WEBINAR

19/09/23

Welcome to

ERKNet/ESPN Educational Webinars on Pediatric Nephrology & Rare Kidney Diseases

Galloway Mowat syndrome

Speaker: Guillaume Dorval (Paris, France)

Moderator: Elena Levtchenko (Amsterdam, NL)

ERKNet The European Rare Kidney Disease Reference Network

european society for paediatric nephrology

ERKNet
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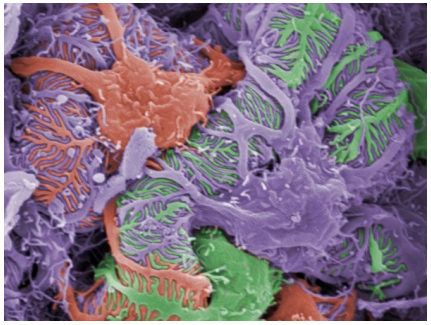
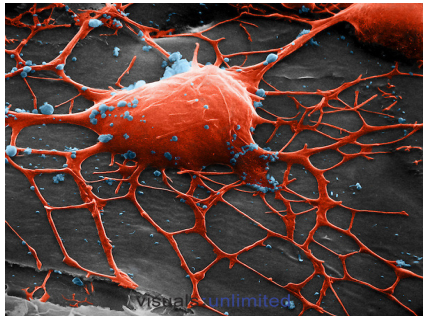
Galloway Mowat Syndrome





Guillaume DORVAL

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Imagine Institute
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Université Paris Descartes
Paris, France

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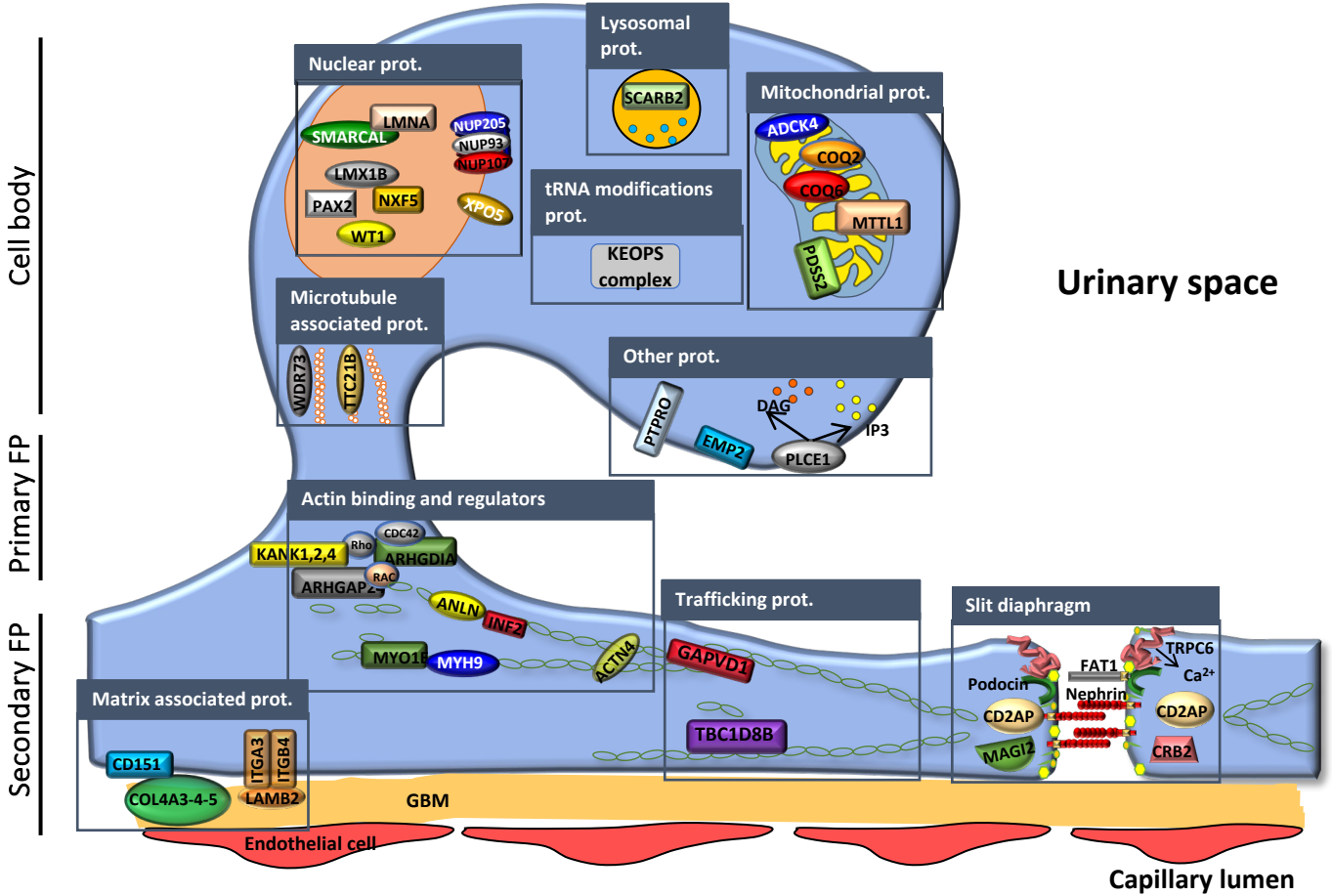
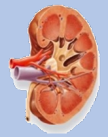
Genetic basis of hereditary nephrotic syndrome

Genetic studies on familial cases -> causal genes crucial for podocyte function



Isolated or syndromic SRNS

Isolated SRNS



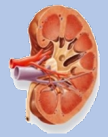
Syndromic SRNS

Affected organs :

Adapted from Sarah Goncalves

Isolated or syndromic SRNS

Isolated SRNS



- *NPHS2* } Kidney

Syndromic SRNS

Affected organs :

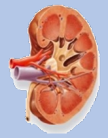
Tissue-specific gene expression ?

- *LAMB2* ⟹ Kidney + Brain + Eye
  (Pierson syndrome)
- *WT1* ⟹ kidney + urogenital tract
  (Denys-Drash/Frasier syndrome)

Adapted from Sarah Goncalves

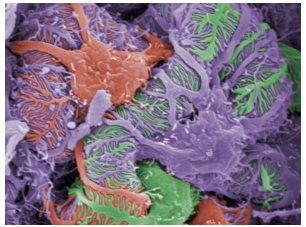
Isolated or syndromic SRNS

Isolated SRNS



Syndromic SRNS

Affected organs :



Tissue-specific gene expression ?

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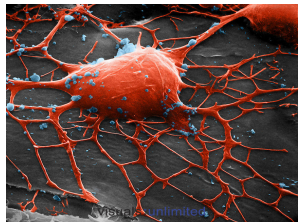


Signaling pathways and tissue homologies ?

- *ACTN4*
- *MYO1E*
- *TRPC6*
- *ADCK4*

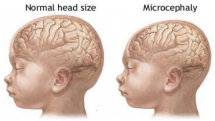
} Ubiquitous expression, only one affected organ

- *WDR73*
- *NFX5, NUP205*
- *INF2*
- *KEOPS*

} Ubiquitous expression, only few affected organs

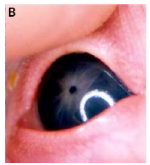
Adapted from Sarah Goncalves

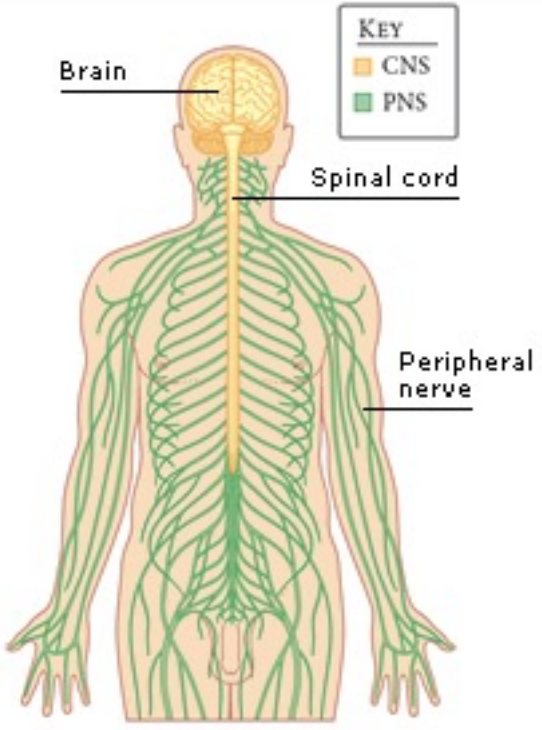
SRNS and neurological involvement



Central nervous system anomalies

- **Galloway-Mowatt Syndrome:** ***WDR73, OSGEP, TP53RK, TPRKB, LAGE3, NUP133, NUP107, WDR4***
- Pierson Syndrome : *LAMB2*
- Mitochondriopathies
- SRNS and epilepsy (*TRIM8*)





Peripheral neuropathy +/- CNS involvement

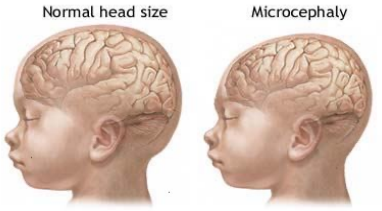
- CMT-FSGS : *INF2*

Galloway-Mowat Syndrome (GAMOS)

- 1rst description in 1968 by Galloway and Mowat (100 cases)
- Very rare autosomal recessive disorder
- **Steroid-resistant nephrotic syndrome (SRNS)**
- **Microcephaly**
- **Central nervous system anomalies**
- Clinically highly heterogeneous

- **Severe prognosis : death before the age of 6 years**

Galloway-Mowat Syndrome (GAMOS)



- 1rst description in 1968 by Galloway and Mowat (100 cases)
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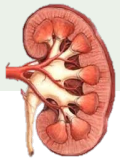
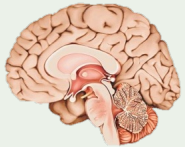
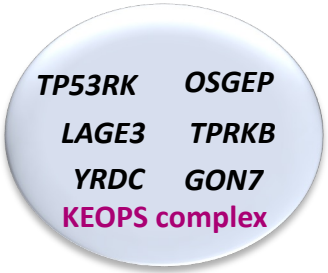
Renal disease	Microcephaly	Neurological manifestations/brain anomalies
Proteinuria to SRNS (ESKD)	Primary (at birth)	Developmental delay, hypotonia
Variableage of onset (congenital or later in childhood)	Secondary (post-natal)	Cortical and/or cerebellar atrophy
DMS or FSGS 		Gyration defects (lissencephaly to polymicrogyria)
		Myelination defects

