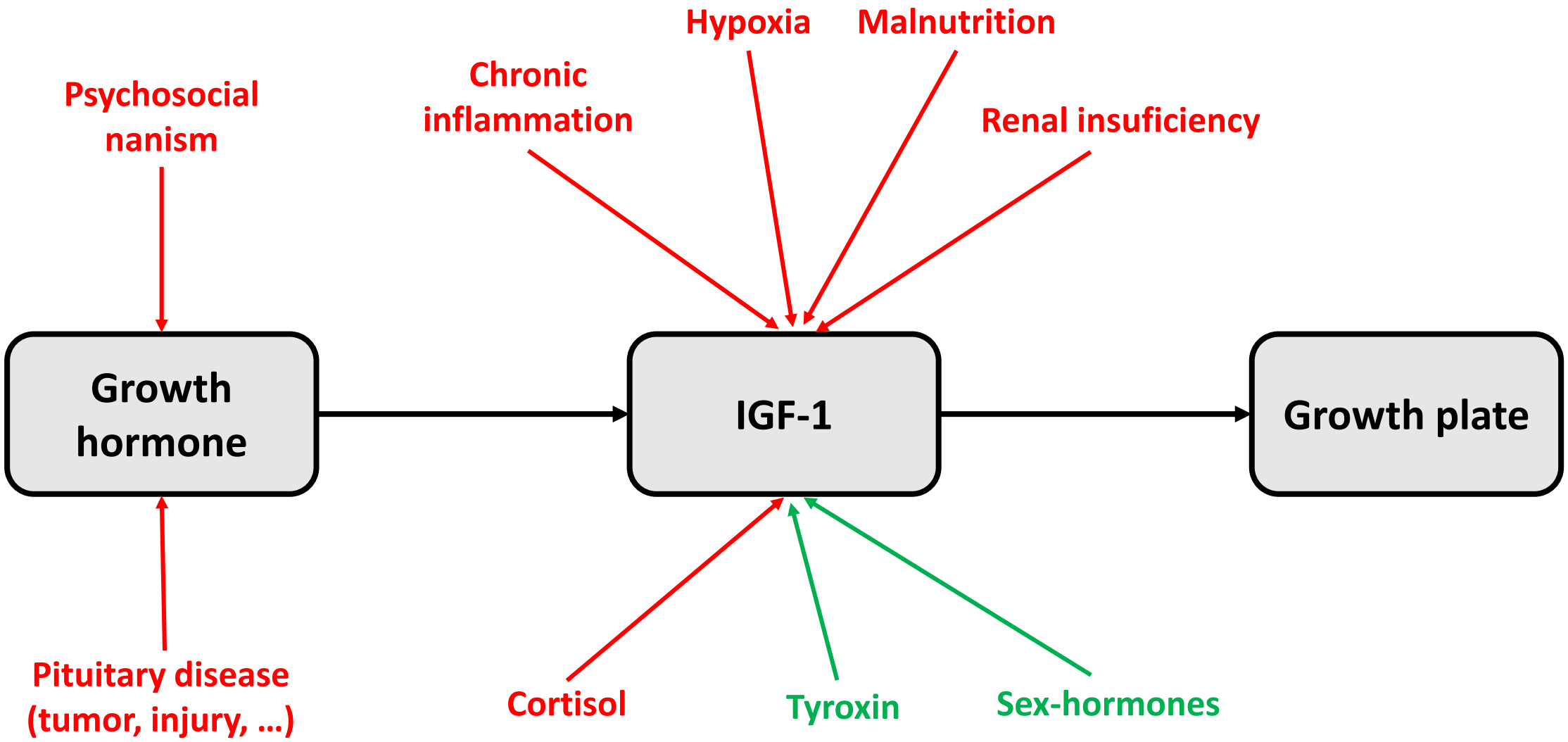
Genetic examination in children with familial short stature confirms the new paradigm of growth disorders pathogenesis

Lukáš Plachý, Petra Dušátková, Lenka Elblová, Dana Zemková, Zdeněk Šumník, Jan Lebl, Štěpánka Průhová

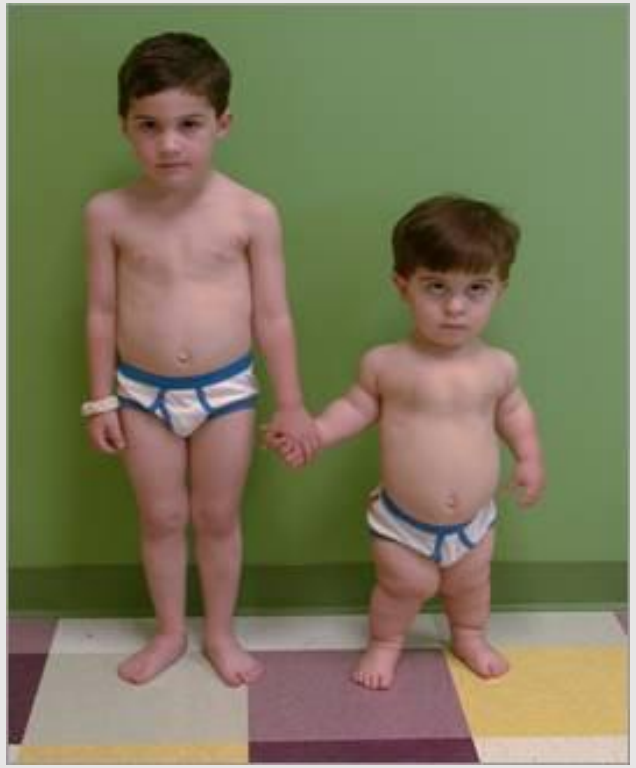
2nd Faculty of Medicine, Charles University in Prague and Motol University Hospital

Etiology of short stature



Lebl et al. Preclinical pediatrics

Bone dysplasia



Achondroplasia
(*FGFR3* gene)

Leri-Weil syndrome
(*SHOX* gene)

