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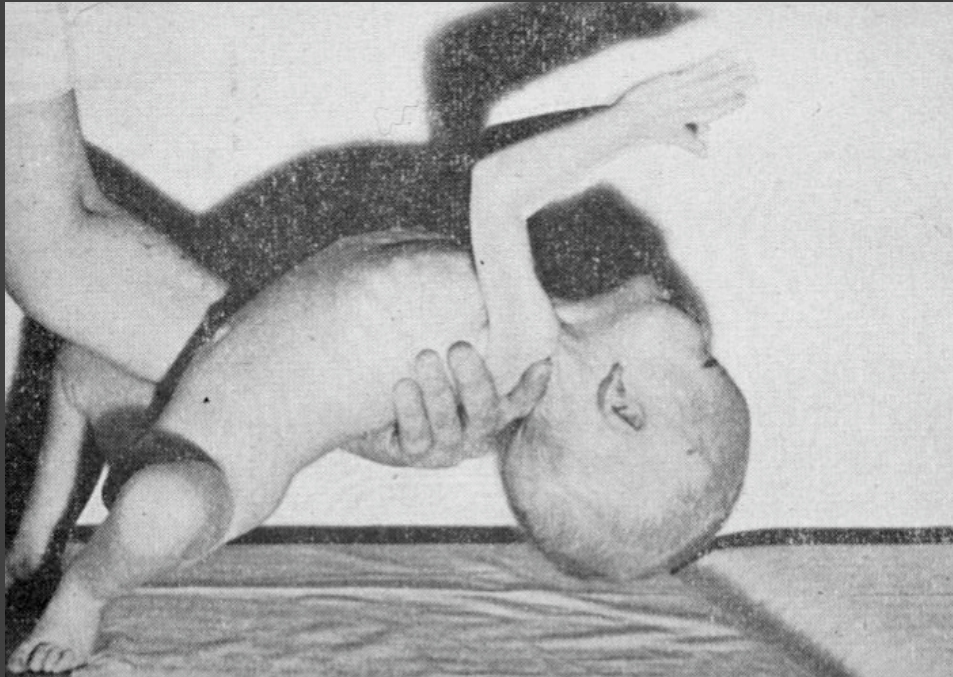
PREPL, a putative oligopeptidase deleted in patients
with hypotonia-cystinuria syndrome (HCS)

John Creemers
Center for Human Genetics
K.U. Leuven



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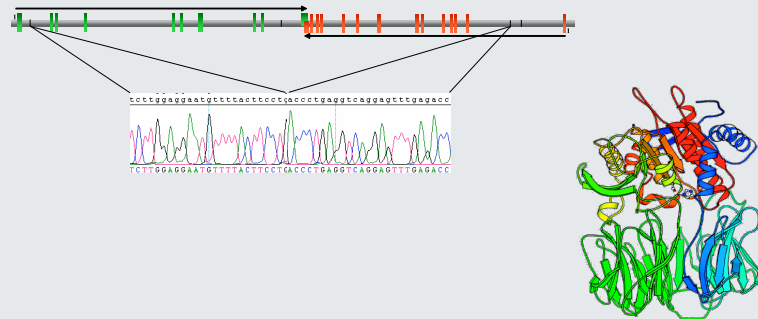
Clara R & Lowenthal A (1966)

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The genetic basis of HCS

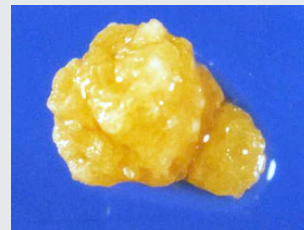
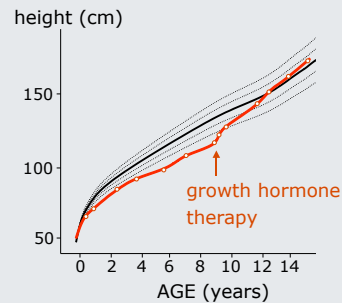
Functional characterization of PREPL



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The syndrome is characterized by hypotonia, cystinuria and growth delay