- **Severe prognosis : death before the age of 6 years**

GAMOS genetic overview



32 mutations (17 *OSGEP*)
44 families

1 mutation/1family

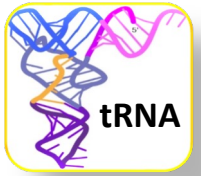
13 mutations/**22 families**

4 mutations/7 families

1 mutation/1 family

GAMOS genetic overview

RNA metabolism



t⁶A modification

TP53RK ***OSGEP***
LAGE3 ***TPRKB***
YRDC ***GON7***
KEOPS complex

32 mutations (17 *OSGEP*)
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m⁷G modification

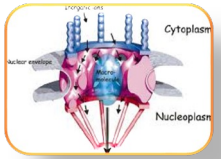
WDR4

1 mutation/1family

WDR73

13 mutations/**22 families**

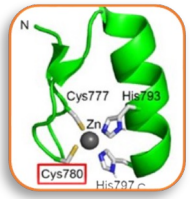
Nucleocytoplasmic transport



NUP107 / NUP133

4 mutations/7 families

Transcriptional regulation

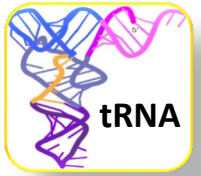


PRDM15

1 mutation/1 family

GAMOS genetic overview

RNA metabolism



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WDR73

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LOF hom+

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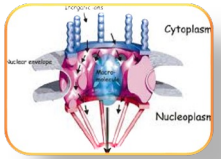

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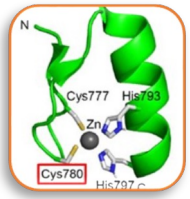


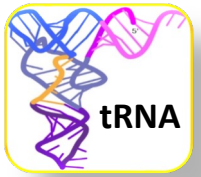
PRDM15

1 mutation/1 family

missense hom

GAMOS genetic overview

RNA metabolism



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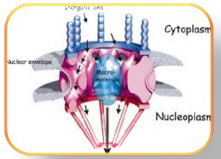


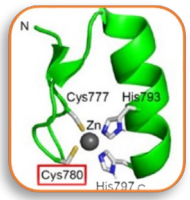
NUP107 / NUP133

4 mutations/7 families

LOF hom+

Isolated SRNS
(*NUP107/NUP133*)
Premature ovarian failure
(*NUP107*)

Transcriptional regulation



PRDM15

1 mutation/1 family

missense hom

Isolated SNCR

Other diseases

None

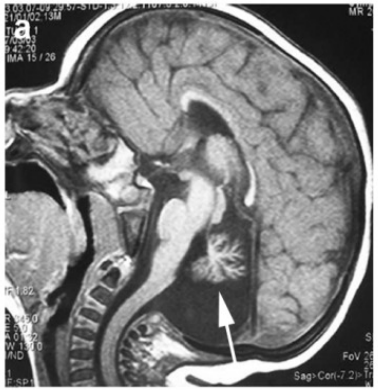
Microcephalic primordial dwarfism

None

Genetic basis of GAMOS: mutations in *WDR73*

Particular subset of GAMOS-affected children

- **Secondary microcephaly**
- No brain gyration defects
- **Severe cerebellar atrophy**



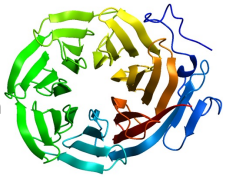
- Visual impairment/optic atrophy
- Seizures

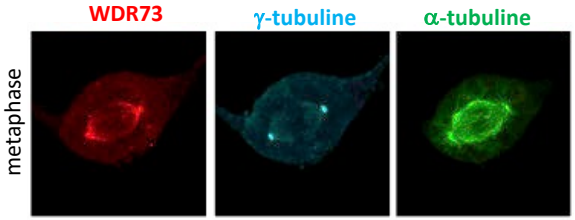
- Late renal disease
- **Incomplete penetrance of the renal disease**

- Homozygous mutations mostly truncating mutations

Colin et al., AJHG, 2014; Ben-Omran et al., J Med Genet, 2015; Vodopiutz et al., Hum Mutation, 2015 ; Jinks et al., Brain, 2015; Rosti et al., Am J Med Genet, 2016 ; Jiang et al., Clin Chim Acta, 2017; El Younsi, Eur J Med Genet, 2019

WDR73 – Integrator complex – UsnRNA/snoRNA - Cell cycle

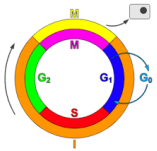




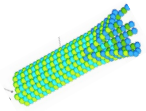
WDR73 localised to spinle poles /MT asters

Role of WDR73

(**Colin** et al., 2014
Jinks et al., 2015)



Cell cycle

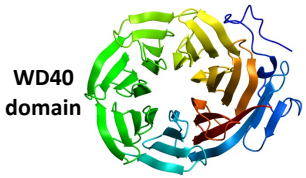


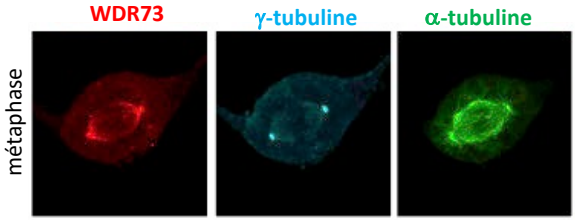
Microtubule dynamics

- Zebrafish model with MO (**Ben-Omran** et al, 2015)
  - Significant brain growth and morphology defects
  - Smaller/poorly differentiated midbrain & cerebellum

Crucial role of WDR73 in neural progenitor survival

WDR73 – Integrator complex – UsnRNA/snoRNA - Cell cycle





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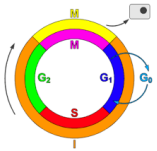
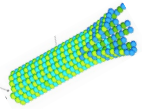
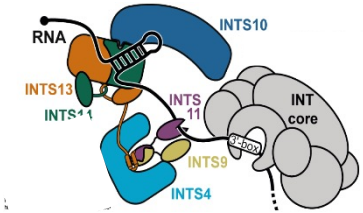


Cell cycle



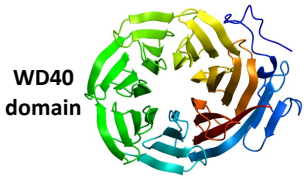
Microtubule dynamics

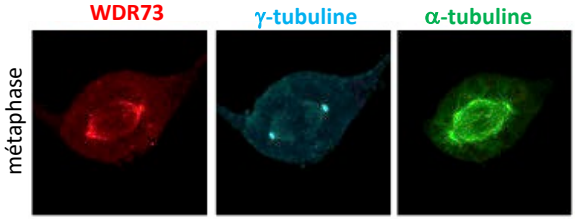
- Integrator complex (Tilley et al., Sci Rep 2021)
  - Interaction with **Integrator complex (INTS9/INTS11)**
  - RNA (UsnRNA) maturation/ Transcription regulation



  - Mutations *INTS1/INTS8* : severe ID / microcephaly/cerebellar hypoplasia

WDR73 – Integrator complex – UsnRNA/snoRNA - Cell cycle





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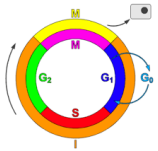
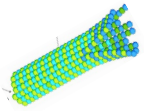


Cell cycle

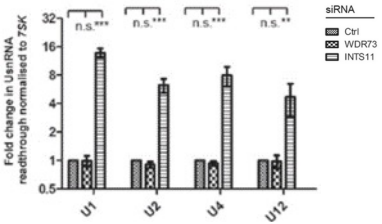


Microtubule dynamics

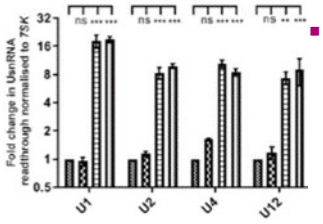
- Integrator complex (Tilley et al., Sci Rep 2021)
  - Interaction with **Integrator complex (INTS9/INTS11)**
  - RNA (UsnRNA) maturation/ Transcription regulation
  - **Implication of WDR73 in 2 integrator-regulated cellular pathways**
    - Processing of UsnRNA (and snoRNA)
    - Response of early response genes to EGF stimulation

Involvement of WDR73 in:

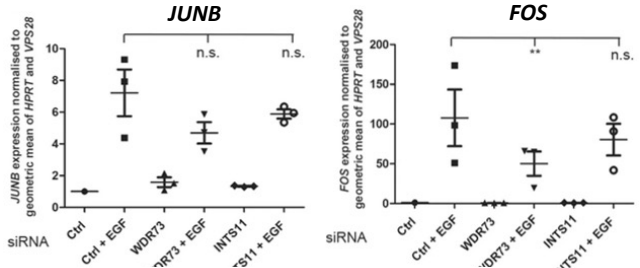
Human immortalized podocytes



Neural progenitor cells



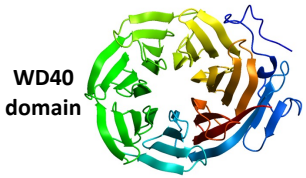
- **Processing of UsnRNA /snoRNA**

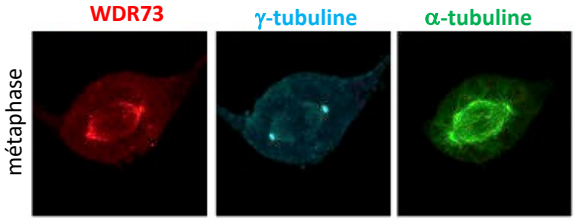


- **Response to EGF stimulation**

Human immortalized podocytes

WDR73 – Integrator complex – UsnRNA/snoRNA - Cell cycle





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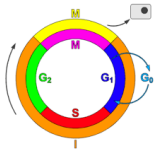
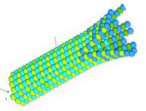


Cell cycle

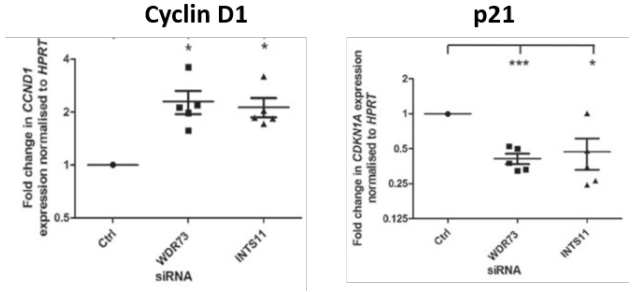


Microtubule dynamics

- Integrator complex (Tilley et al., Sci Rep 2021)