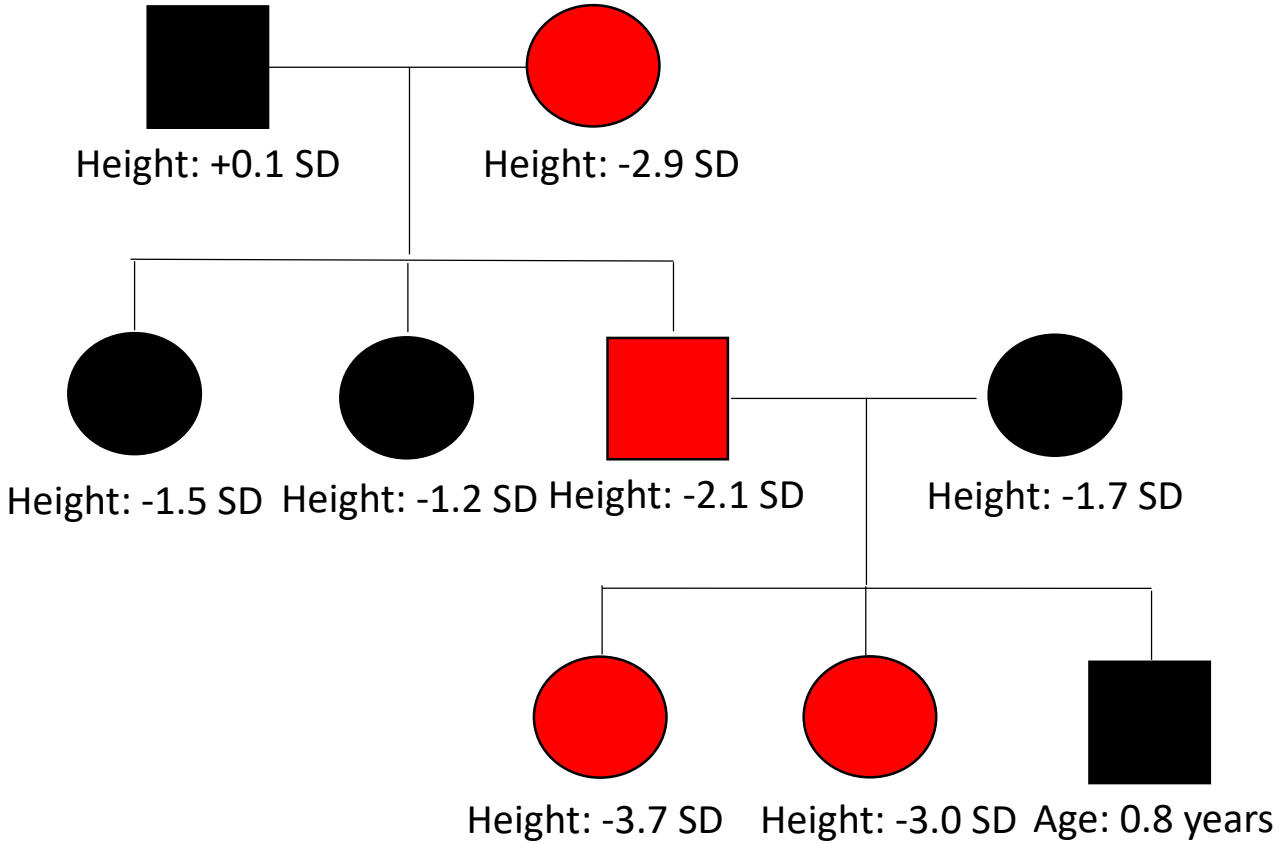
Spondyloepiphyseal dysplasia
(*COL2A1* gene)

→ **Growth plate**

Lebl et al. Pediatric endokrinology and diabetology, author‘s own archive

Familial short stature

Vertically transmitted growth disorder
(heigth <-2 SD in child and his/her shorter parent)



Familial short stature

Vertically transmitted growth disorder
(heigth <-2 SD in child and his/her shorter parent)

- **Heterogenous aetiology**
- **Polygenic inheritance**

vs. monogenic inheritance

Barstow et al. Am Fam Physician 2015

Aim

To elucidate monogenic growth disorders in children with familial short stature

Methods

Study cohort characteristics		
	Median	**Range**
Age	12 years	5 to 19
Height	-3.0 SD	-2.1 to -6.3
Birth weight	-2.1 SD	-0.6 to -3.0
Birth length	-2.6 SD	-2.0 to -4.2

Short stature on GH treatment (747)

→ **Secondary causes of short stature** (brain tumor, irradiation, …)

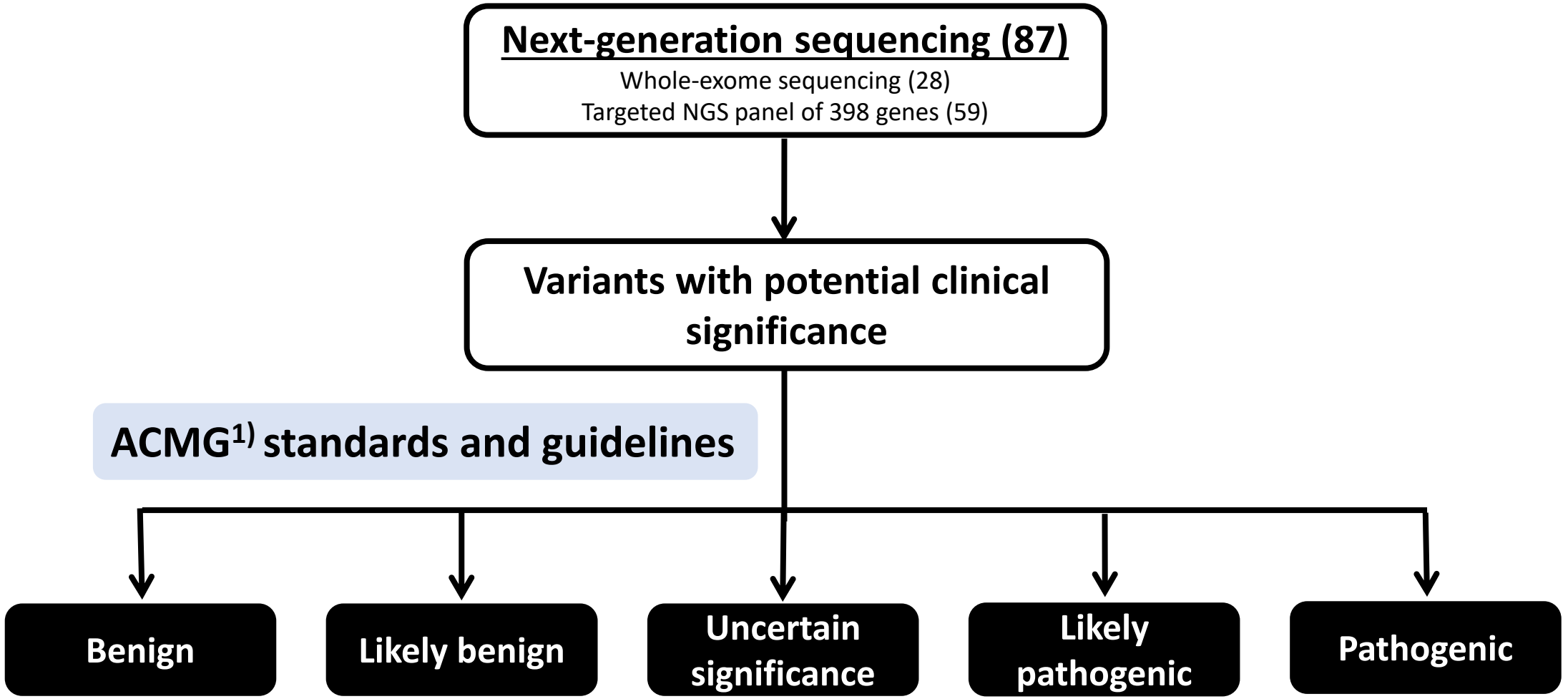
Familial short stature (126)
(Life-minimum heigth <-2 SD in child and shorter parent)

