing data without boosting VNTR enrichment.
- We have improved target enrichment step in exome sequencing using Twist Exome Kit with adding spike in probes with 4x VNTR tiling. This increased the VNTR coverage significantly and boosted the sensitivity of the genotyping.
- It is possible to find true positives with regular exome (Twist), but the sensitivity is not 100%.
- VNtyper apply two independent genotyping methods (Kestrel and code-adVNTR) for result comparison.
- Our tool is freely available on my GitHub repository and can be smoothly installed in the HPC cluster.

Laboratory of Hereditary Kidney Diseases

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Thank you for your attention!!

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