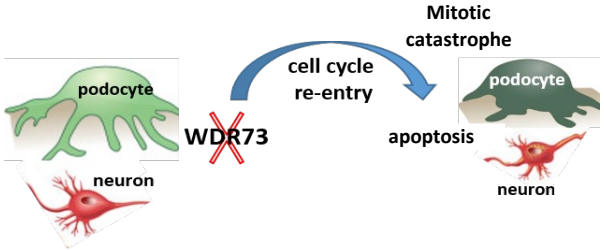
Involvement of WDR73 in:

- Dysregulation of cell cycle genes in *WDR73* KO podocytes, especially those encoding proteins promoting G1/S phase transition.
- no significant changes in the proportion of cells in each cell-cycle phases



Human immortalized podocytes

- **Cell cycle progression** (G1/S)



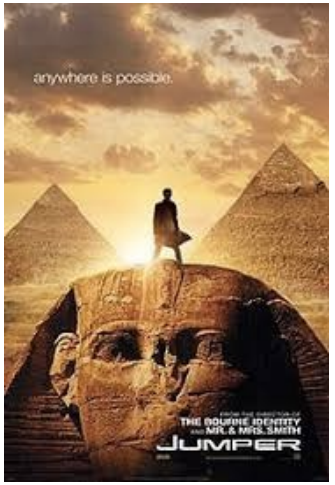
Role of WDR73 in maintaining neuron and podocyte differentiation state by inhibiting their re-entry into the cell cycle?

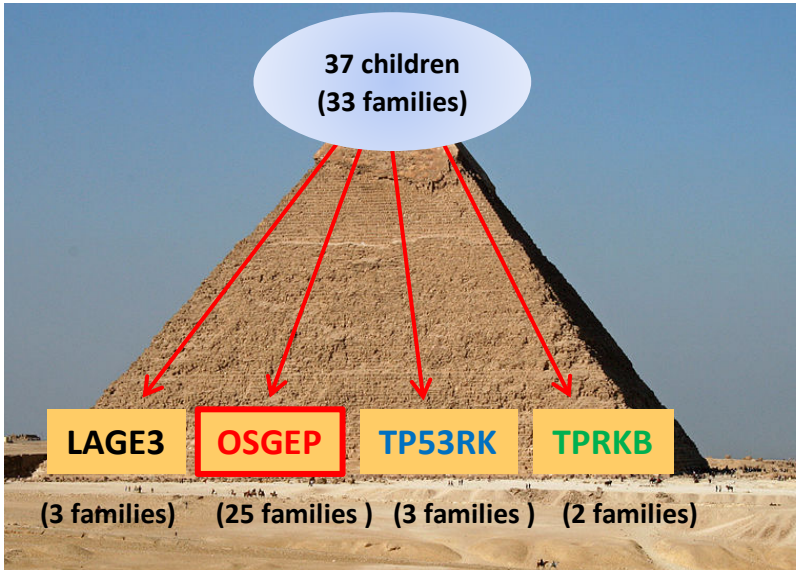
Genetic basis of GAMOS: KEOPS complex-genes

Mutations in KEOPS-complex genes cause nephrotic syndrome with primary microcephaly

Daniela A Braun[1,76], Jia Rao[1,76], Geraldine Mollet[2,3,76], David Schapiro[1], Marie-Claire Daugeron[4], Weizhen Tan[1], Olivier Gribouval[2,3], Olivia Boyer[2,3,5], Patrick Revy[3,6], Tilman Jobst-Schwan[1], Johanna Magdalena Schmidt[1], Jennifer A Lawson[1], Denny Schanze[7], Shazia Ashraf[1], Jeremy F P Ullmann[8,9], Charlotte A Hoogstraten[1], Nathalie Boddaert[3,10,11], Bruno Collinet[4,12,13], Gaëlle Martin[2,3], Dominique Liger[4], Svjetlana Lovric[1], Monica Furlano[2,3,14], I Chiara Guerrera[15], Oraly Sanchez-Ferras[16], Jennifer F Hu[17], Anne-Claire Boschat[18], Sylvia Sanquer[19,20], Björn Menten[21], Sarah Vergult[21], Nina De Rocker[21], Merlin Airik[1], Tobias Hermle[1], Herman van Tilbeurgh[4], Martin Zenker[7], Corinne Antignac[2,3,75] & Friedhelm Hildebrandt[1]

NATURE GENETICS VOLUME 49 | NUMBER 10 | OCTOBER 2017





22 mutations:
-5 truncating
-17 missense

- A truncating mutation is always associated to a missense mutation

(coll. Pr Hildebrandt, Boston, USA)

Clinical features of KEOPS-related GAMOS patients

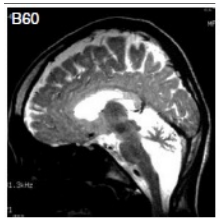
- **Primary microcephaly**
- Developmental delay
- Hypotonia, seizures

- **Cortical and cerebellar atrophy**
- **Gyration** (lissencephaly/pachygyria) and **myelination defects**

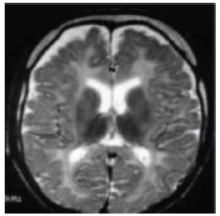
- Early-onset proteinuria at median age of 3 months (birth to 13 years)

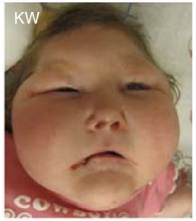
- **ESKD at median age of 11 months** (1 month-13 years)

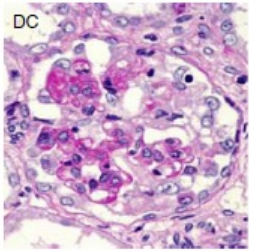
- **Histology**: Lesions of FSGS/ DMS and FPE



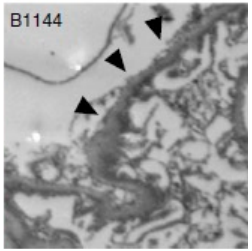
Polymicrogyria and diffuse cerebellar atrophy


Reduced myelination of the white matter





FSGS



FPE

Very severe phenotype

Death at a median age of 6 months (6 weeks to 25 years)

Braun et al., *Nat Genet*, 2017

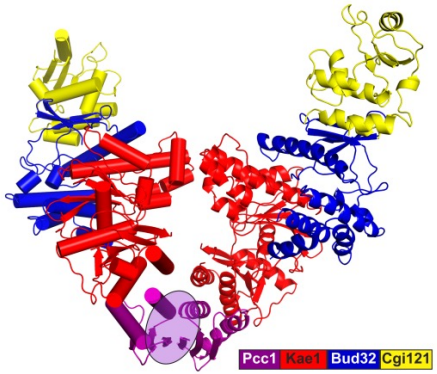
KEOPS: a universally conserved complex

Kinase **E**ndopeptidase and **O**ther **P**roteins of **S**mall size

KEOPS: a universally conserved complex

Kinase Endopeptidase and Other Proteins of Small size

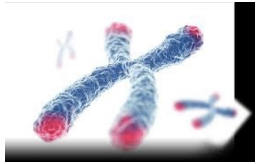
TP53RK OSGEP LAGE3- TPRKB-*(GON7 in yeast)*



KEOPS: a universally conserved complex

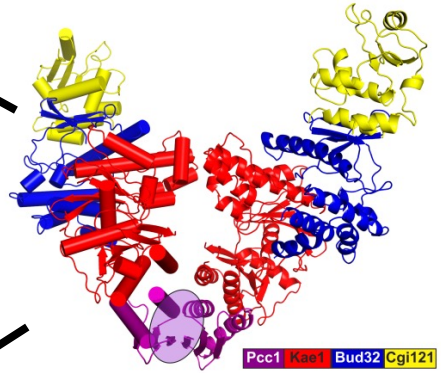
Kinase **E**ndopeptidase and **O**ther **P**roteins of **S**mall size

TP53RK **OSGEP** **LAGE3- TPRKB-*(GON7 in yeast)***



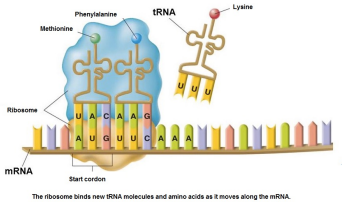
Telomere maintenance

(Downey et al., Cell, 2006)



Transcription regulation

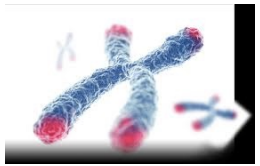
(Kisseleva-Romanova et al., EMBO J, 2006)



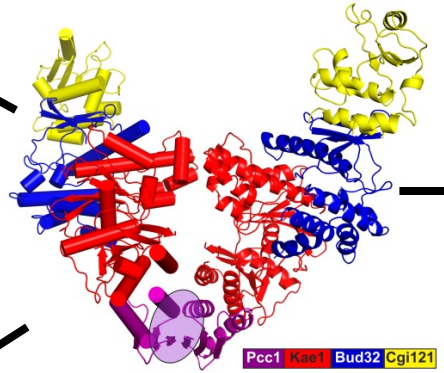
KEOPS: a universally conserved complex

Kinase **E**ndopeptidase and **O**ther **P**roteins of **S**mall size

TP53RK **OSGEP** **LAGE3- TPRKB-*(GON7 in yeast)***

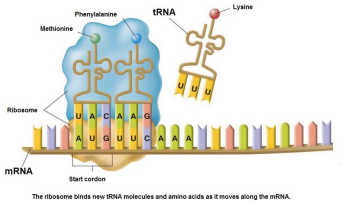


Telomere maintenance
(Downey et al., Cell, 2006)