→ **Normal height in both parents**

← **Known genetic cause of short stature (9)**
- *SHOX* (5)
- *ACAN* (2)
- *PTPN11 (2)*

Next-generation sequencing (87)

→ **Refused genetic testing** (30)

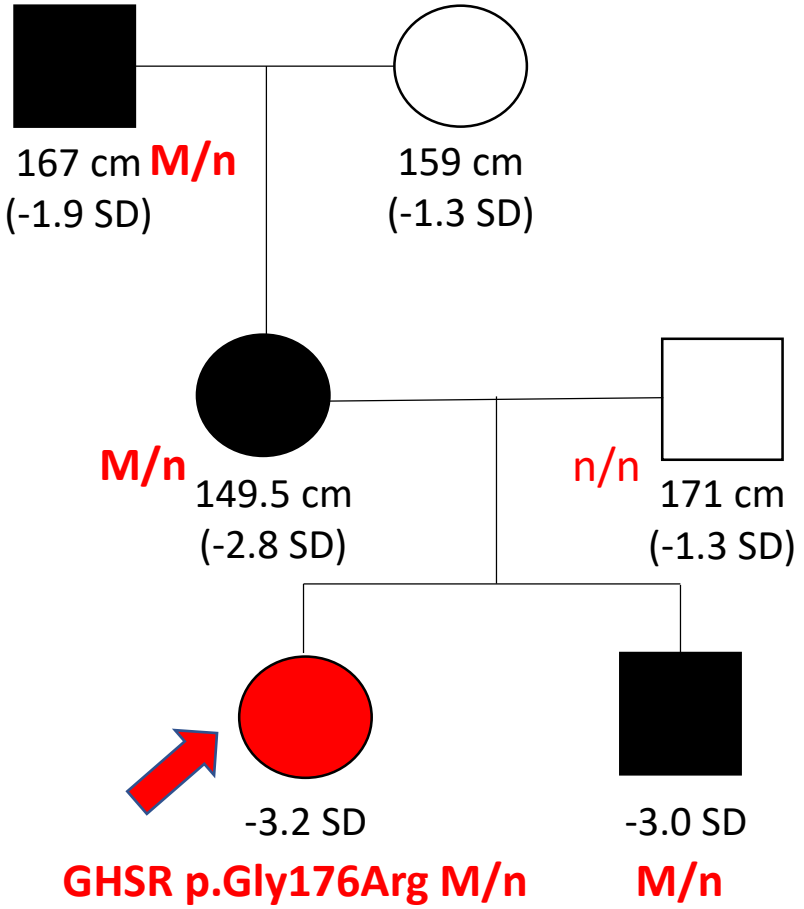


1) Richards et al. Genet Med. 2015 17(5): 405-24

Results evaluation

ACMG Standards and Guidelines

Jane



In silico tests:

- Mutation taster: Disease causing
- SIFT: Tolerated
- PolyPhen: Probably damaging
- CADD: 32 (damaging)

Population frequency:

- ExAC European frequency: 0

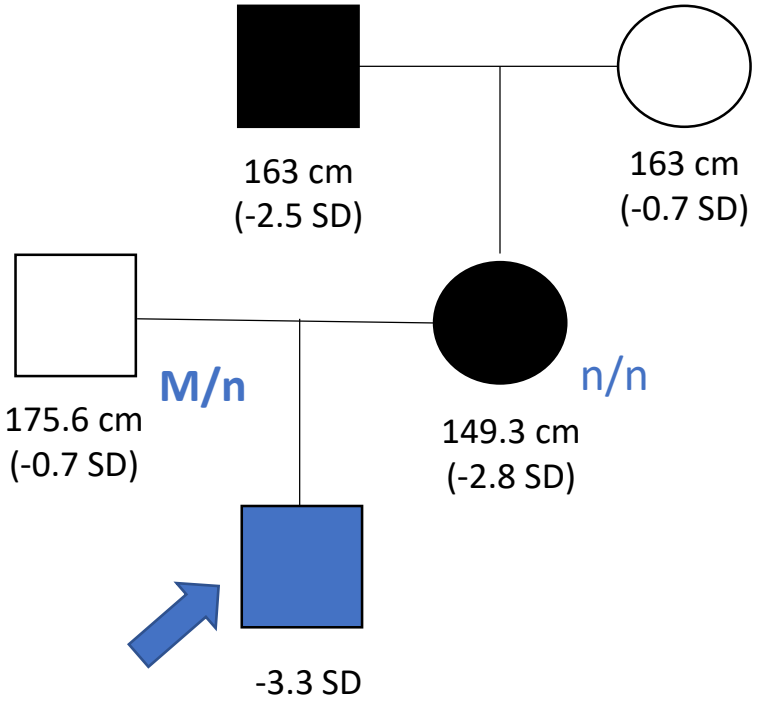
In silico tests:

- Mutation taster: Disease causing
- SIFT: Damaging
- PolyPhen: Probably damaging
- CADD: 34 (damaging)

Population frequency:

