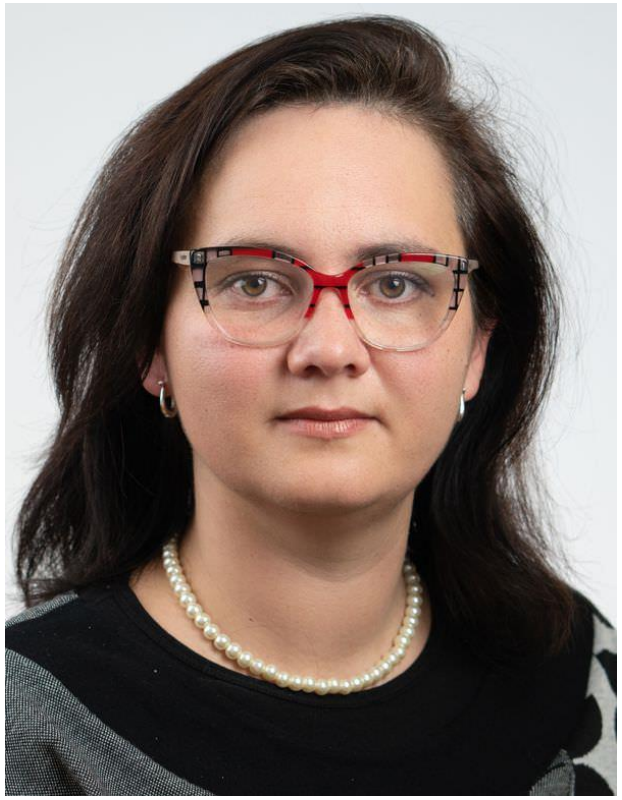

Schimke immune-osseous dysplasia

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Schimke immuno-osseous dysplasia

Webinar 7th May 2019

Have you ever met a patient with Schimke?

A. YES, I have diagnosed at least one patient.

B. YES, I took care of at least one patient.

C. YES, I have seen a Schimke patient during training.

D. NO, I have never met a patient with Schimke.

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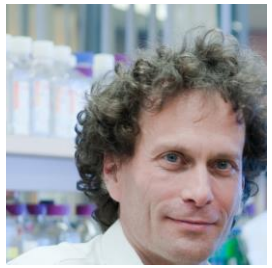
Schimke immuno-osseous dysplasia

Robert Neil Schimke
1971



Cornelius Boerkoel
2002

- MIM #242900
- *https://www.ncbi.nlm.nih.gov/books/NBK1376/*

- an autosomal recessive disorder
- characterized by the combination of:
  - defective cellular immunity with episodic lymphopenia
  - spondyloepiphyseal dysplasia with growth retardation
- caused by biallelic mutation of the *SMARCAL1* gene

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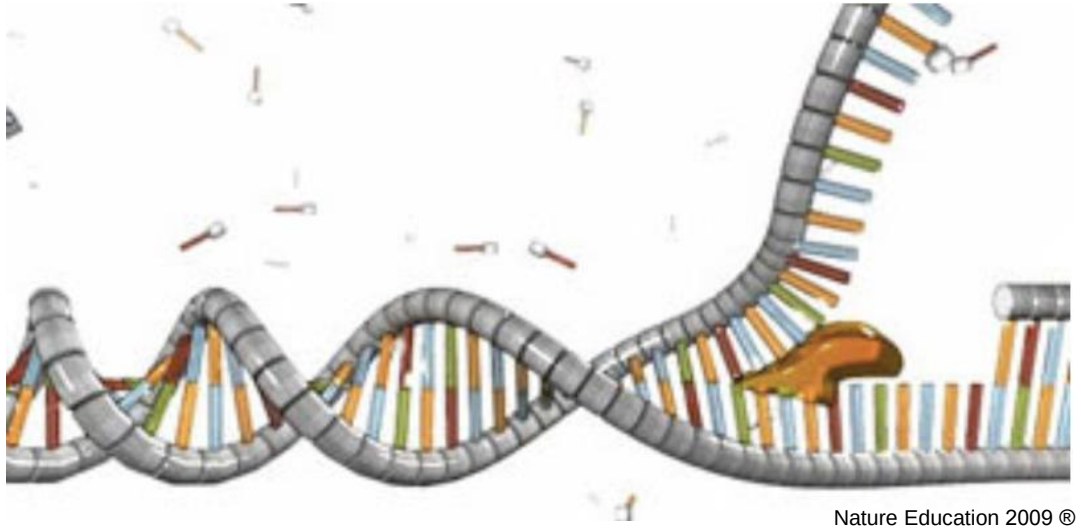
SMARCAL1 *- the gene encoding SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin subfamily A-like protein-1*

- SWI2/SNF2 family of ATP-dependent chromatin remodeling proteins
- contains a conserved helicase ATPase domain for DNA remodeling
- interacts specifically with branched DNA structures such as replication forks
- is critical to the stability of DNA replication

The precise cellular mechanisms how replication fork malfunctioning leads to the specific phenotype of SIOD are still elusive