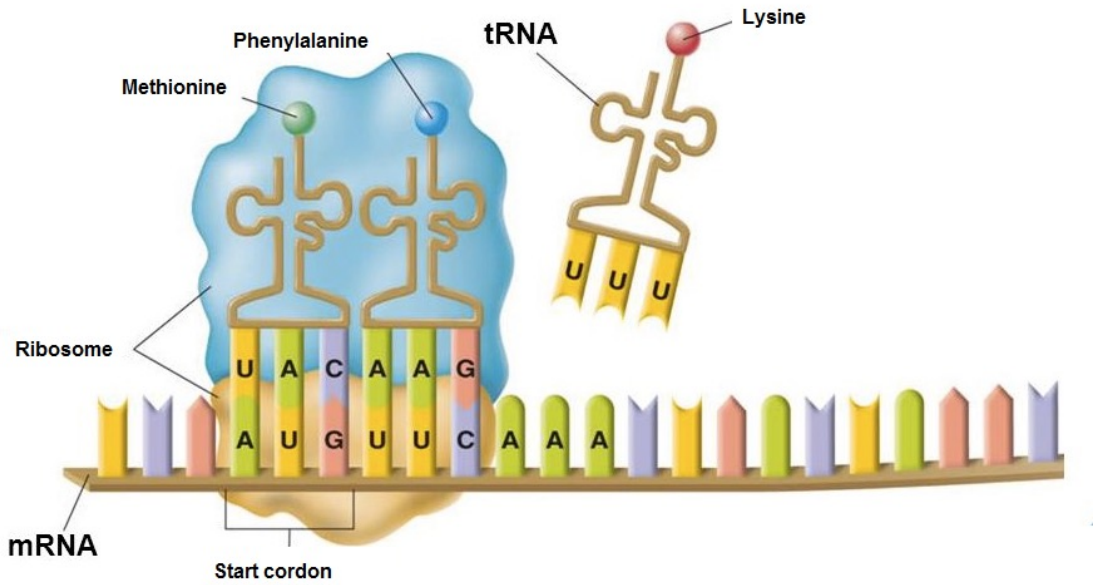
Biogenesis of t^6A modification on tRNA
(Srinivasan et al, EMBO J, 2011)

Transcription regulation
(Kisseleva-Romanova et al., EMBO J, 2006)



KEOPS is involved in multiple cellular processes essential to sustain life in yeast

Hypomodified tRNAs and human disease



The ribosome binds new tRNA molecules and amino acids as it moves along the mRNA.

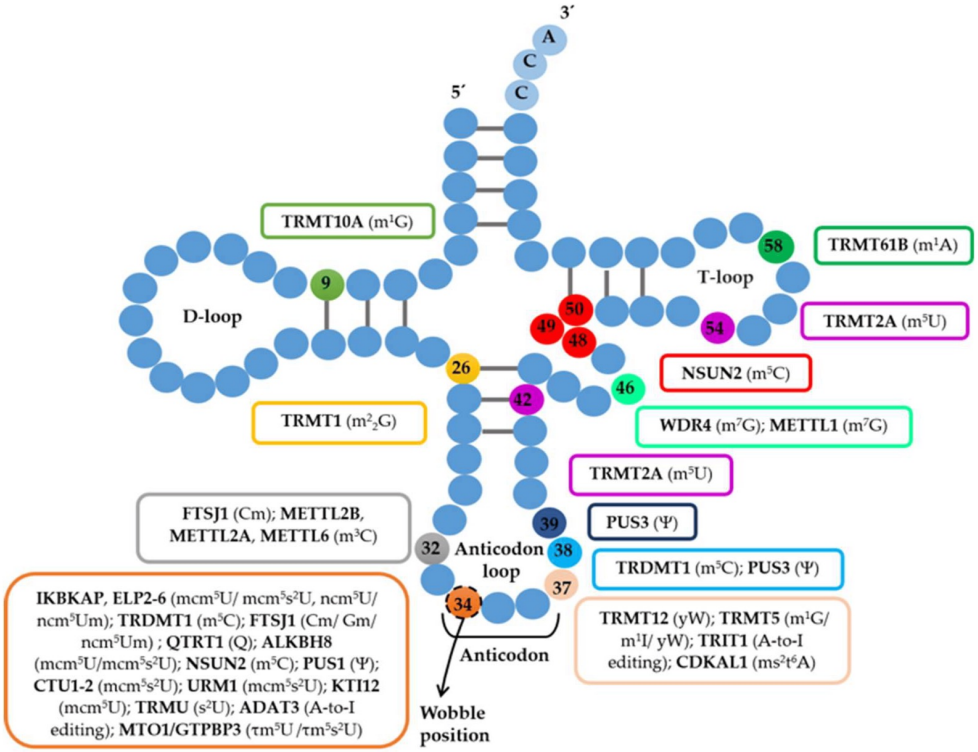
RNA codon table

1st position	2nd position U	2nd position C	2nd position A	2nd position G	3rd position
U	Phe	Ser	Tyr	Cys	U
	Phe	Ser	Tyr	Cys	C
	Leu	Ser	stop	stop	A
	Leu	Ser	stop	Trp	G
C	Leu	Pro	His	Arg	U
	Leu	Pro	His	Arg	C
	Leu	Pro	Gln	Arg	A
	Leu	Pro	Gln	Arg	G
A	Ile	Thr	Asn	Ser	U
	Ile	Thr	Asn	Ser	C
	Ile	Thr	Lys	Arg	A
	Met	Thr	Lys	Arg	G
G	Val	Ala	Asp	Gly	U
	Val	Ala	Asp	Gly	C
	Val	Ala	Glu	Gly	A
	Val	Ala	Glu	Gly	G

Amino Acids

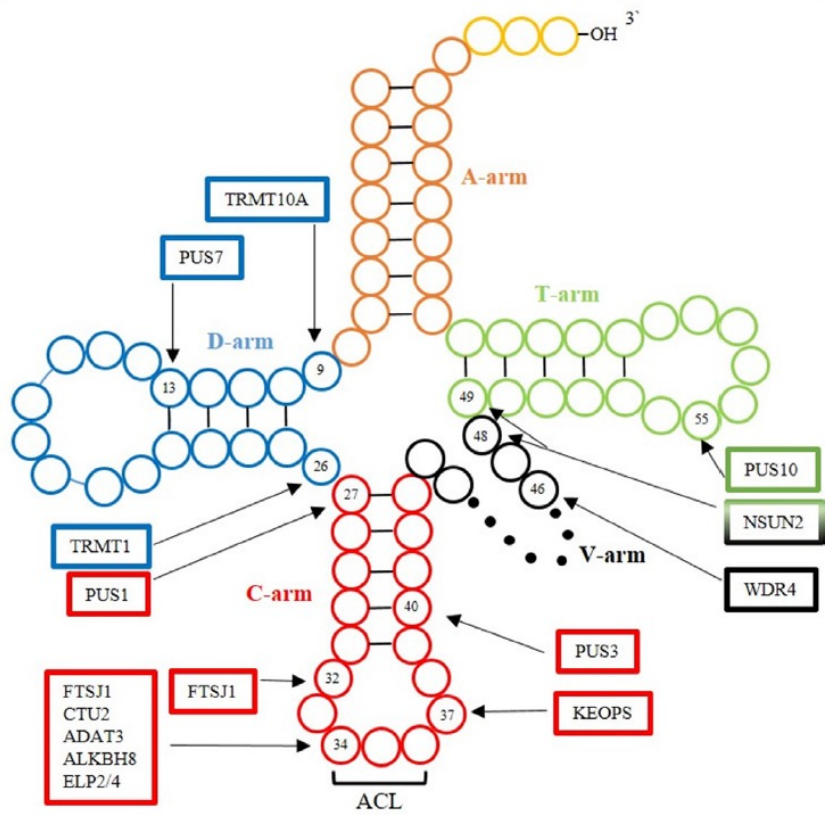
Ala: Alanine, Arg: Arginine, Asn: Asparagine, Asp: Aspartic acid, Cys: Cysteine, Gln: Glutamine, Glu: Glutamic acid, Gly: Glycine, His: Histidine, Ile: Isoleucine, Leu: Leucine, Lys: Lysine, Met: Methionine, Phe: Phenylalanine, Pro: Proline, Ser: Serine, Thr: Threonine, Trp: Tryptophane, Tyr: Tyrosine, Val: Valine

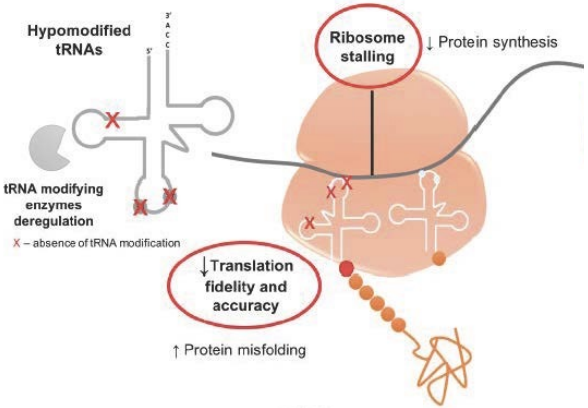
Hypomodified tRNAs and human disease

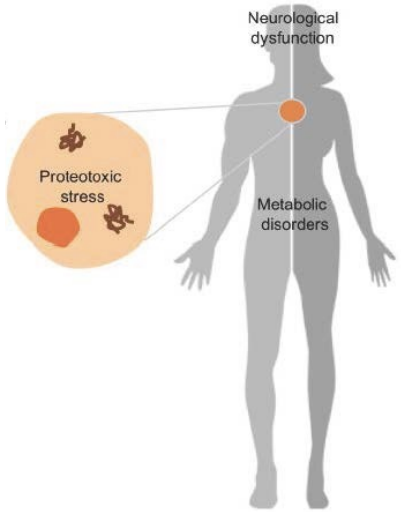


Pereira *et al. Int. J. Mol. Sci.* **2018**

Hypomodified tRNAs and human disease



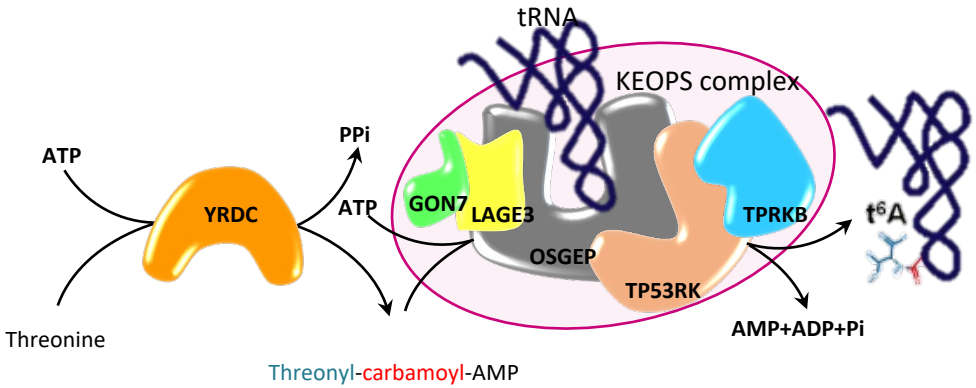




Pereira *et al. Int. J. Mol. Sci.* **2018**

t^6A biosynthesis pathway

t^6A = N6-threonyl carbamoyl adenosine modification
= one of the few universally conserved tRNA modification



tRNA-$t^6A^{(ANN)}$
(including the Met-initiator tRNA)