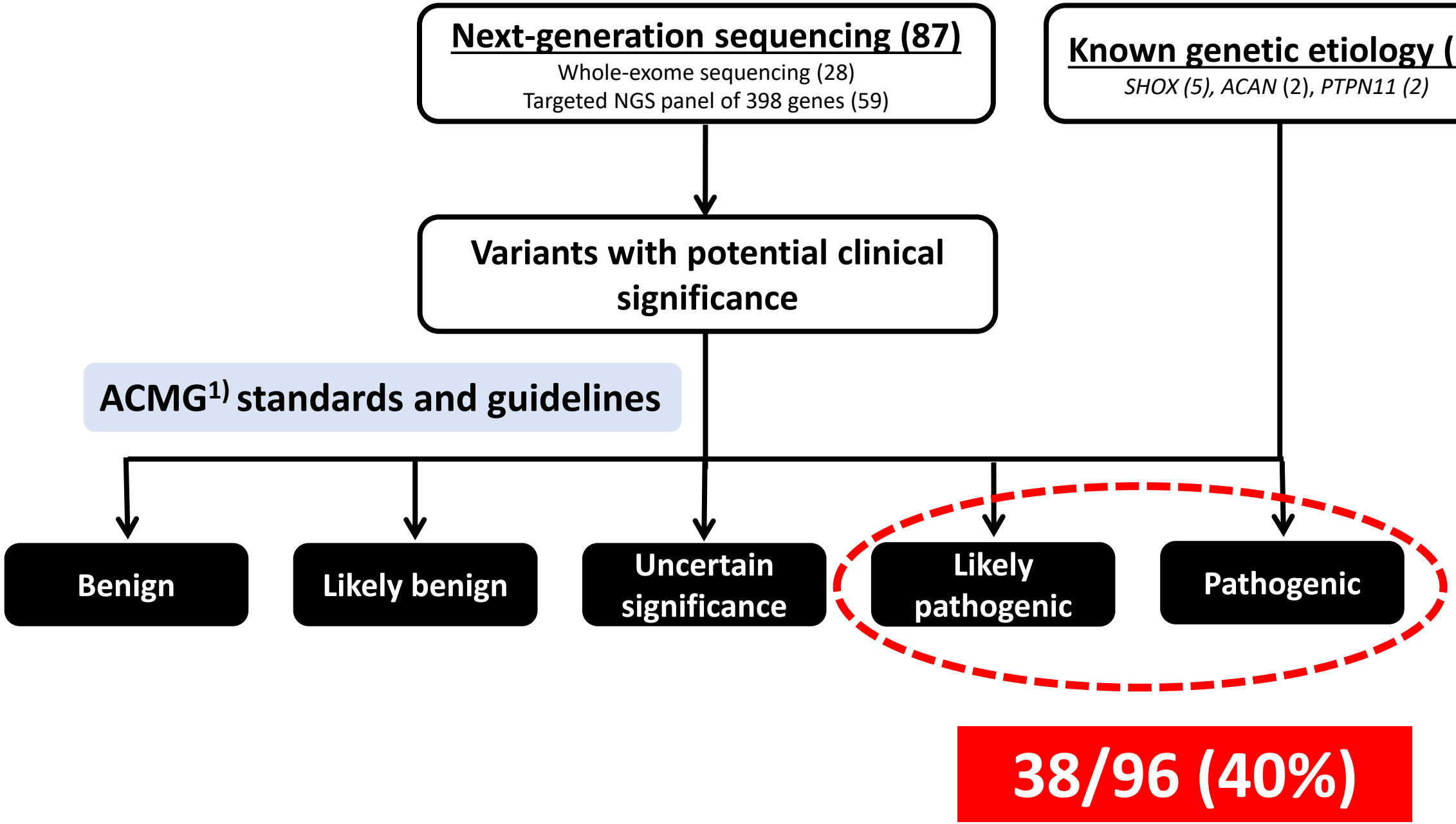
- ExAC European frequency: 0

John



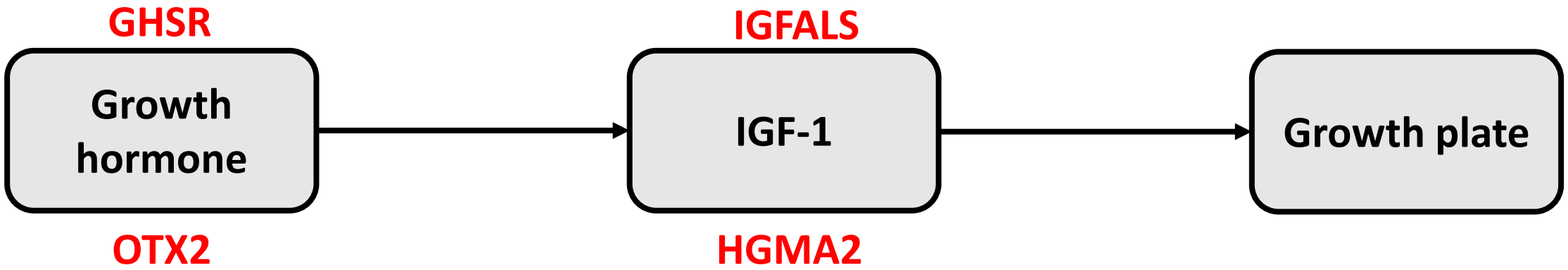
Pathogenic

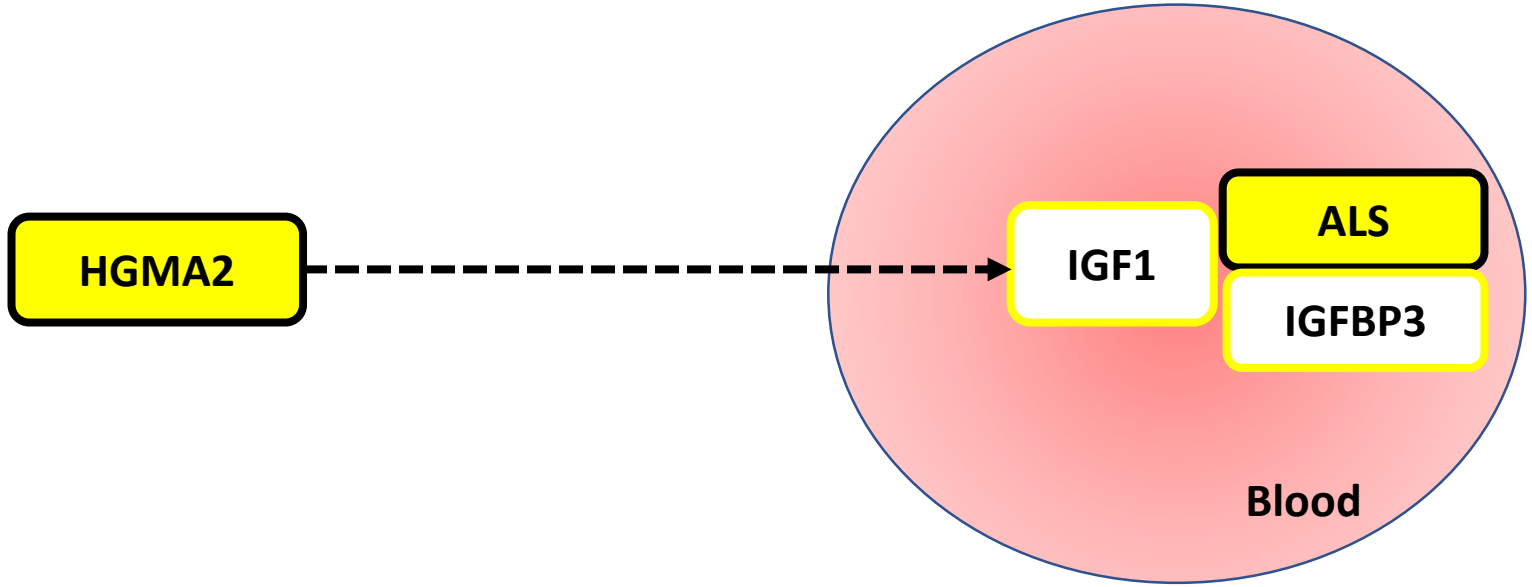