Nature Education 2009 ®

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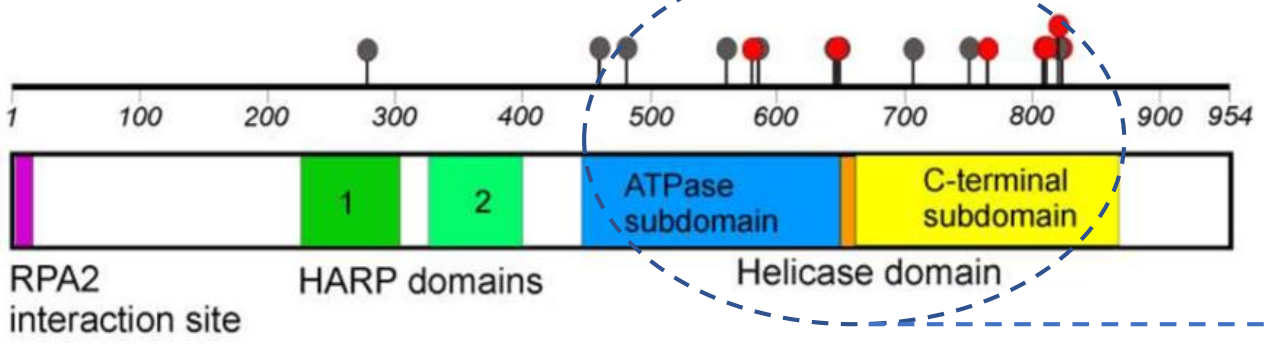
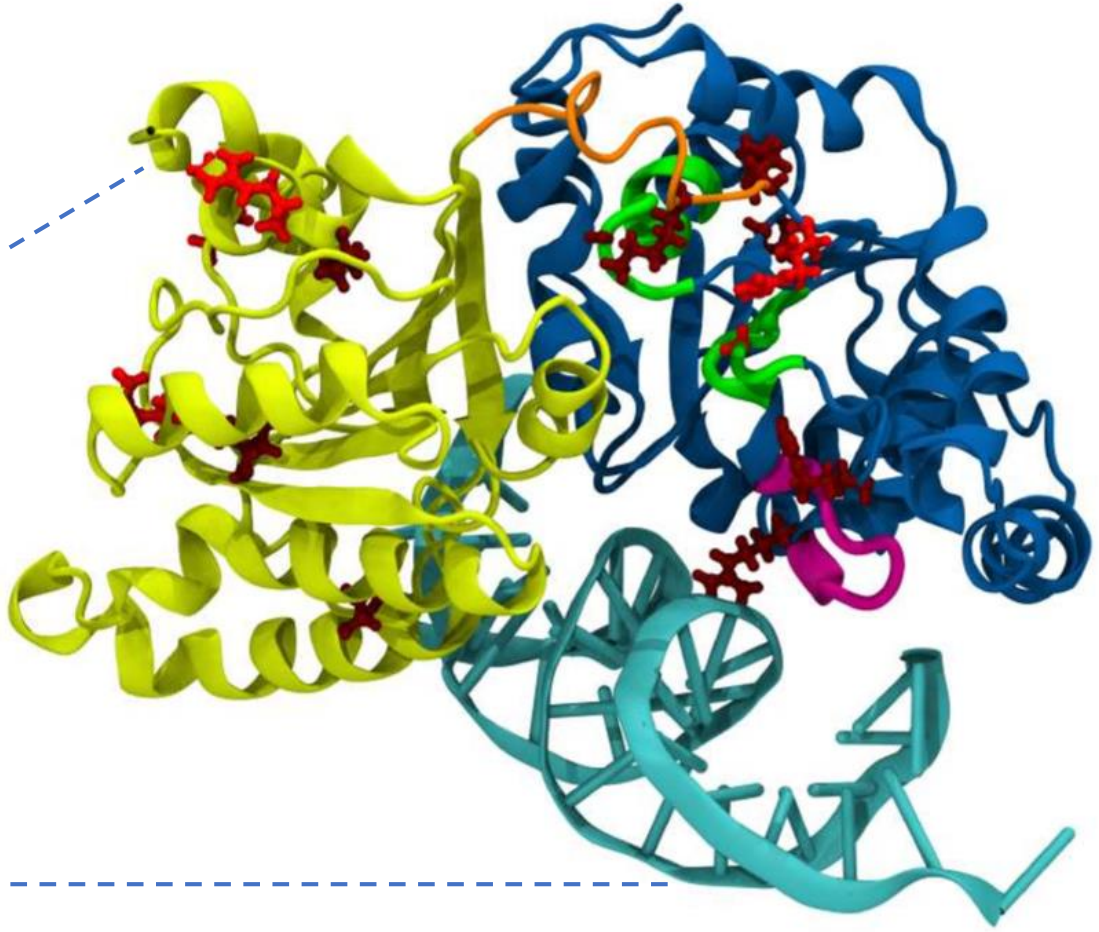
Hinge region - orange.
ATP binding site motifs – green.
DNA sensor switch - magenta.
Residues affected by missense mutations – red.

SMARCAL1 - *the structure of the helicase domain*

Both subdomains wrap around the DNA molecule,
the plausibly mobile C-terminal subdomain forming a pocket
around the ATPase active site of the N-terminal subdomain





Lipska-Ziętkiewicz BS,. et al.(2017) PLoS ONE 12(8):e0180926

Schimke immuno-osseous dysplasia

- MIM #242900, *606622
- a progressive proteinuric glomerulopathy

and a combination of:

- defective cellular immunity with episodic lymphopenia
- spondyloepiphyseal dysplasia with growth retardation
- peculiar dysmorphic features inc. pigmentary skin lesions
- …

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PODOCYTOPATHIES
THE ROLE OF GENETIC TESTING

When?

What test?

What next?

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What is your 1st tier strategy for genetic diagnosis of a progressive proteinuric glomerulopathy?

A. Perform WES in all cases.

B. Perform NGS-based gene panel testing.

C. Perform Sanger testing for selected genes.

D. I do not order genetic testing for my proteinuric patients

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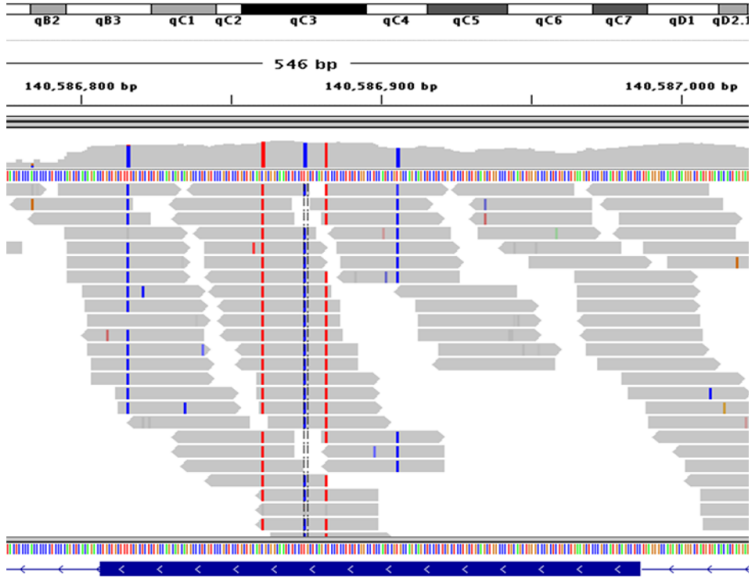
HEREDITARY PODOCYTOPATHIES

1st CHOICE GENETIC TEST:



NGS-based GENE PANEL:

- *Fast*
- *Cheap*
- *Good quality*
- *Robust*
- *No incidental findings*

- *Simulataneous analysis of SNV+CNV+mosaicism*

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Schimke immuno-osseous dysplasia