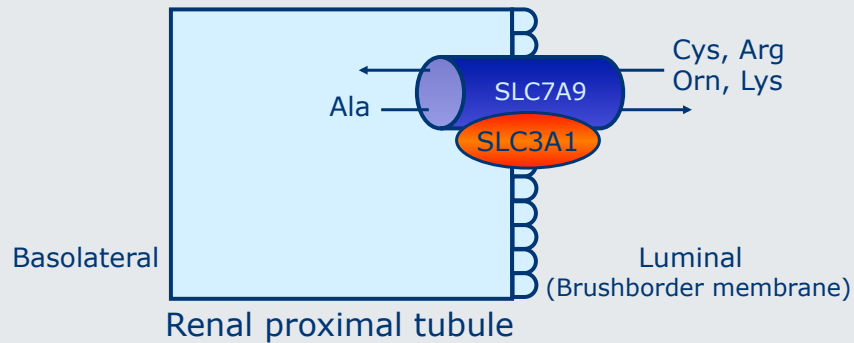


cystine kidney stone

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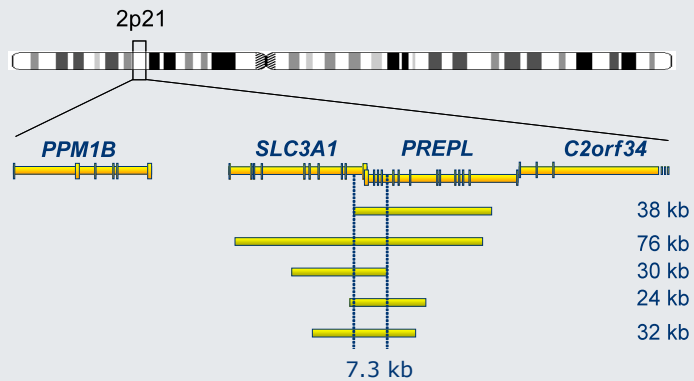
Mutations in *SLC3A1* cause cystinuria type I



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PREPL and *SLC3A1* are deleted
in HCS patients



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HCS has been found in 4 continents



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How prevalent is PREPL deficiency?



Microdeletions

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How prevalent is PREPL deficiency?



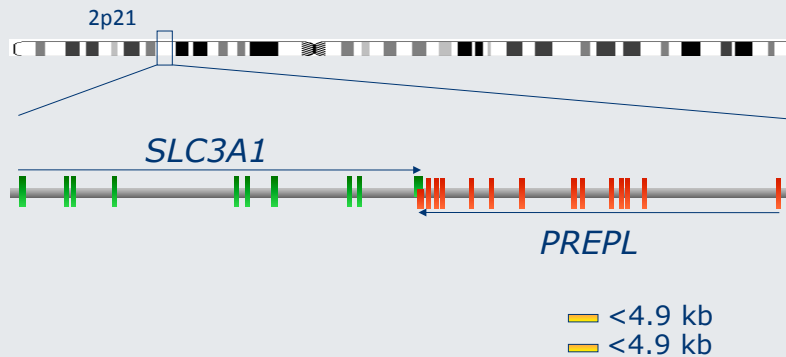
Microdeletions

Point mutations and
small microdeletions

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Can patients with hypotonia-syndrome without cystinuria be found?