Benign



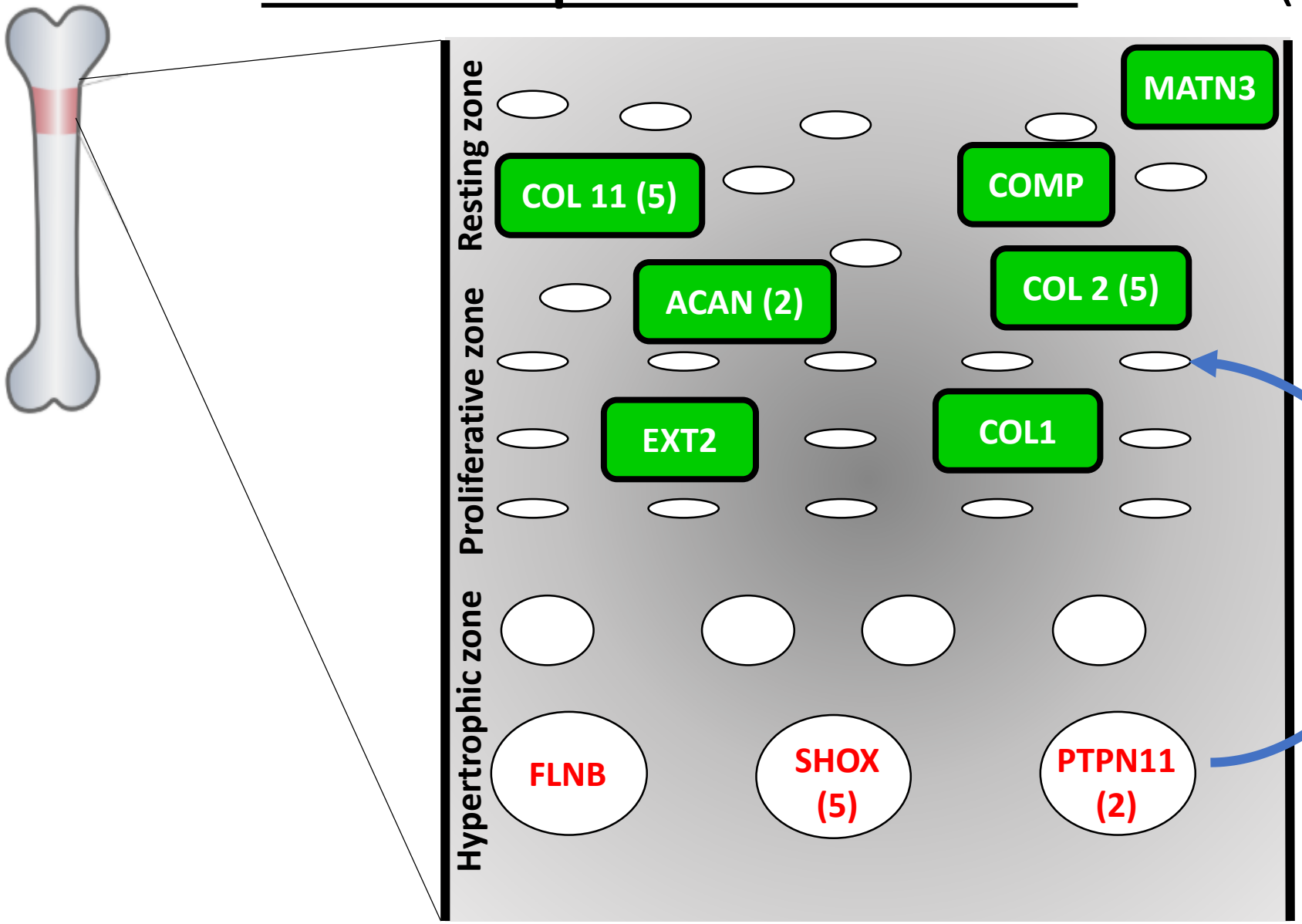
1) Richards et al. Genet Med. 2015 17(5): 405-24

GH-IGF1 axis 11% (4/38)





Growth plate disorders 82% (31/38)