Prevalence 1: 1-3 000,000 (an orphan disease)

~1% SRNS:

0.8% (n=9) among 1105 consecutively screened SRNS cases (EuRenOmics)
1.0% (n=16) among 1614 SRNS families (SRNS Study group)

Equally distributed worldwide; possible founder effects

c.1756C>T (p.Arg586Trp) – Indian
c.2542G>T (p.Glu848*) – Eastern (Slavic) Europeans

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1. Syndromic forms

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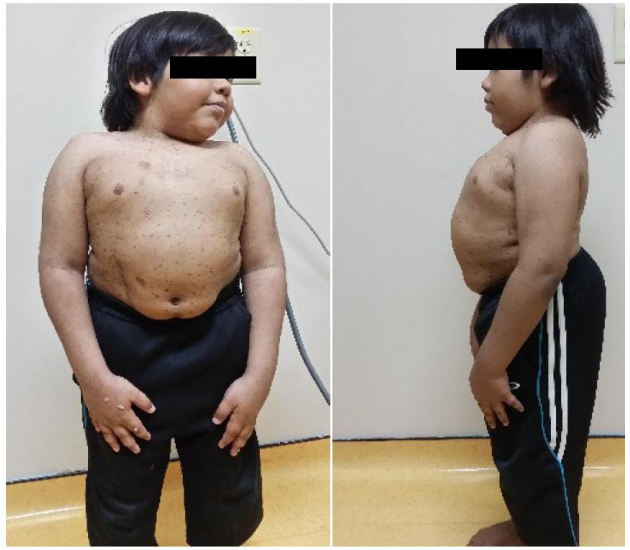
POSSIBLE SCENARIOs – patients with extra-renal manifestations:

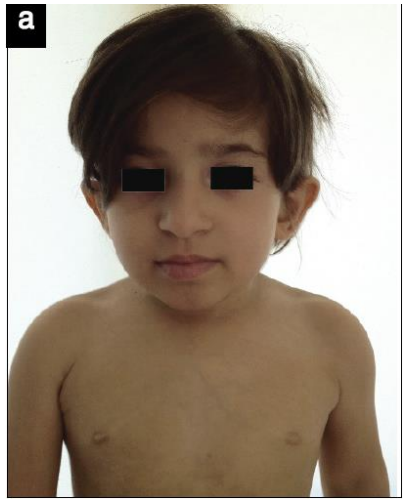
a 4-year old boy with multiple pigmented macules diagnosed with proteinuria during evaluation for short stature



Lipska-Ziętkiewicz BS,. et al.(2017) PLoS ONE 12(8):e0180926

short neck and trunk,
disproportionate short stature,
lumbar lordosis,
protruding abdomen ~99%

numerous pigmented macules predominantly on the trunk.



Candan et al. (2012)
Turk Arch Ped 47: 315-317

triangular face
broad nasal bridge
bulbous nasal tip ~70%

microdontia,
hypodontia,
malformed deciduous
permanent molars

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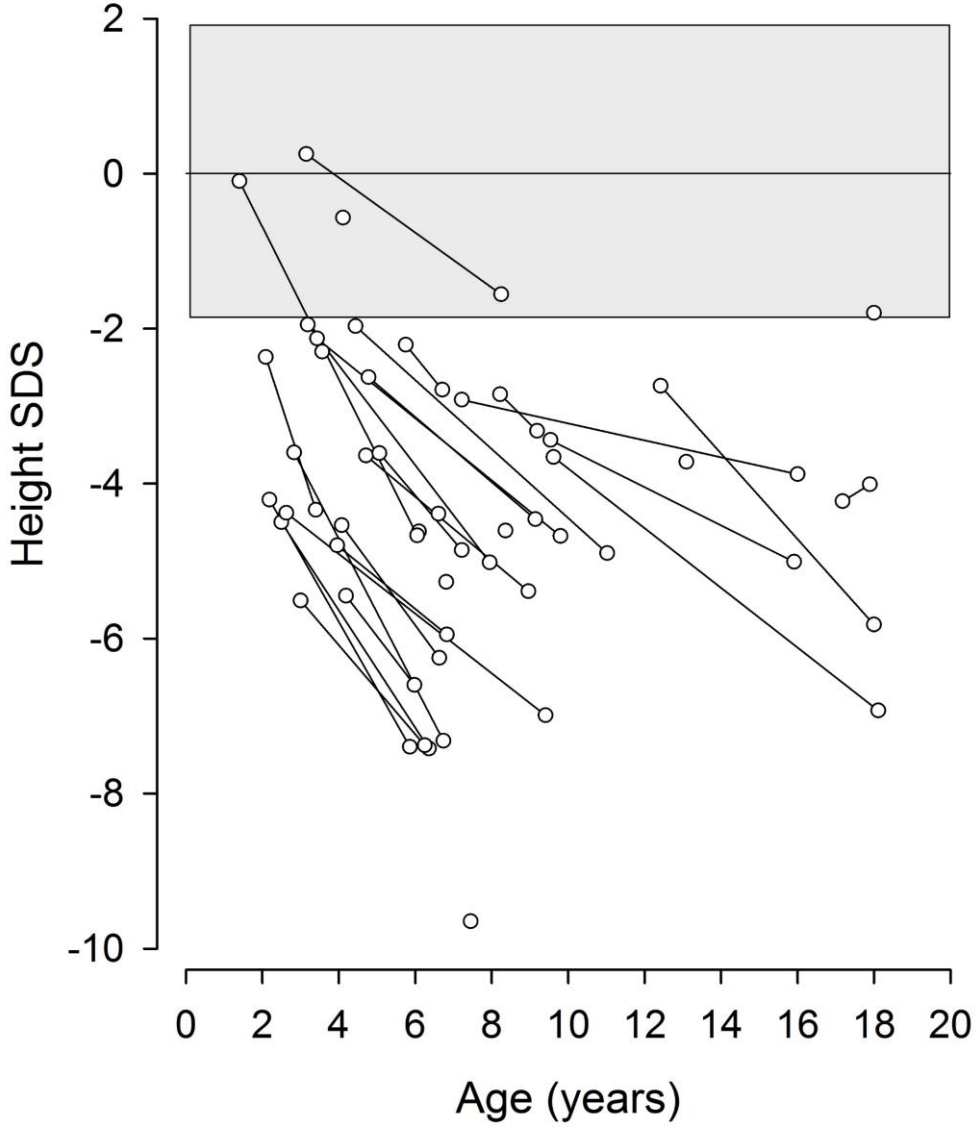
DISPROPORTIONATE SHORT STATURE IS THE CARDINAL FEATURE OF SCHIMKE IMMUNO-OSSEOUS DYSPLASIA

Height SDS at diagnosis	-3.30 ± 1.46
Height SDS at last observation	-5.24 ± 1.84

Intrauterine growth retardation	96.4%
Preterm delivery	60.7%

Lipska-Ziętkiewicz BS,. et al.(2017) PLoS ONE 12(8):e0180926



Lipska-Ziętkiewicz BS,. et al.(2017) PLoS ONE 12(8):e0180926

Height in those who have survived to adulthood is 136-157 cm for men and 98.5-143 cm for women.