= tRNA that read start-codons
⇒ Translation initiation

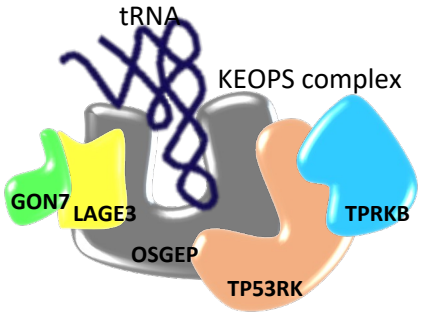
Efficiency and fidelity of translation

Protein biosynthesis

KEOPS role in humans was unkown

Functional characterization of KEOPS (1)

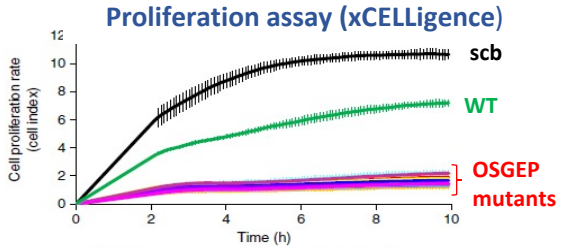
Knockdown in human podocyte cell lines (OSGEP/TP53RK/TPRKB)

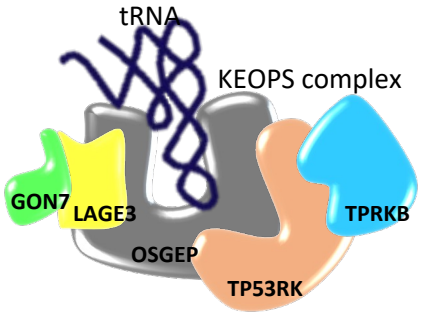


Functional characterization of KEOPS (1)

Knockdown in human podocyte cell lines (OSGEP/TP53RK/TPRKB)

- ↘ proliferation and cell migration
- ↘ cell survival and ↗ apoptosis
- Defects rescued only by wild-type proteins



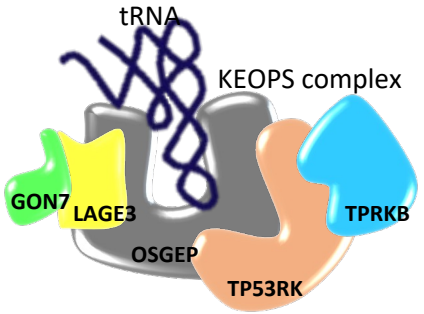


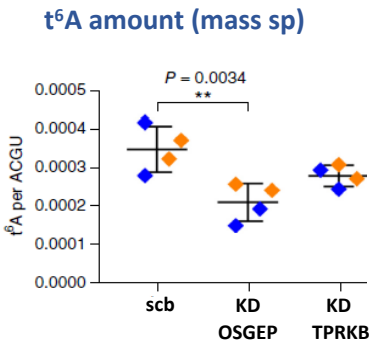
Functional characterization of KEOPS (1)

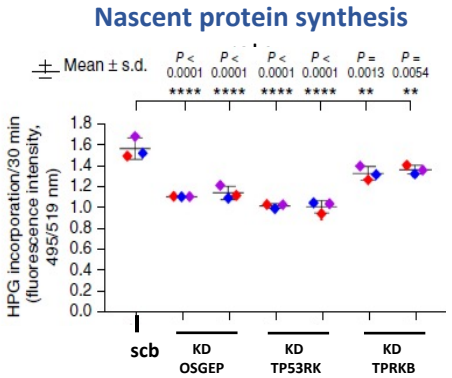
Knockdown in human podocyte cell lines (OSGEP/TP53RK/TPRKB)

- Decrease of t^6A levels

- Decrease in *de novo* protein synthesis
  (reflecting a defect in translation)

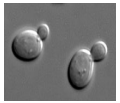




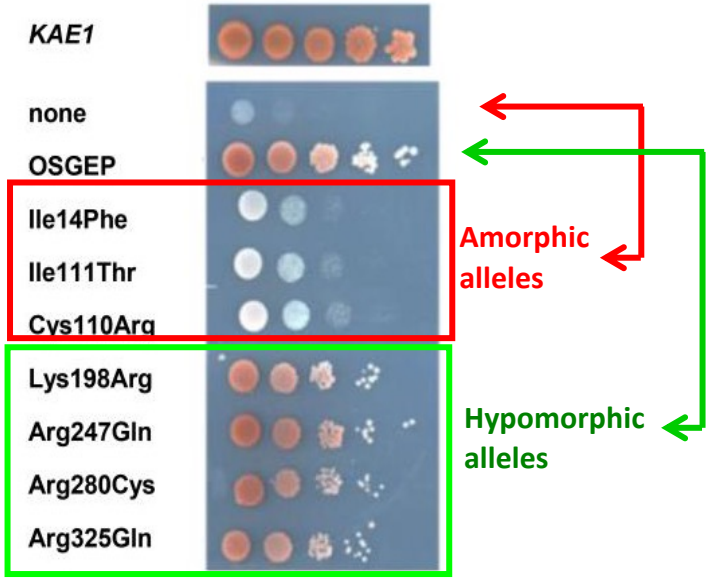


Functional characterization of KEOPS (2)

Yeast growth complementation studies

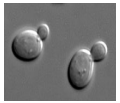


ΔKae1 yeast

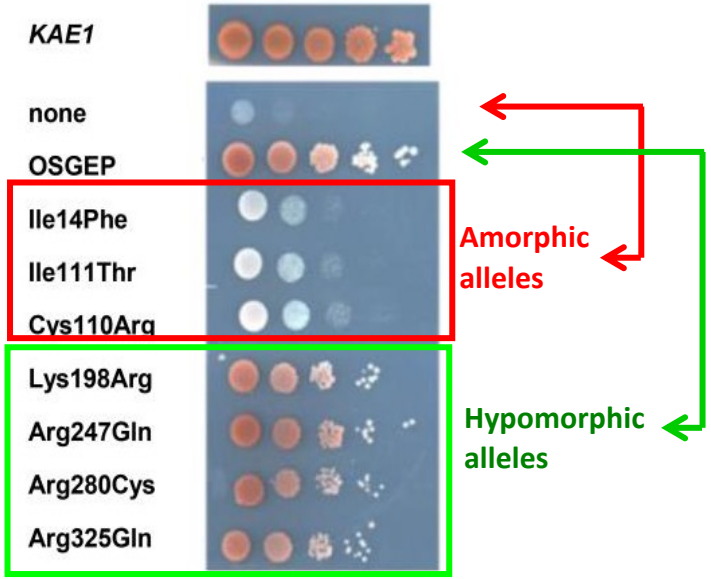


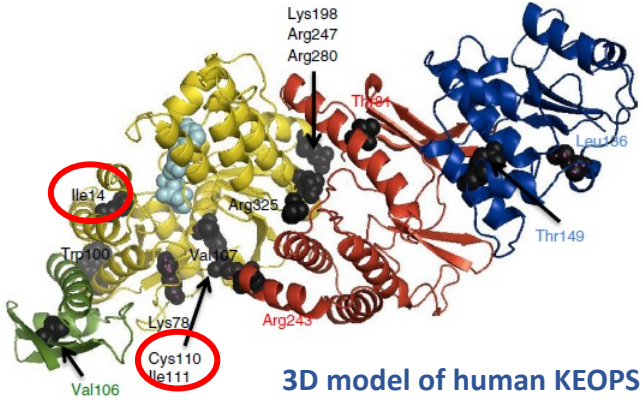
Functional characterization of KEOPS (2)

Yeast growth complementation studies



ΔKae1 yeast



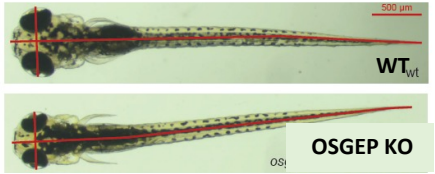


3D model of human KEOPS

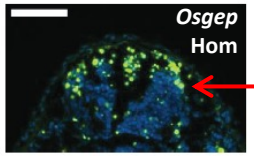
KEOPS & t^{6}A : animal models (1)

Zebrafish

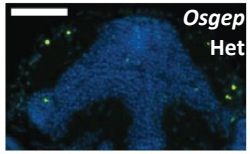
- **Microcephaly**



- **TUNEL staining (transverse brain section)**

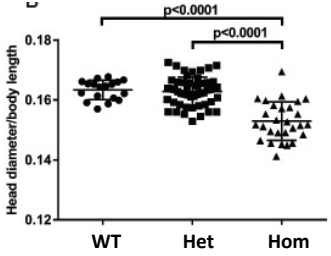


↗ apoptotic cells in the cortex



3 dpf

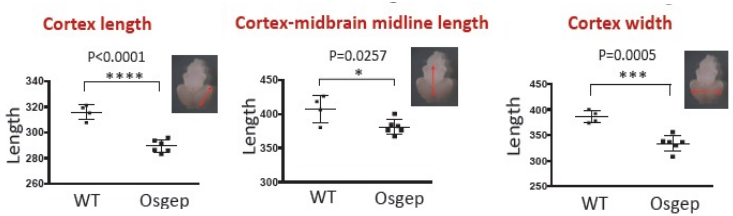
- **Head diameter/body length**



- ***Osgep* KO: embryonic lethality**
- **Microcephaly in KO models, not in KI**
- **No renal phenotype**