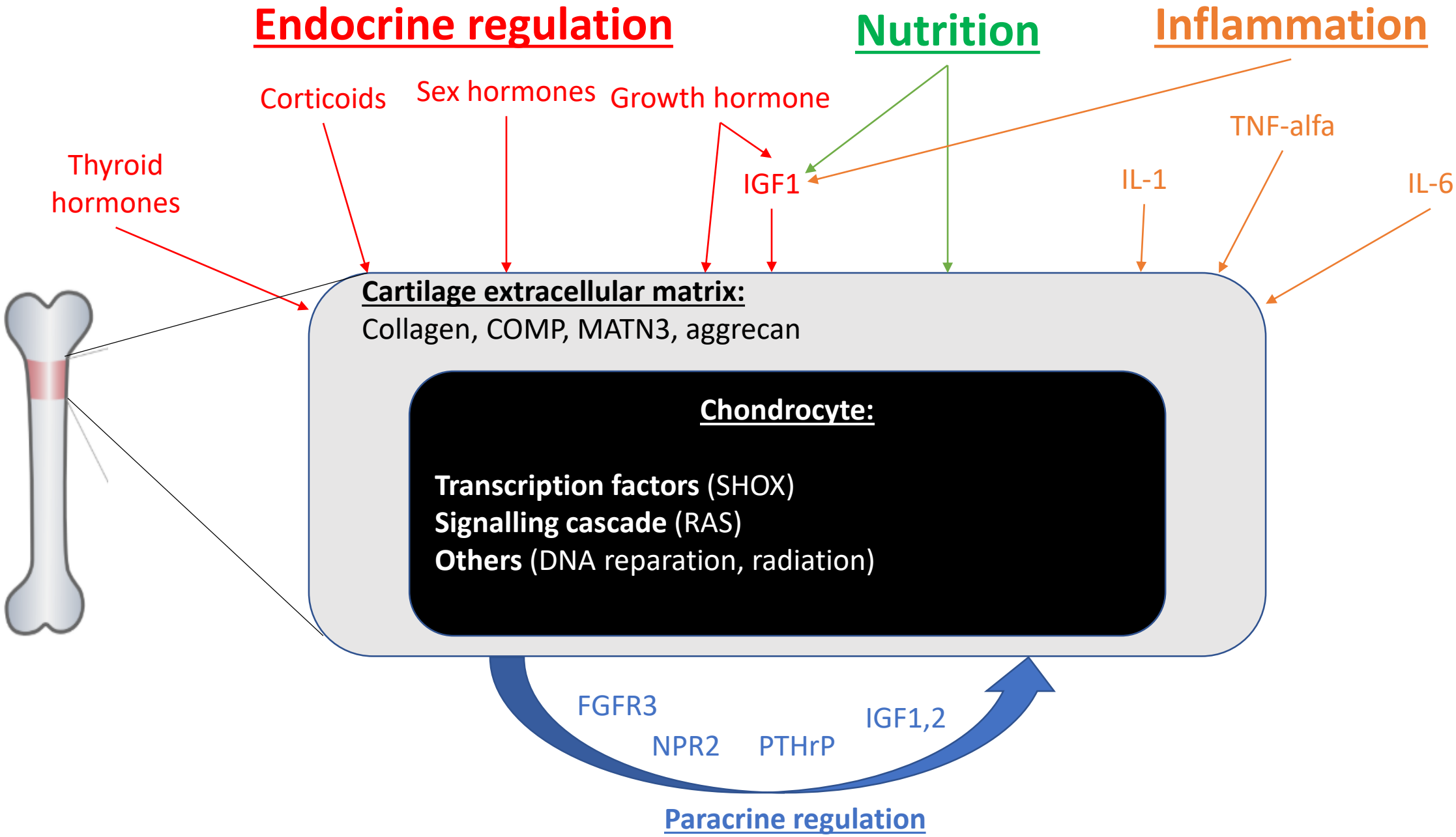
Extracellular matrix proteins (16/31)

FGFR3 (2)

Paracrine signaling (7/31)

NPR2 (5)

Intracellular processes (8/31)



Baron J et al. Nat Rev Endocrinol 2015

Homogenous groups of short children

COL2 (5)

COL11 (5)

ACAN (2)

NPR2 (5)

FGFR3 (2)

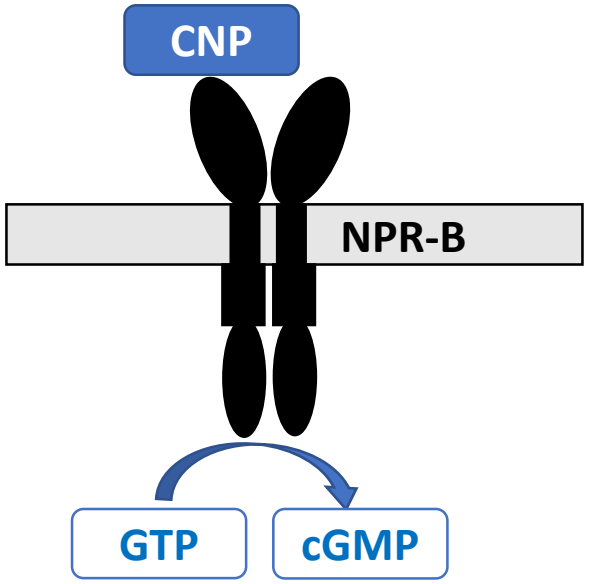
SHOX (5)

Aim

In children with heterozygous *NPR2* gene mutations:

1) To describe the phenotype
2) To evaluate GH treatment outcomes

Natriuretic peptide receptor type B (*NPR2* gene)



Cell proliferation
Cell differentiation
Extracellular matrix synthesis

Acromesomelic dysplasia, Maroteaux type

- Autosomal recessive
- Height <-5 SD
- Disproportionate
- Bone deformities
- Brachydactyly

Khan S et al. Molecular genetics of isolated acromesomelic dysplasia

Irfannulah et al., J Biochem Cell Biol. 2018. 102: 76-86

Natriuretic peptide receptor type B (*NPR2* gene)

Acromesomelic dysplasia, Maroteaux type

Khan S et al. Molecular genetics of isolated acromesomelic dysplasia

- Autosomal recessive
- Height <-5 SD
- Disproportionate
- Bone deformities
- Brachydactyly

Heterozygous *NPR2* mutations

- Autosomal dominant
- Height -1.5 to -4.3 SD
- (Dis)proportionate
- Bone dysplasia