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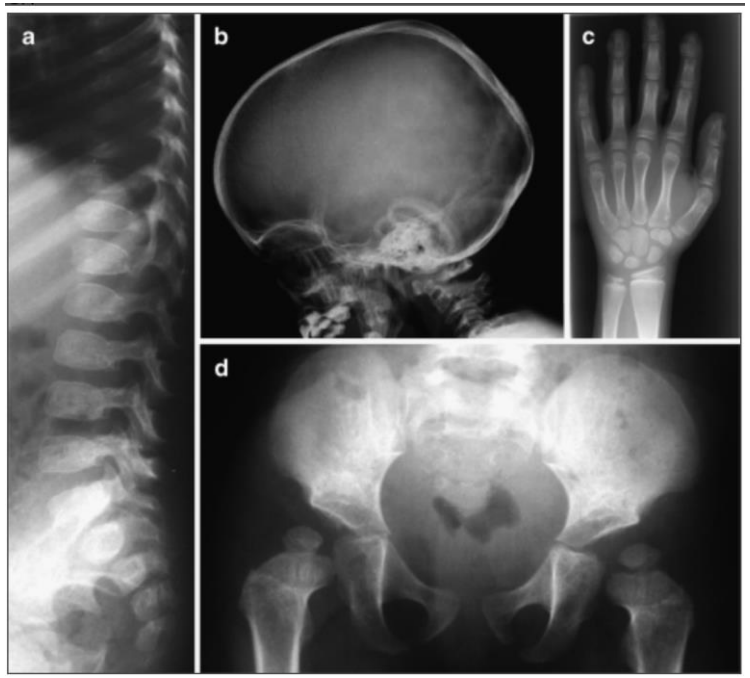
a 4-year old boy with multiple pigmented macules diagnosed with proteinuria during evaluation for short stature



Hunter KB et al. (2010) Eur J Pediatr. 169(7):801-11

Spondyloepiphyseal dysplasia (SED)

essentially limited to the spine, pelvis, capital femoral epiphyses, and the sella turcica; the hands and other long bones are basically normal.

Typical findings on skeletal radiographs:

- dorsally flattened, pear-shaped vertebral bodies
- Dysplastic hips:
  - small, laterally displaced capital femoral epiphyses,
  - hypoplastic basilar ilia
  - upslanting and poorly formed acetabula

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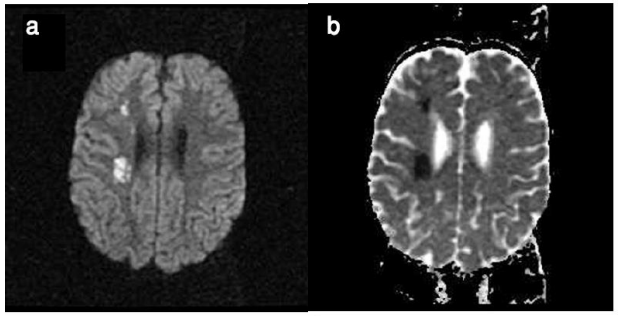
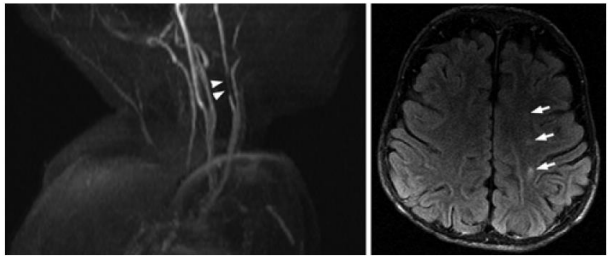
POSSIBLE SCENARIOs – patients with extra-renal manifestations:

a 5 year girl hospitalized in status epilepticus; in the following weeks she had additional episodes and became triplegic with motoric aphasia. So far she had normal neurologic development. A nephrotic proteinuria of 1-2 g/m2/day without hematuria and a blood pressure of 90/65 mmHg (diastolic - 95th percentile for height) was noted.



Candan et al. (2012)
Turk Arch Ped 47: 315-317



Westbroek EK et al. (2015) J Neurosurg Pediatr 15:189–191

migraine-like headaches
moyamoya phenomenon,
transient cerebral ischemia,
cerebral infarction ~50%
The pulmonary and systemic hypertension

moderate cognitive impairment
mild developmental delay ~20%

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POSSIBLE SCENARIOs – patients with extra-renal manifestations:

a 4 year old boy with hx of reccurent infections, short stature, facial dysmorphic features, solitary left kidney and proteinuria (FSGS on biopsy) who developed sudden neurological deterioration in the course of reccurent episodes of TIAs.

February 2010:	diarrhea- *Rotavirus*;
February 2010:	fungal UTI;
March 2010:	generalized **sepsis** *E.Coli*;
May 2010:	broncopneumonia;
October 2010:	diffuse interstitial pneumonia- *Pneumocystis and CMV*

Recurrent infections (fungal, viral, bacterial) ~50%
Defective cellular immunity
Absent mitogenic response
T-cell deficiency ~80%
Decreased CD4+ and CD3+/CD4+ lymphocytes
Abnormal immunoglobulin levels
Lymphoproliferative disorders (non-Hodgkin limphoma)

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POSSIBLE SCENARIOs – patients with extra-renal manifestations:

a 3 year old girl with hx of IUGR, neonatal transistent thrombocytopenia, left-sided unilateral renal agenesis but normal voiding cystography presenting with a nephrotic-range proteinuria and hypertension

a 5,5 year old boy with persistent proteinuria since the age of 3 who developed ITP and anemia without splenomegaly; lab test confirmed presence of antiplatelet antibodies, HGB 7 g/dl, reticulocytes 3.1%, positive direct antiglobulin test

Autoimmune thrombocytopenia
Autoimmune anemia
Evans syndrome
Autoimmune bowel disease
Pericarditis, anti-cardiolipin antibodies
Acute disseminated encephalomyelitis

~20%

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2. (oligo)syndromic forms

with the advent of comprehensive gene panel screening/ WES
more cases with less severe, largely renal-limited phenotypes are being detected.