Mouse

E18.5

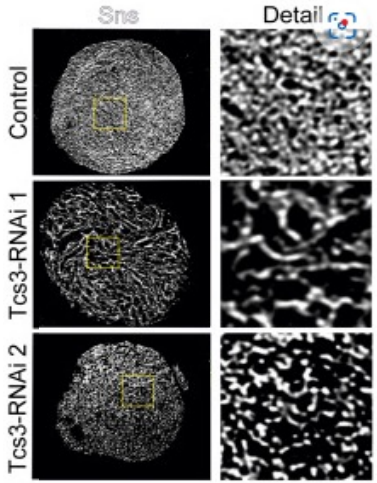


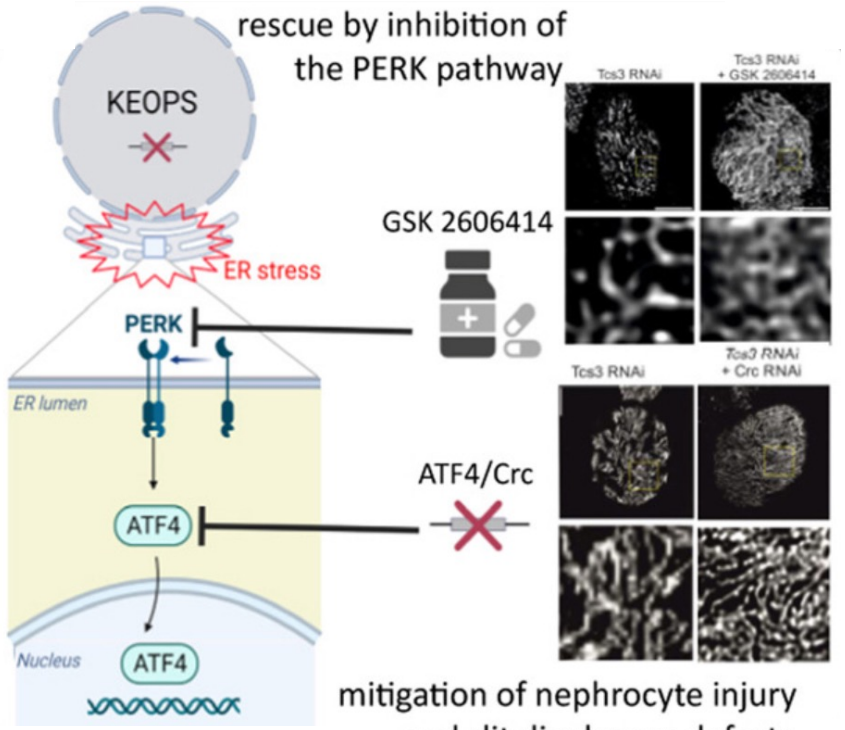
- Acute CRISPR KO *Lage3*/*Osgep*/*Tprkb* **microcephaly** @ E18,5 – No renal phenotype (**Braun** et al, 2017)
- Constitutive CRISPR KO :
  - *Gon7* KO : no renal/brain anomalies
  - *Osgep* KO: early embryonic lethality
- Constitutive CRISPR KI:
  - *Lage3* KI hemizygous (human p.Phe137Ser)
  - *Osgep* KI homozygous (human p.Arg325Gln) No renal/brain anomalies

(**Braun** et al, 2017; **Jobst-Schwan** et al, 2018, **Krausel** et al. 2023))

KEOPS & t^{6}A : animal models (2)

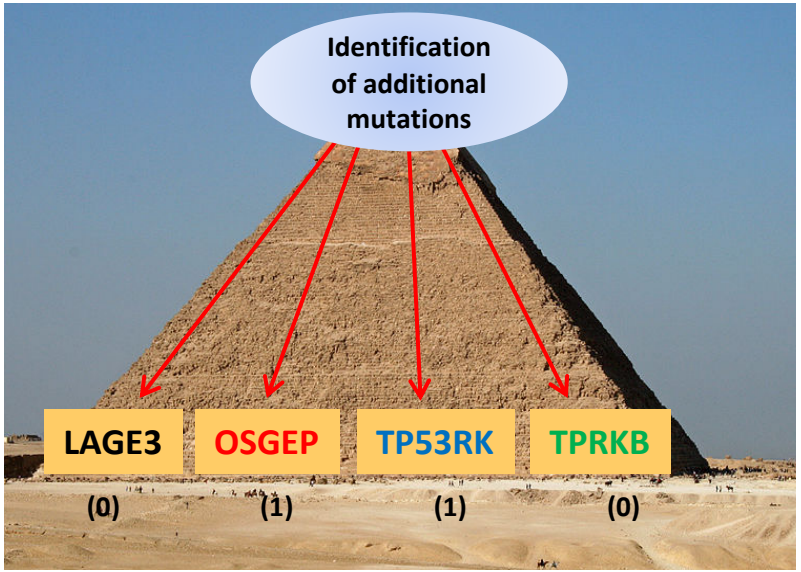
Drosophila Melanogaster





(**Braun** et al, 2017; **Rojeas Benitez** et al, 2017, **Jobst-Schwan** et al, 2018, **Krausel** et al. 2023))

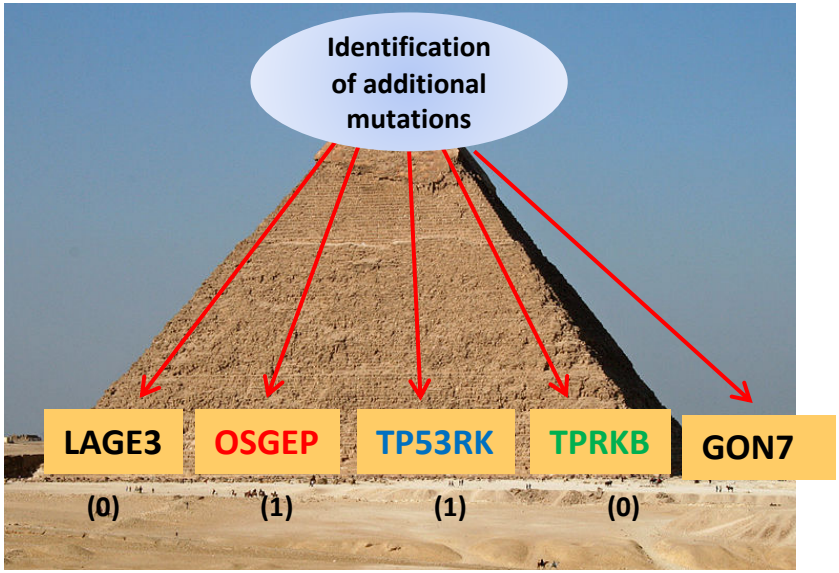
Functional characterization of KEOPS complex-genes : further delineation of the phenotype



OSGEP variant p.Arg325Gln

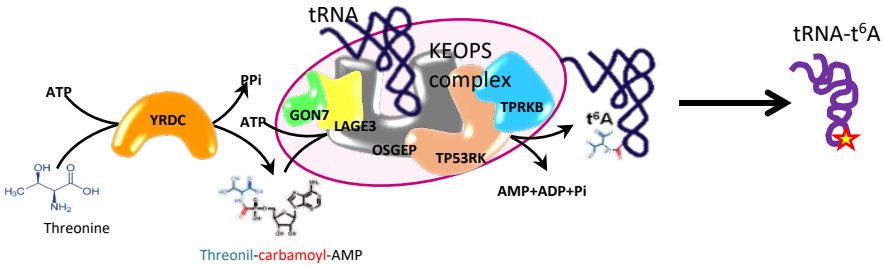
- Hypomorphic variant
- Acquired microcephaly, hypotonia, severe ID
- MRI: cerebellar atrophy/leukodystrophy
- Different kidney phenotype in the homozygous state: hypomagnesemia and non-nephrotic proteinuria without renal insufficiency

Functional characterization of KEOPS complex-genes : further delineation of the phenotype



OSGEP variant p.Arg325Gln

- Hypomorphic variant
- Acquired microcephaly, hypotonia, severe ID
- MRI: cerebellar atrophy/leukodystrophy
- Different kidney phenotype in the homozygous state: hypomagnesemia and non-nephrotic proteinuria without renal insufficiency

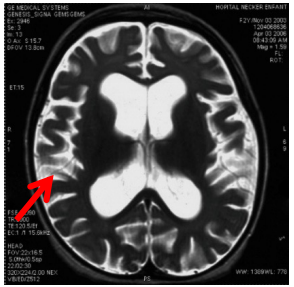


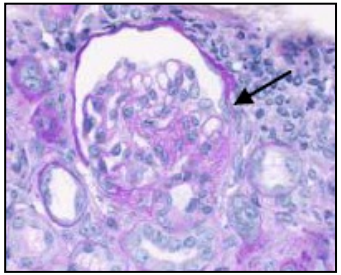
Mutations in *C14Orf142* – patient phenotypic description

4 consanguineous families
(Aurès region, Algeria)
c.21 C>A : p.Tyr7*

+

1 consanguineous family
c.19dup : p.Tyr7Leufs*16





- **Secondary microcephaly**
- Developmental delay
- Hypotonia
- **Cortical and cerebellar atrophy/hypoplasia**
- Thin corpus callosum
- Ventricular dilation
- **Myelination defects (rarely)**
- No gyration defect

- Early-onset proteinuria (2 to 5 years)
- ESKD (2.5 and 6 years)

- **Histology:** Lesions ranging from DMS to FSGS

→ **More attenuated form of the disease in patients mutated for *C14* than for the KEOPS genes**

C14/GON7 - Functional studies

- C14: Small disordered protein of unknown function
- Same size as yeast Gon7, but very weak sequence similarity
- C14 = GON7 = 5th element of human KEOPS ?

- Interacts with LAGE3 (proteomic studies, co-IP)

Géraldine Mollet

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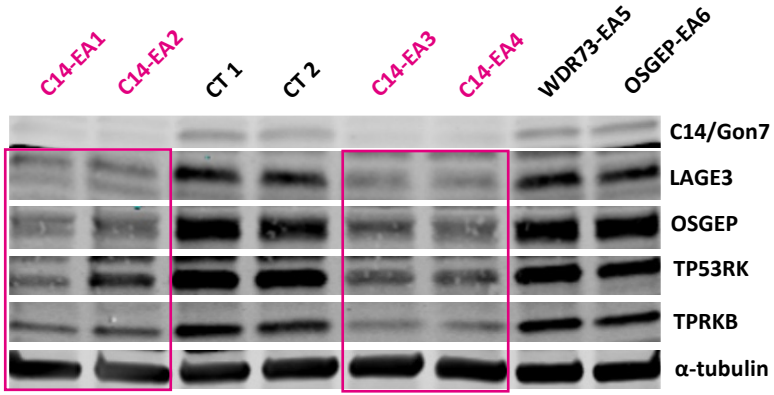
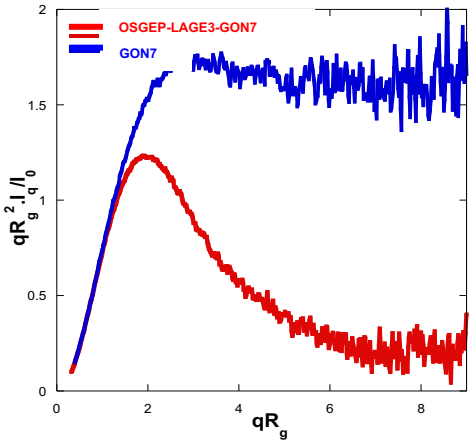
C14/GON7 - Functional studies

- C14: Small disordered protein of unknown function
- Same size as yeast Gon7, but very weak sequence similarity
- C14 = GON7 = 5th element of human KEOPS ?