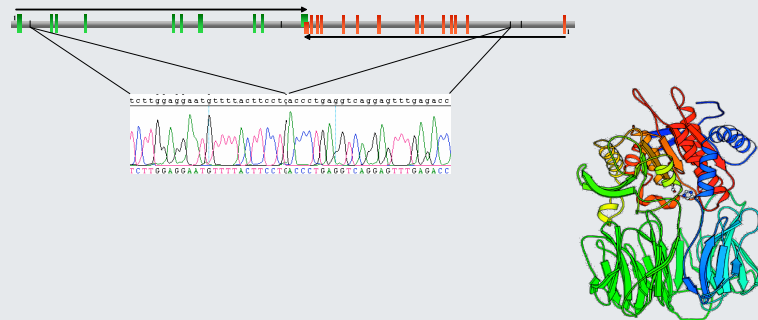


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The genetic basis of HCS

Functional characterization of PREPL



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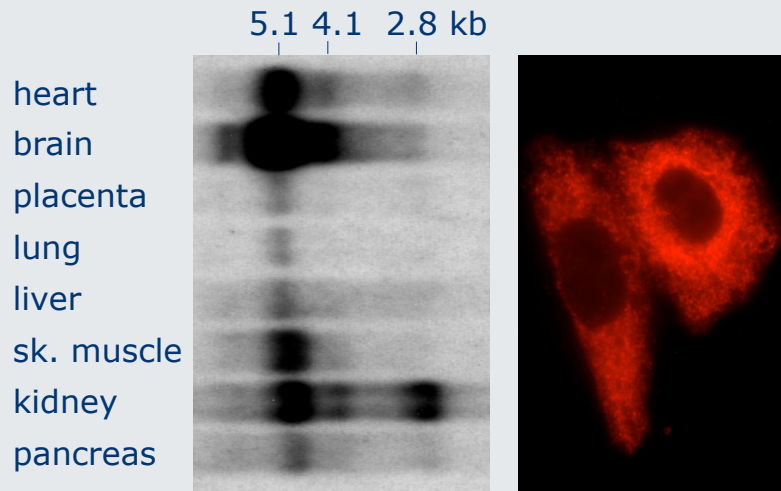
PREPL is a brain-enriched cytosolic protein



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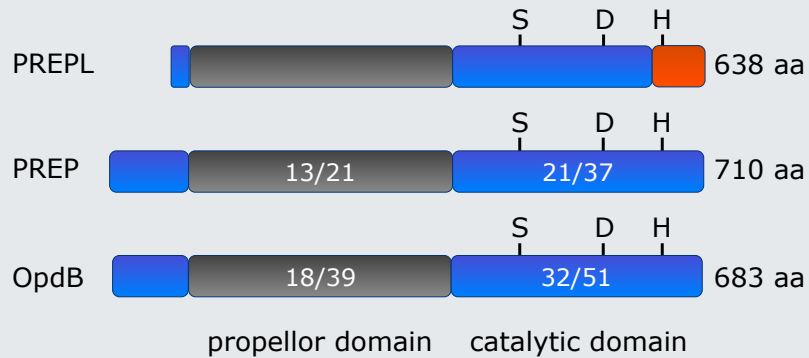
PREPL is a brain-enriched cytosolic protein



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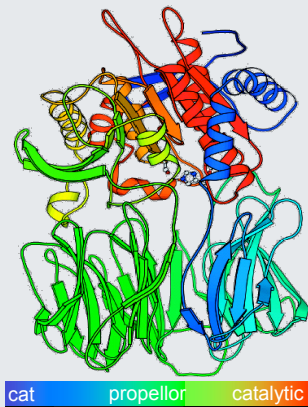
PREPL is a putative oligopeptidase



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PREPL is structurally different from PREP

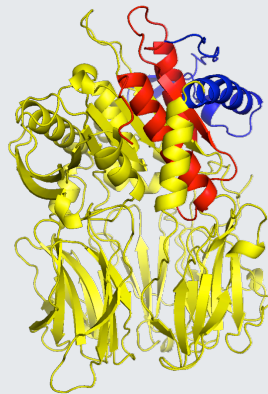


Fulop et al. Cell 1998

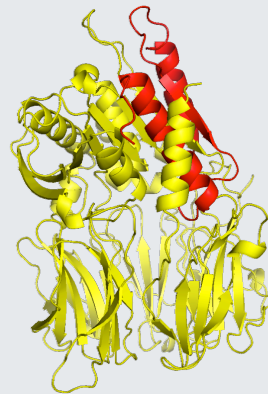
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PREPL is structurally different from PREP



PREP



PREPL

Fulop et al. Cell 1998

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PREPL does not cleave PREP
nor OpdB substrates