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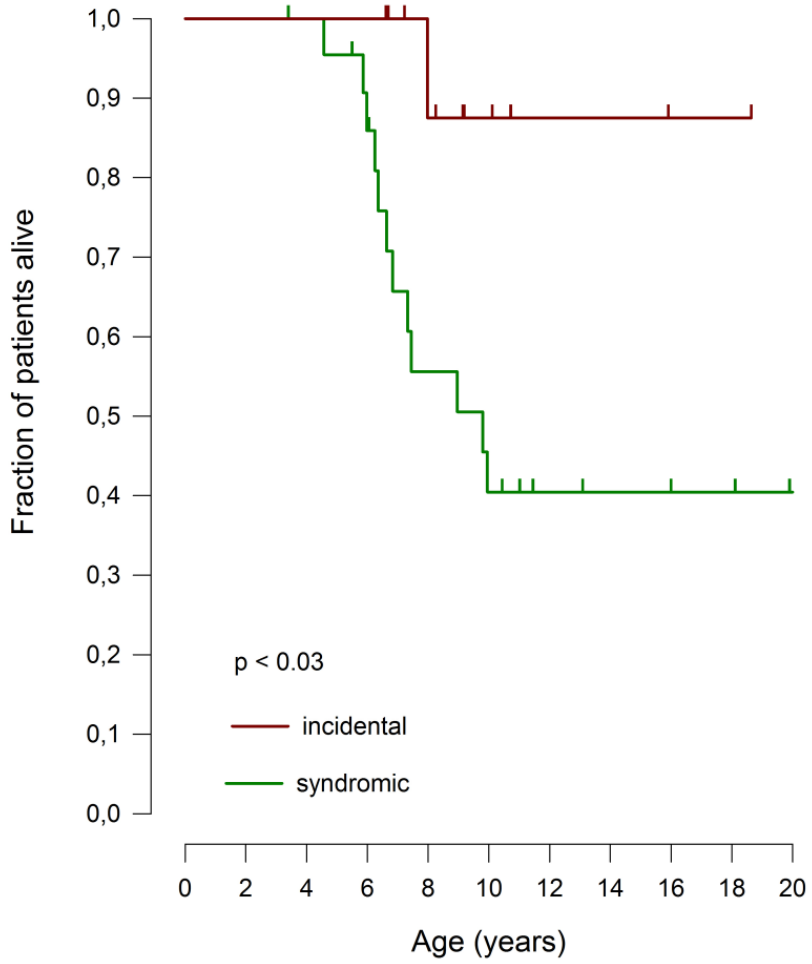
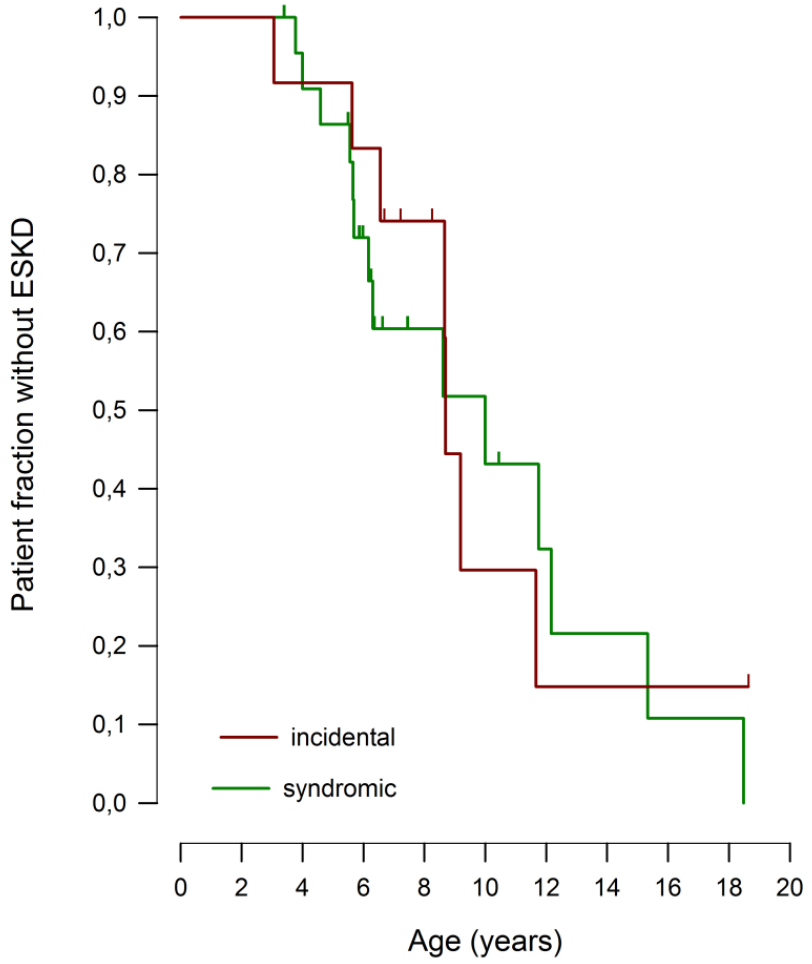
Schimke immuno-osseous dysplasia
an incidental finding

- MIM #242900, *606622
- a progressive presumably idiopathic proteinuric glomerulopathy
- and a combination of:
  - defective cellular immunity with episodic lymphopenia
  - spondyloepiphyseal dysplasia with growth retardation
  - peculiar dysmorphic features inc. pigmentary skin lesions
  - …