- Interacts with LAGE3 (proteomic studies, co-IP)
- Becomes structured upon interaction with LAGE3 (SAXS)
- Increases stability of the KEOPS proteins





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GON7 stabilizes the KEOPS complex to modulate its function(s)

- Decreased expression of KEOPS protein when GON7 is absent
- Lower effect on proliferation, apoptosis and protein synthesis than the other KEOPS subunits

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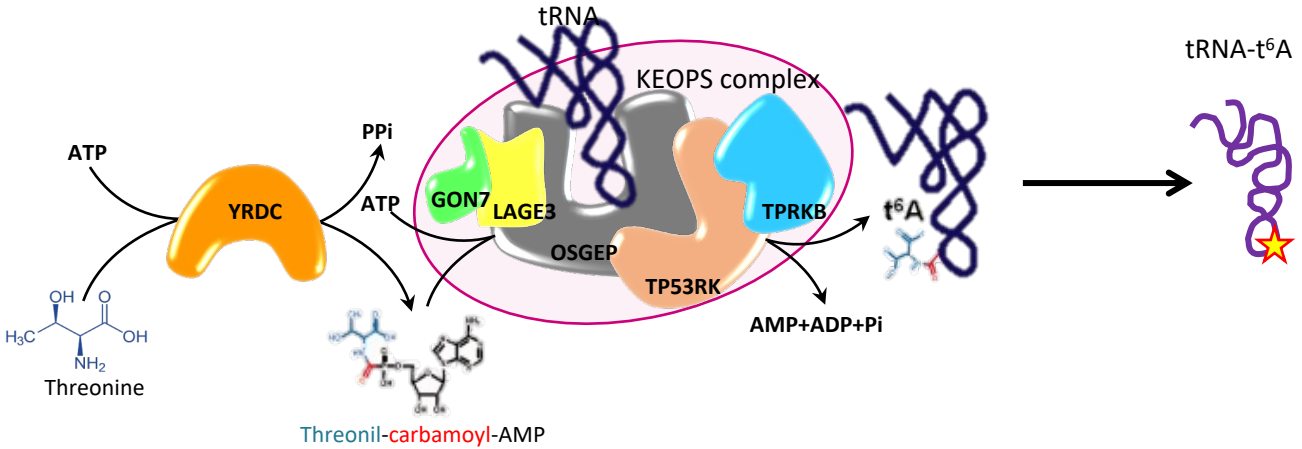
Identification of new genes involved in GAMOS



***YRDC* (Sua5)**

GON7

Very severe phenotype, similar to that of KEOPS mutated patients

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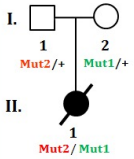
YRDC – patient phenotypic description

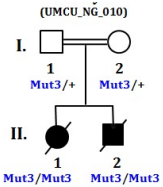


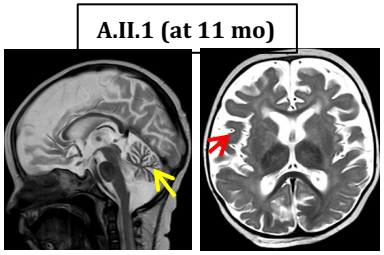
Family A

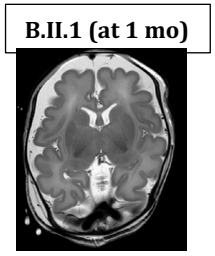
c.251 C>T (p.Ala84Val) (Mut1)
c.721_724 del (p.Val241Ile fs*72) (Mut2)

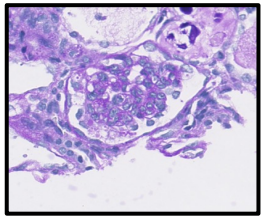
Family B

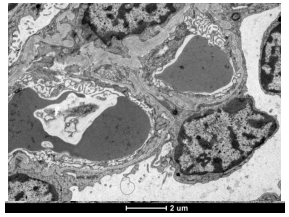
c.794_796 del (Mut3) Hom











Clinical manifestations:

- ✓Primary/secondary microcephaly
- ✓Facial dysmorphy, hypotonia, seizures
- ✓ Hypothyroidism

MRI anomalies:

- ✓ **Patient A.II.1** : normal MRI at 5 months, then progressive major cerebellar and cortical atrophy
- ✓Marked abnormality of myelination
- ✓ **Patient B.II.1**: gyration defects

Clinical manifestations:

- ✓ Congenital nephrotic syndrome
- ✓ ESKD (1-4 months), death < 1 year

Renal histology:

- ✓ Lesions of DMS and FPE

→ Very severe phenotype, similar to that of KEOPS mutated patients

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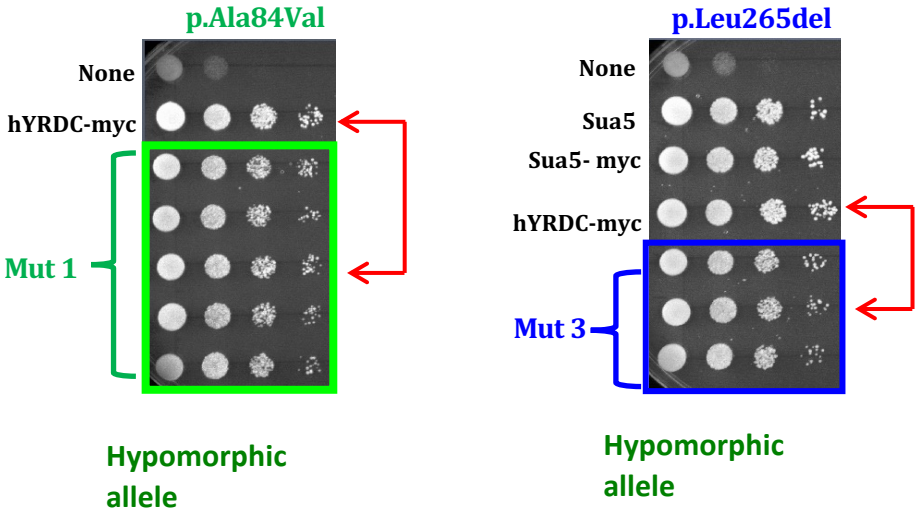
YRDC- Functional studies

YRDC

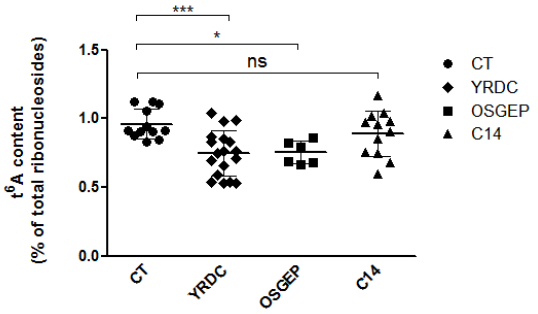
✓ First enzyme of the t6A biosythesis

Growth complementation studies in Δsua5



Hypomorphic allele

Hypomorphic allele



t⁶A content in patient's fibroblasts

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YRDC- Functional studies

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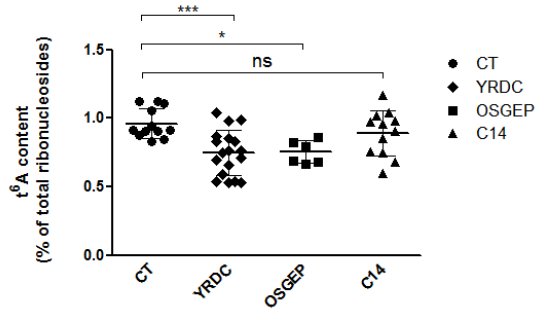

t^{6}A content
in patient's fibroblasts

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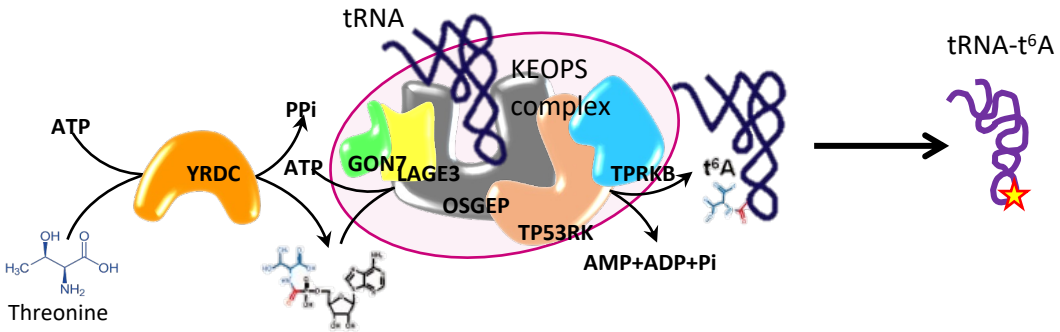
Crucial role of t6A modification in the pathogenesis of GAMOS

✓**27 mutations** in all the **6 components** of the t^6A biosynthesis pathway
✓ Mutations responsible for Galloway-Mowat Syndrome
✓ Early-onset renal disease



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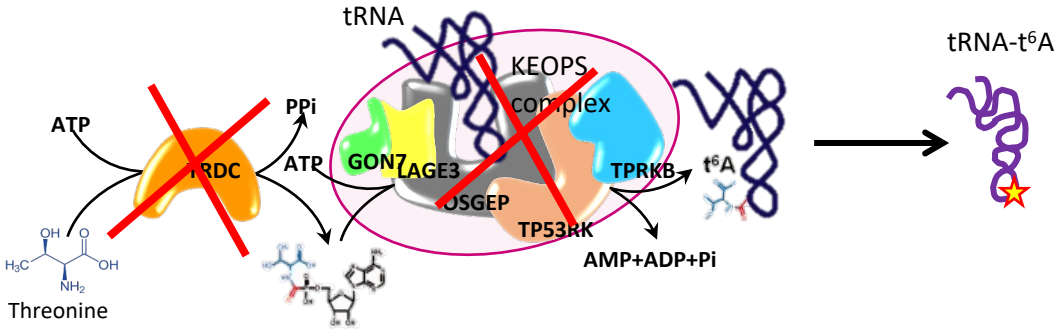

✓ No bi-allelic truncating mutations (lethal ?)