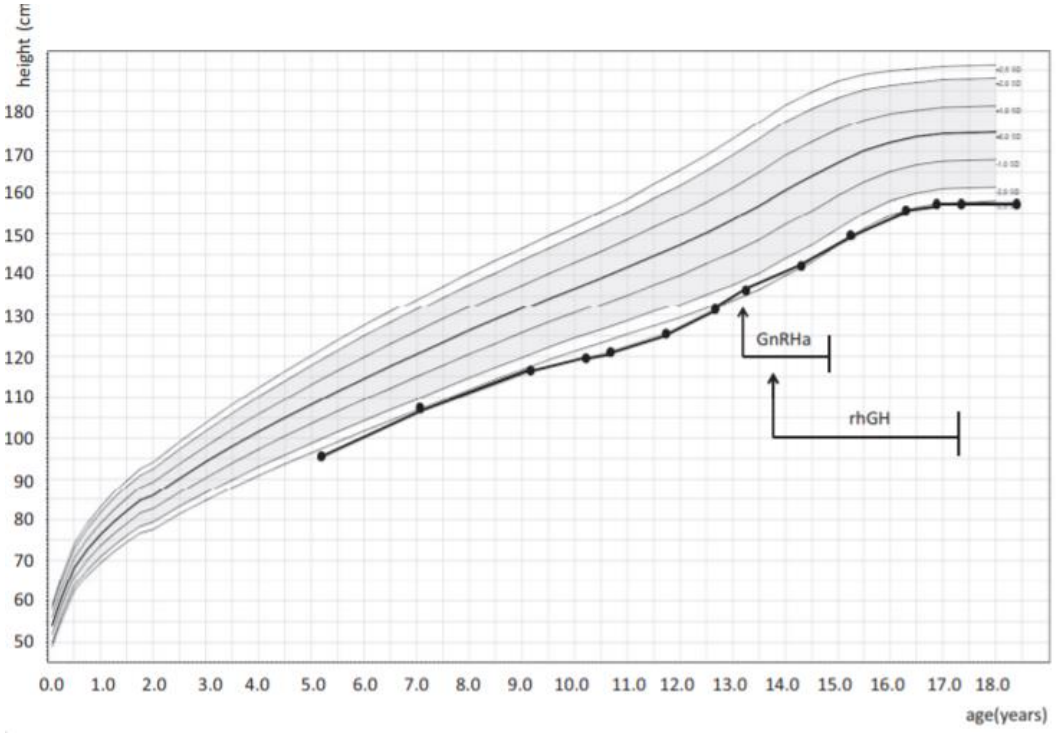
2-6 % children with ISS[1,2,3]

3 % LWS children with SHOX-D excluded[4]

1) Vasques et al., JCEM. 2013. 98(10): 1636-44
2) Wang et al. Hum Mutat. 2015. 36(4): 471-81
3) Amano et al. JCEM. 2014. 99(4): 713-8
4) Hisado-Oliva et al. JCEM. 2015. 100(8): 1133-42

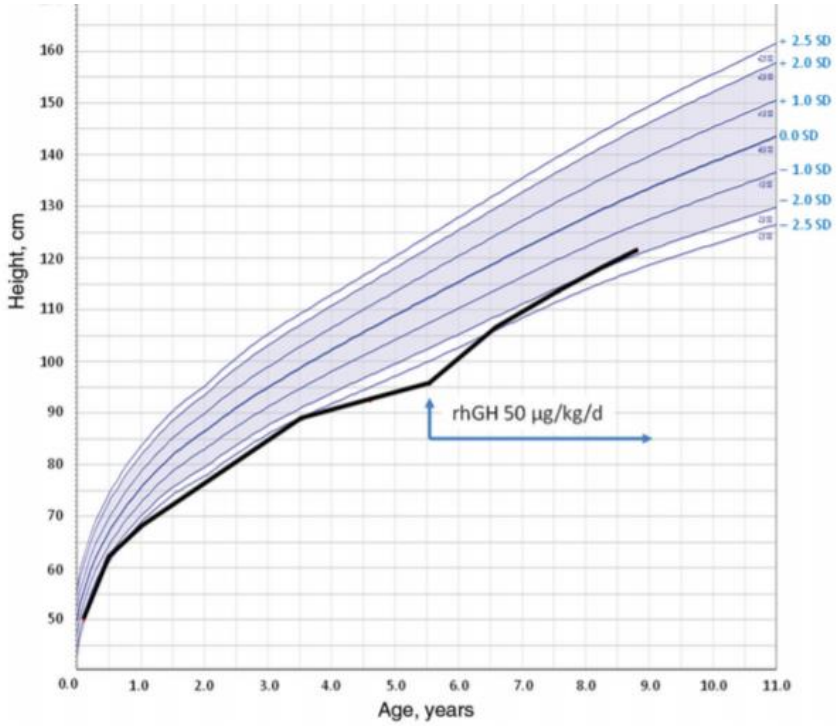
Heterozygous *NPR2* mutations: GH treatment