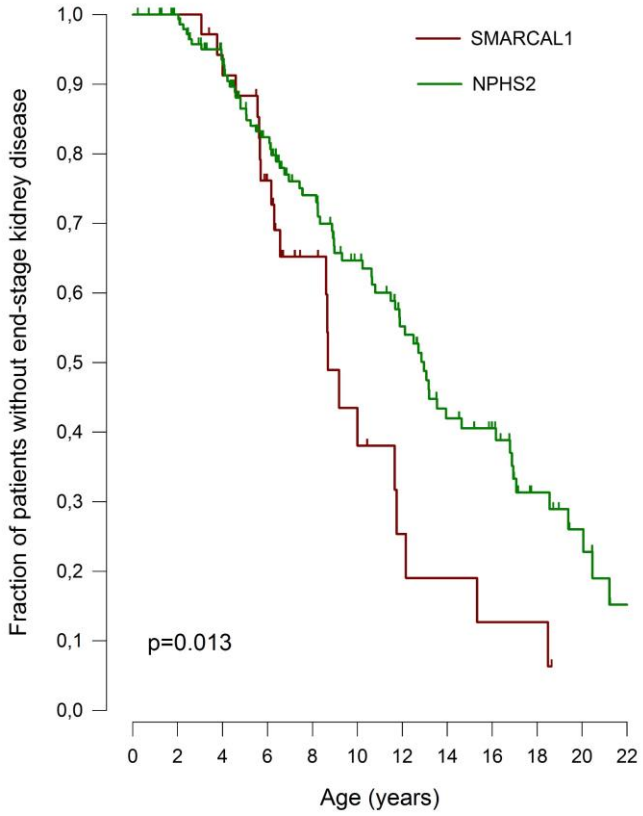
Comparison of syndromic and ‚incidental' SIOD





Schimke immuno-osseous dysplasia

the renal phenotype



Median age at diagnosis (IQR) [years]	4.5 (3.2–7.2)
Nephrotic range proteinuria at diagnosis	69.0%
Histopathological findings	
FSGS	81.5% (22/27)
MCN	18.5% (5/27)
Median age at ESKD (IQR) [years]	8.7 (5.6–10.0)
Patient survival at age 10 yrs	53.6 ±9.7%

Lipska-Ziętkiewicz BS,. et al.(2017) PLoS ONE 12(8):e0180926

Lipska-Ziętkiewicz BS,. et al.(2017) PLoS ONE 12(8):e0180926

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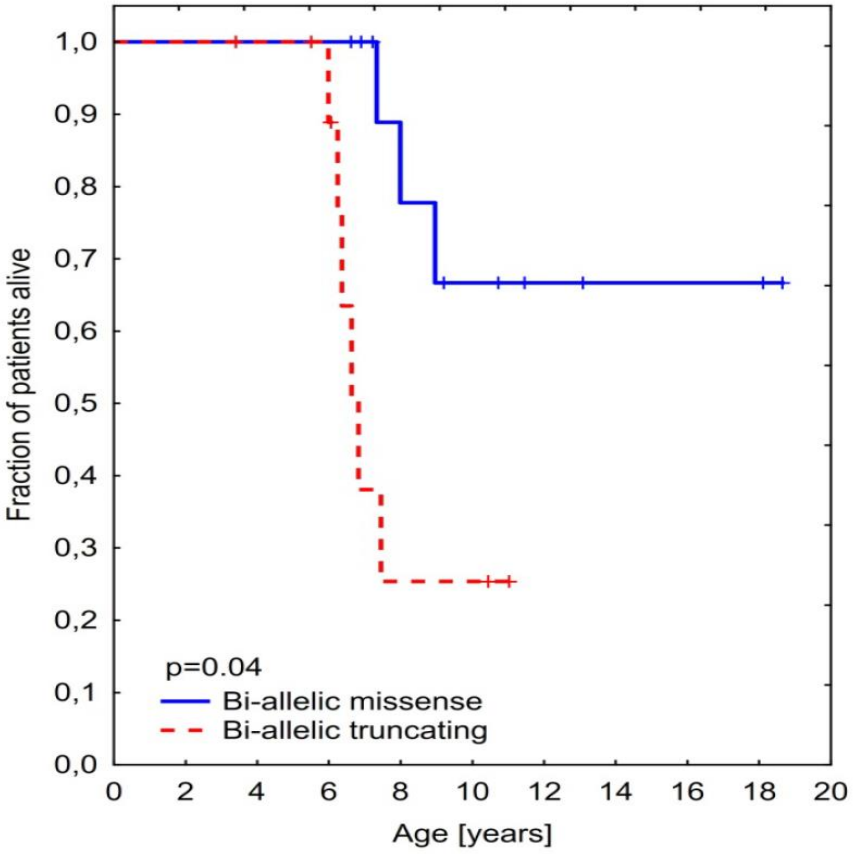
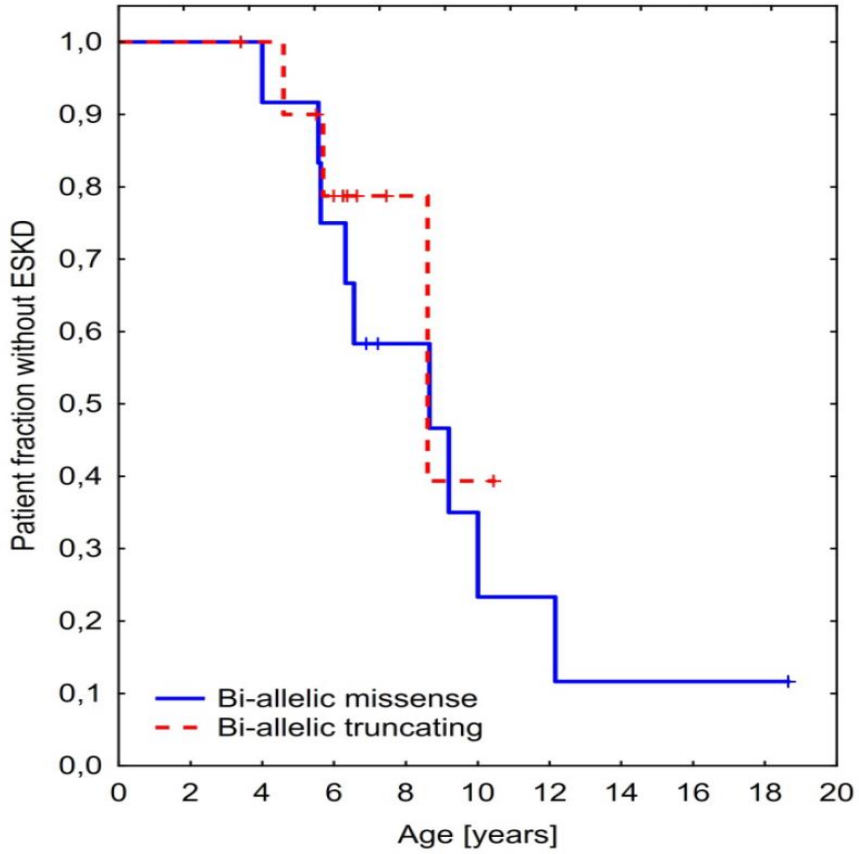
genotype – phenotype correlations