✓ Very severe neurological phenotype

- **primary microcephaly**
- **gyration and myelination defects**

KEOPS or YRDC

Role in t^{6}A biogenesis

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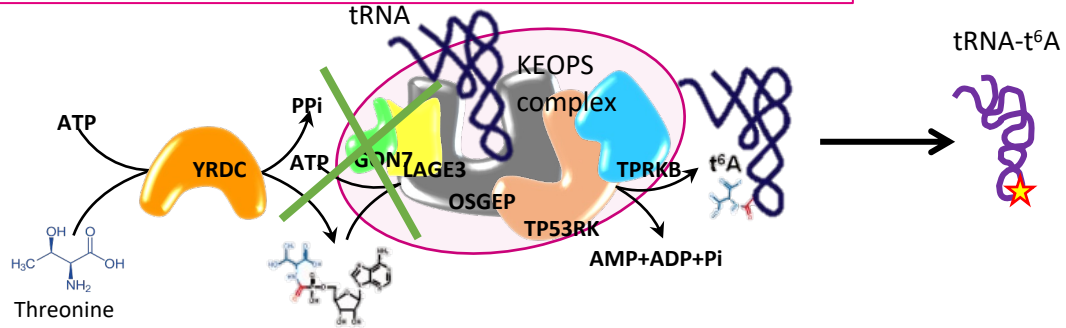


KEOPS or YRDC

✓ No bi-allelic truncating mutations (lethal ?)

✓ Very severe neurological phenotype
- primary microcephaly
- gyration and myelination defects

Role in t^6A biogenesis

GON7

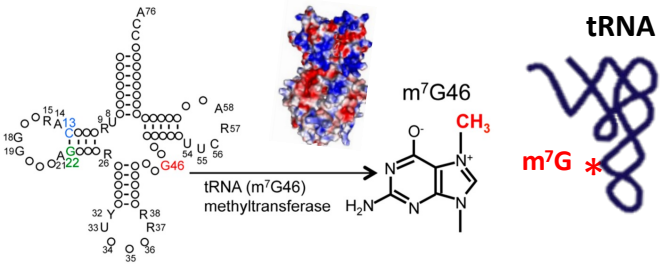
✓ Less severe neurological phenotype
- secondary microcephaly
- no gyration and myelination defects

Role in KEOPS complex stabilization and/or KEOPS function(s) modulation

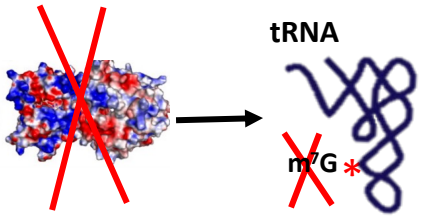
tRNA metabolism: WDR4 and m^{7}G modification

m^{7}G biosynthetic pathway

Holoenzyme WDR4/METTL1
(N7-méthylguanosine méthyltransférase)



- WDR4 non catalytic subunit
- m^{7}G modification both on tRNA and rRNA
- One of the most prevalent tRNA modification, but not essential
- Regulation of mRNA export, splicing and translation

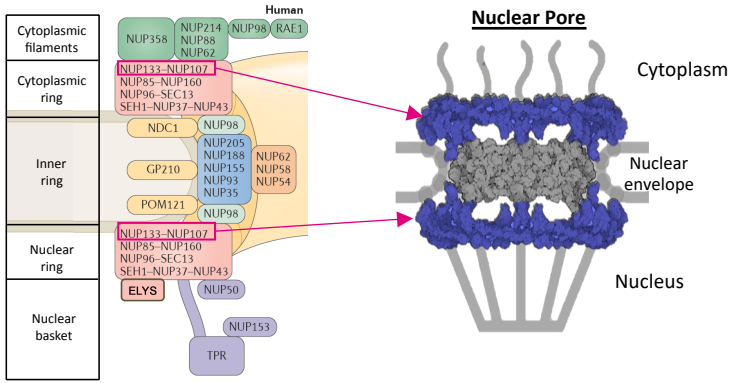


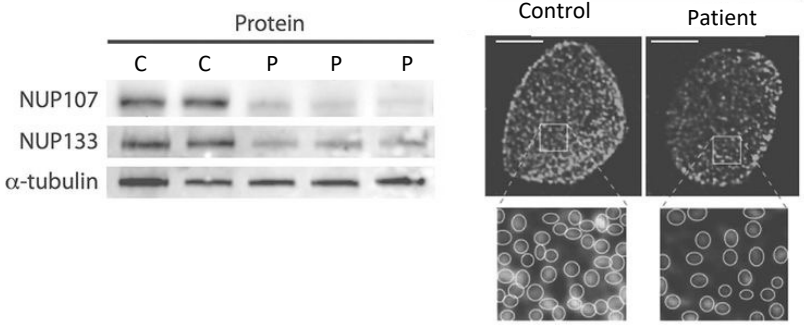
WDR4/METTL1

- Homozygous obligatory splice site mutation (c.454-2A>C) in *WDR4*, known to be mutated in microcephalic primordial dwarfism in 4 siblings with GAMOS (Braun et al., 2018)
- KO WDR4 or METTL1 mouse ES cells ⟶
  Defects in:
  - Translation of cell cycle genes
  - Proliferation (self renewal of murine stem cells)
  - Neural lineage differentiation capacity

(**Lin** et al, 2018)

NUP genes mutations in GAMOS





(Rosti RO et al., 2017)

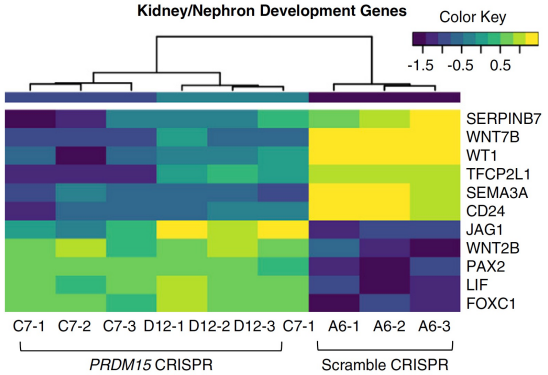
- Roles of NPCs (Nuclear pore complexes)
  - Nucleocytoplasmic transport in both directions
  - Cell division, chromatin organization, gene regulation
- Mutations in several NUP genes in isolated SRNS
- Mutations in genes encoding 2 proteins of the Y complex (NUP133 – NUP107) found in GAMOS (with childhood FSGS and primary microcephaly)

- Interaction defects/ Reduction in NPC density
- *Nup133* MO Zebrafish
  - ↘ midbrain width and axonal number
  - Underdeveloped glomeruli and FPE

(Rosti RO et al., 2017; Fujita A, 2019)

PRDM15 a new player in the field

- *PRDM15*: a Zn finger protein known to regulate the Notch pathway – expression mainly in the lymphoblastoid cell lines
- KD in podocyte cell line → dysregulation of genes involved in **development, cell proliferation and differentiation (including WT1, JAG1, PAX2)**
- **Recent identification of 3 homozygous missense variants in *PRDM15***



(Mzoughi S et al., 2020; Mann N et al., 2021)

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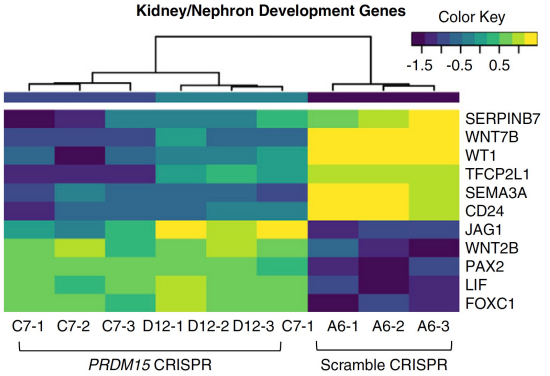
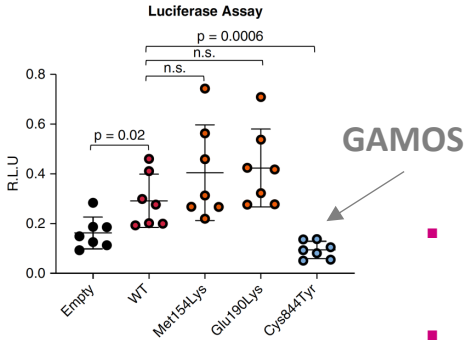
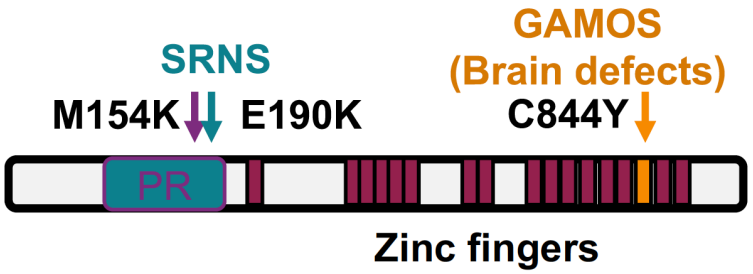




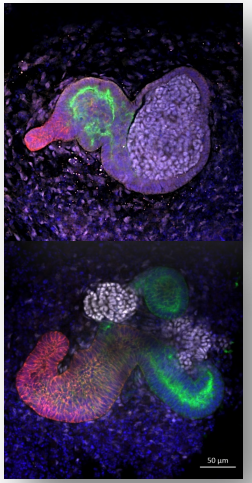


- One located in the Zn finger → **GAMOS** (with polydactyly/microcoria-coloboma/atrial septal defect) – unable to promote transcription in a luciferase assay (Rspo1 promoter) or by ChIP
- Two located in the PR domain lead to SRNS – Role in stability of the protein

(Mzoughi S et al., 2020; Mann N et al., 2021)

Conclusions

- GAMOS patients present mainly with mutations in the genes encoding KEOPS complex and WDR73 proteins, involved in RNA metabolism (tRNA modification, UsnRNA processing).
- Mutations in NUP genes as well as in *PRDM15* show possible alteration, in GAMOS, of other (but related) cellular mechanisms (nucleocytoplasmic transport and transcriptional regulation)
- **Neurons and podocytes, both post-mitotic non dividing cells, are sensitive to translation process alterations, which lead to either decreased proliferation and/or increased apoptosis.**
- Some gene mutations might lead either to GAMOS or isolated SRNS.
- Mouse and zebrafish models are not recapitulating the human renal phenotype**.**
- Studies on cerebral and brain organoids or various cell types derived from patient iPS cells might help better characterizing molecular defects at play in GAMOS.



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Manish Sinha (London, UK)

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Protéomique / Génomique/ CRB/ Imagerie cellulaire / LEAT / iPS / Biochimie métabolomique et protéomique

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Corinne Antignac

Géraldine Mollet

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