	*	*
PREPL	EE	EEWGNPS
OpdB	GE	FEWGNPQ
PREP	AW	TTDYGCSD

* *S1 binding pocket*

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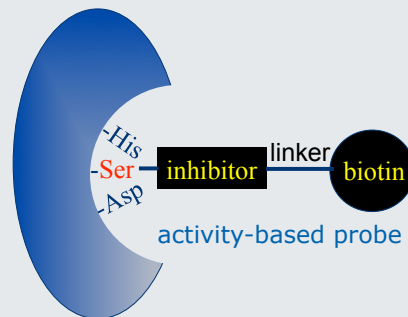
Activity-based probes can be used
to identify active enzymes



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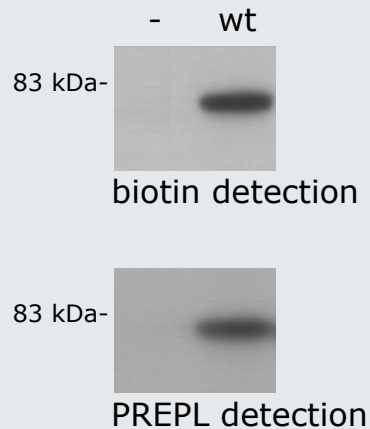
Activity-based probes can be used
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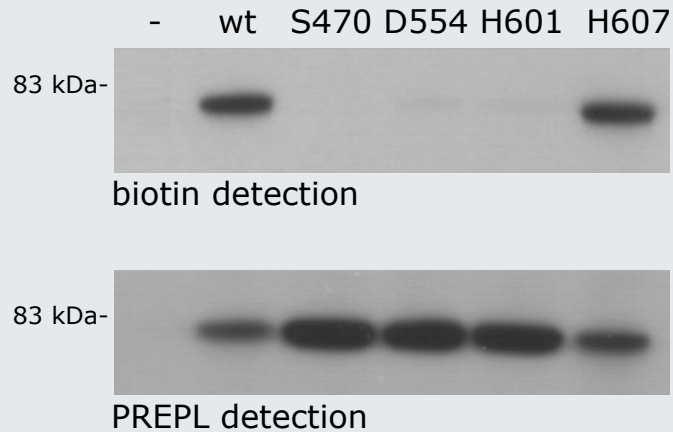
PREPL has an active catalytic triad



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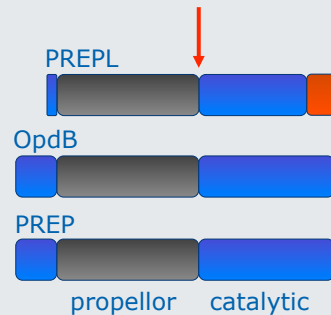
PREPL has an active catalytic triad



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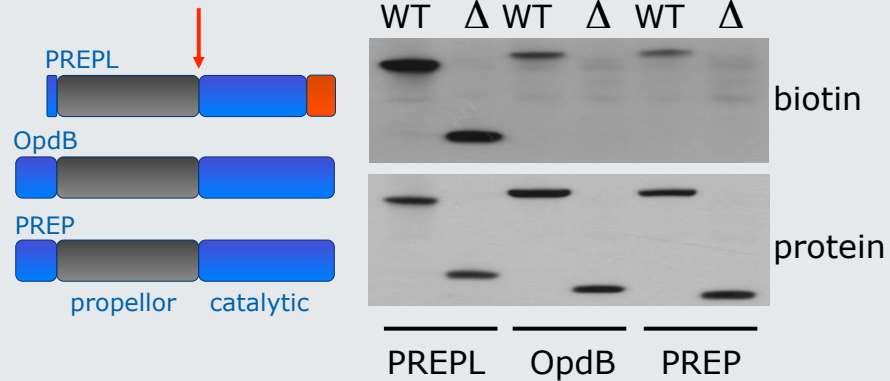
PREPL has no N-terminal catalytic subdomain



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PREPL has no N-terminal catalytic subdomain



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Conclusions

- PREPL deficiency causes hypotonia and growth retardation

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Conclusions

- PREPL deficiency causes hypotonia and growth retardation
- PREPL is a catalytically active serine hydrolase

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Conclusions

- PREPL deficiency causes hypotonia and growth retardation
- PREPL is a catalytically active serine hydrolase
- No physiological substrates of PREPL have been identified

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Acknowledgements

K.U. Leuven

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