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the pitfalls of genotype – phenotype correlations

approximately 50% of SIOD cases are compound heterozygous;
in these families genotype phenotype correlations
are not as straightforward

a wide and highly variable spectrum of extrarenal symptoms,
most of which only emerge over time

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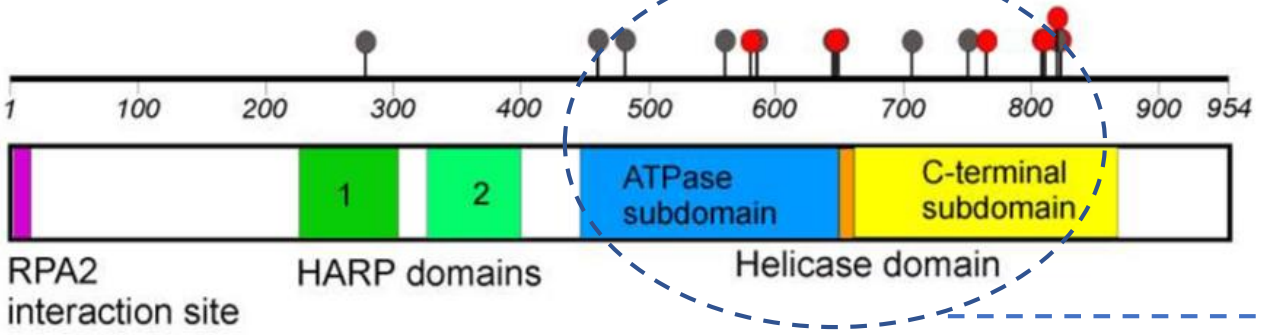
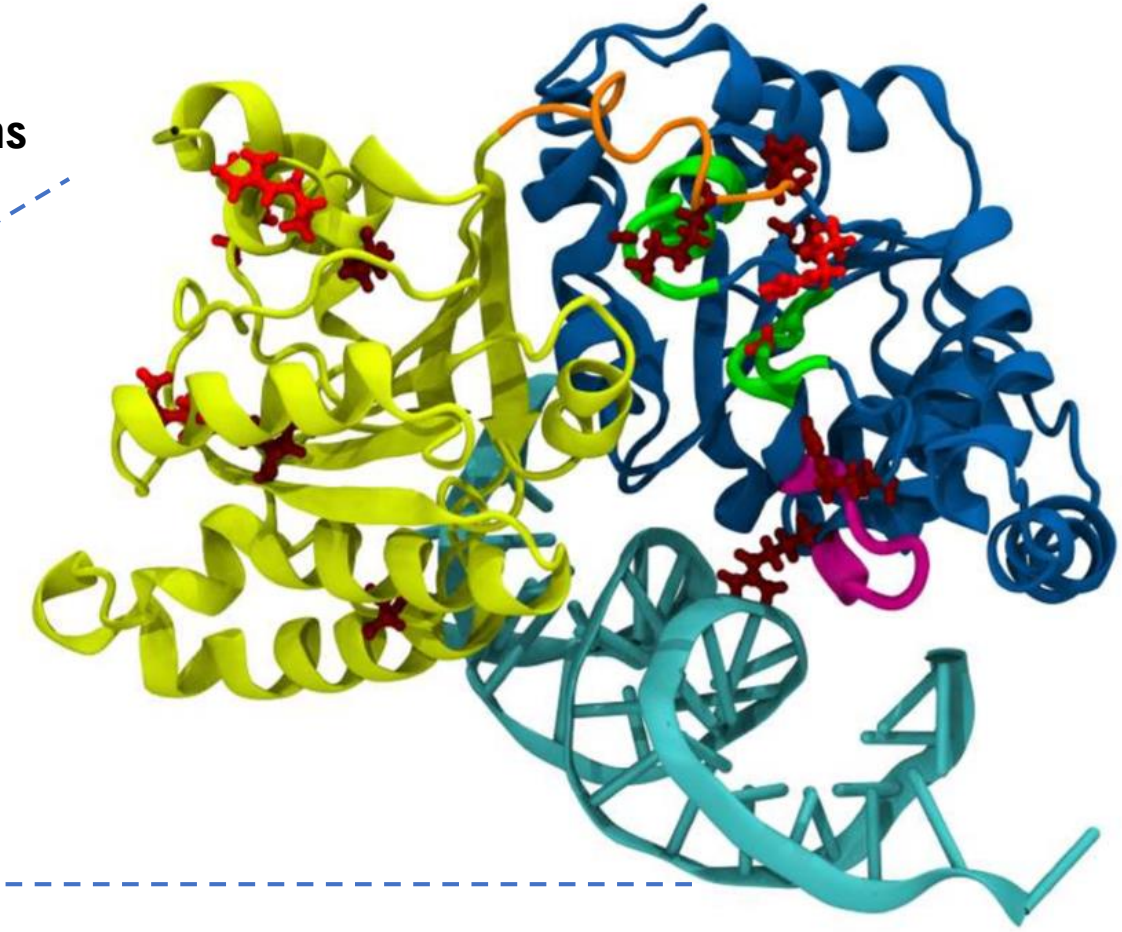
genotype – phenotype correlations

Hinge region - orange.
ATP binding site motifs – green.
DNA sensor switch - magenta.
Residues affected by missense mutations – red.

N-terminal helicase ATP-ase catalytic subdomain missense mutations
cause a clear SIOD phenotype





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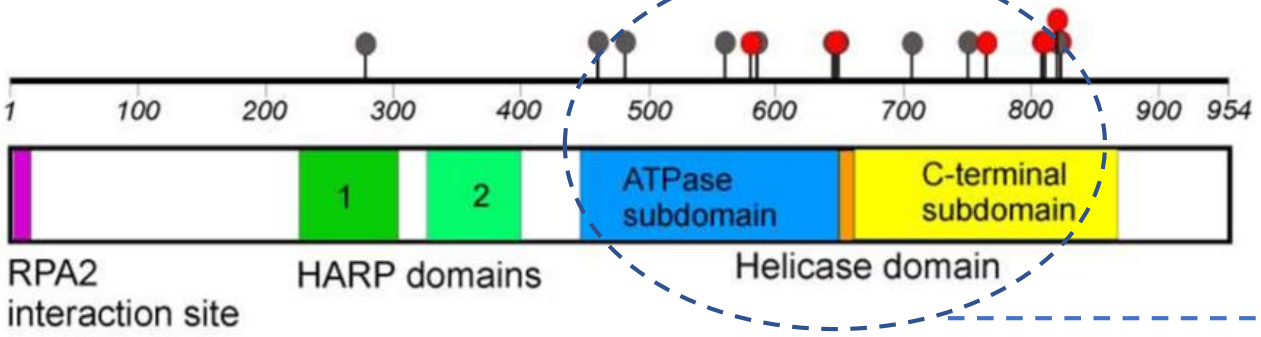
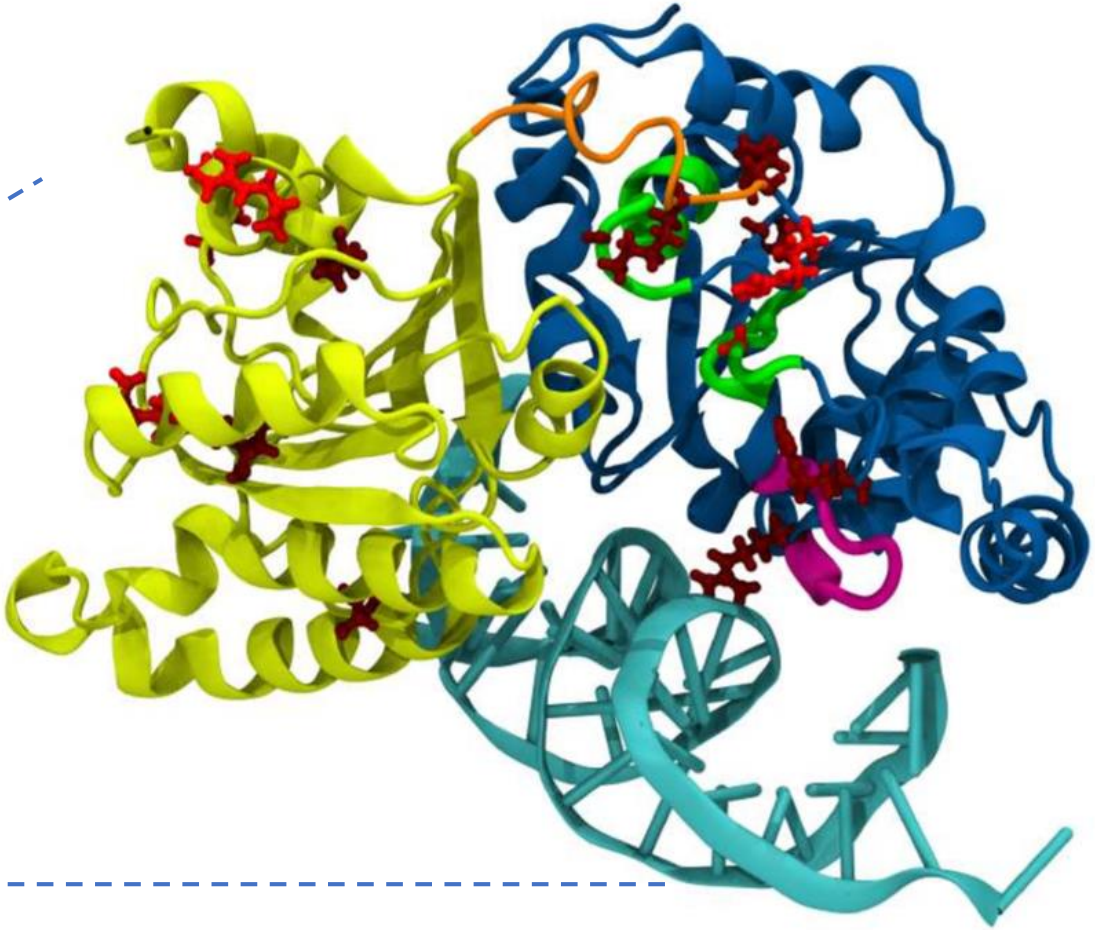
Schimke immuno-osseous dysplasia

genotype – phenotype correlations

Hinge region - orange.
ATP binding site motifs – green.
DNA sensor switch - magenta.
Residues affected by missense mutations – red.

C-terminal truncating mutations
(c.2244+5G>A, c.2207delT, c.2542G>T (p.Glu848*)
are associated with a relatively mild phenotype limited to dysmorphy, skeletal features and renal disease





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Schimke immuno-osseous dysplasia

management – treatment of manifestations

SKELETAL

- physical therapy (standard treatment of scoliosis and/or kyphosis)
- **hip replacement** as needed in older individuals;

RENAL

- a few affected individuals treated with cyclosporin A, tacrolimus, or corticosteroids have had a transient reduction in the rate of renal disease progression.
- **renal transplantation** as indicated using mild immunosuppressive therapy

ENDOCRINE

- standard **treatment for hypothyroidism**
- no affected individual treated with growth hormone supplementation has responded with improved growth

HEMATOLOGY/ IMMUNOLOGY

- granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor for neutropenia;
- **bone marrow transplantation** as indicated;
- **immunosuppressive therapy** for those with autoimmune manifestations;
- acyclovir for recurrent herpetic infections;
- imiquimod and cidofovir for severe disseminated cutaneous papilloma virus infections;
- **agents that improve blood flow or decrease coagulability** to treat transient ischemic attacks or strokes

Schimke immuno-osseous dysplasia

prevention

Prevention of secondary complications:

- Vaccinations according to the protocol for other T-cell immunodeficiencies (i.e., an avoidance of live attenuated vaccines) in individuals with severe early-onset disease;
- prophylaxis against Pneumocystis pneumonia;
- prophylactic *acyclovir* or *valacylovir* if recurrent oral herpetic infections or shingles occur.

Surveillance:

- Regular monitoring of the hips;
- annual monitoring of renal, immune, and hematologic status.

Agents/circumstances to avoid:

- Hypertension; heat, stress, and lack of sleep;
- live attenuated immunizations in those who are T-cell deficient;
- DNA damaging anti-cancer therapies.

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SRNS + short stature always consider Schimke

The next webinar….

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Primary therapy of SSNS

Lutz Weber, Cologne, Germany

21st May, 2019