No significant heigth SDS gain



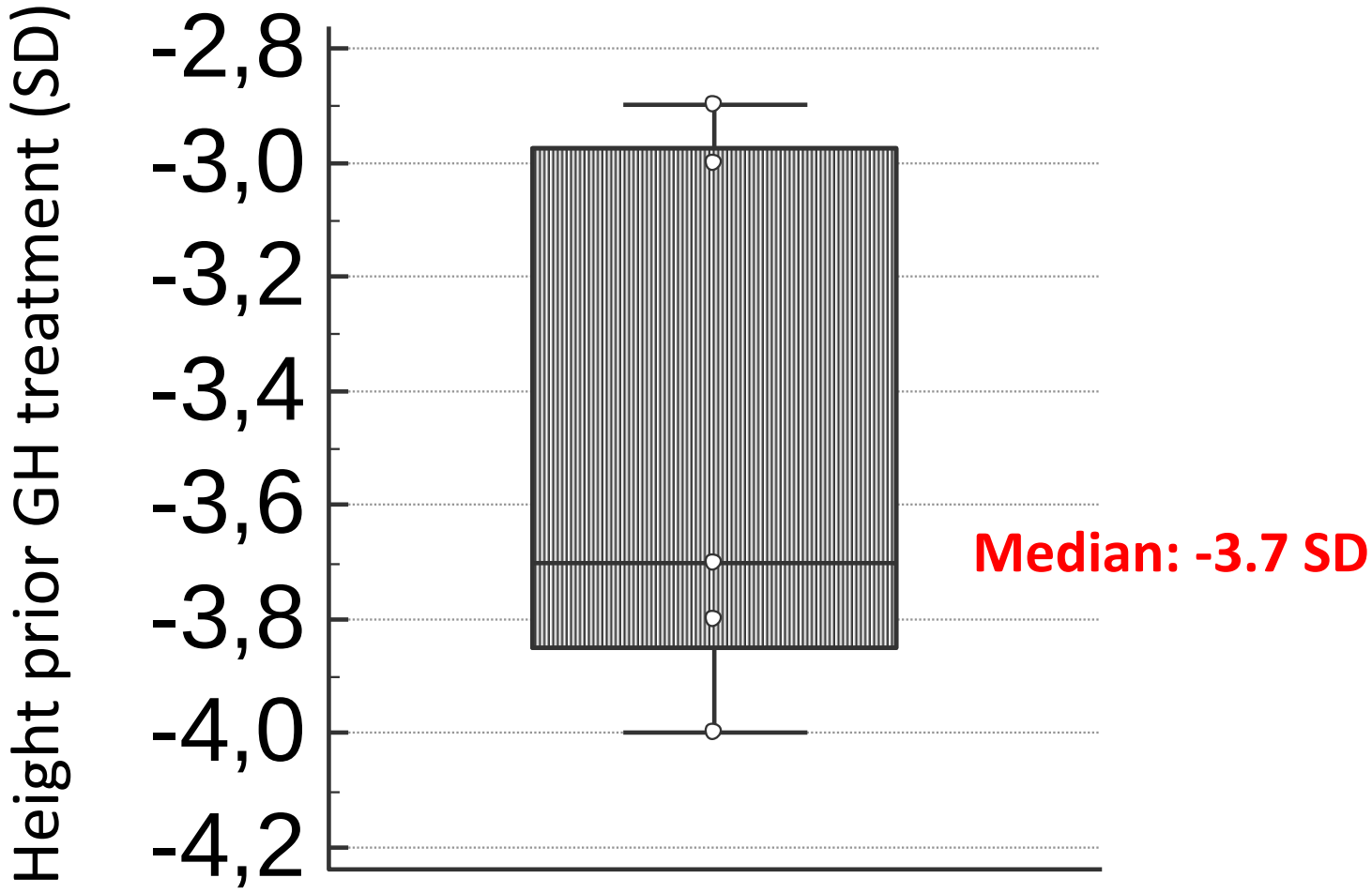
Vasques et al. JCEM. 2013 98(10): 1636-44

Good response to the treatment

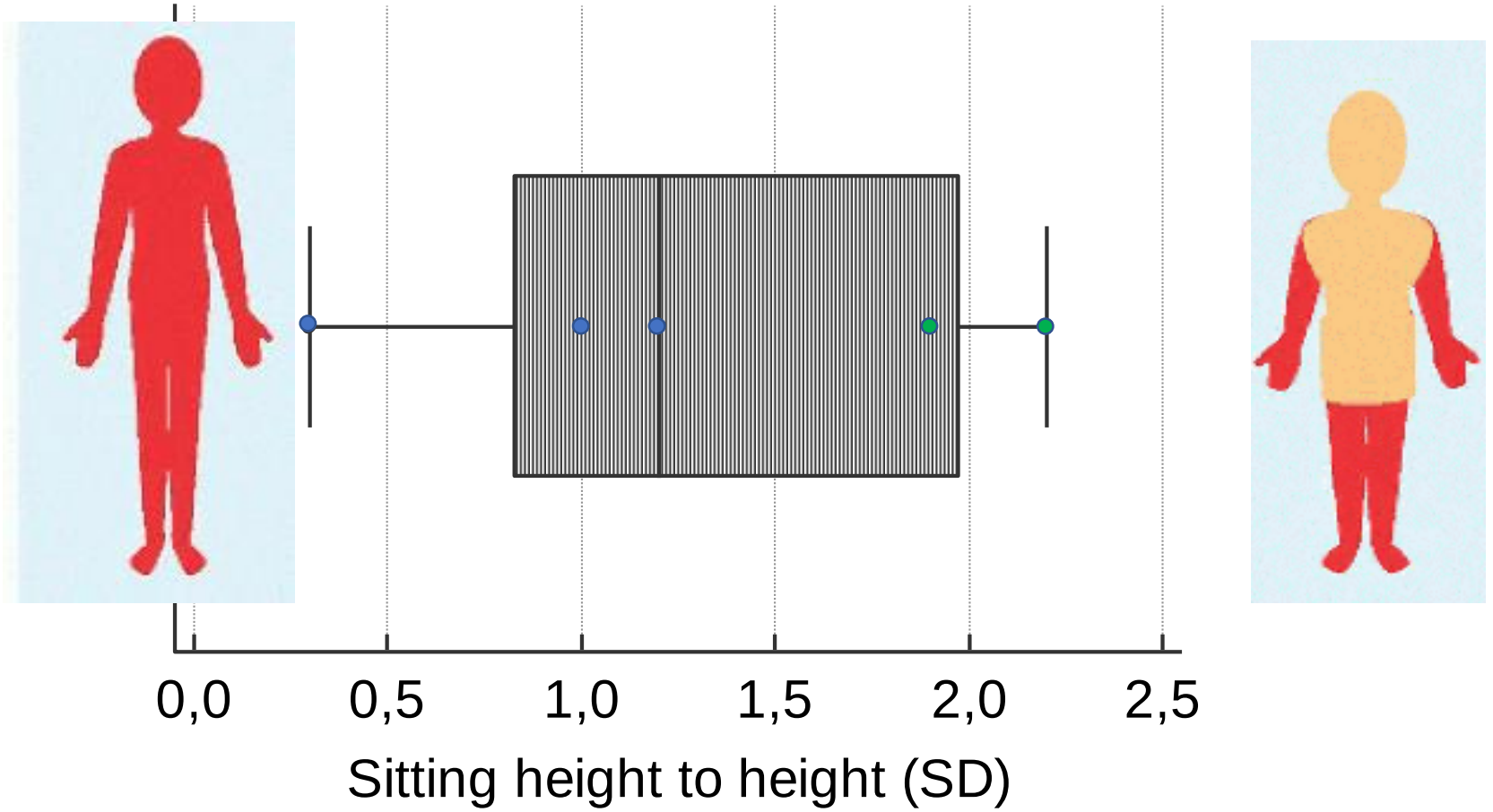


Vasques et al. JPEM. 2017. 30(1) 111-6

Children with heterozygous *NPR2* mutations have severe short stature

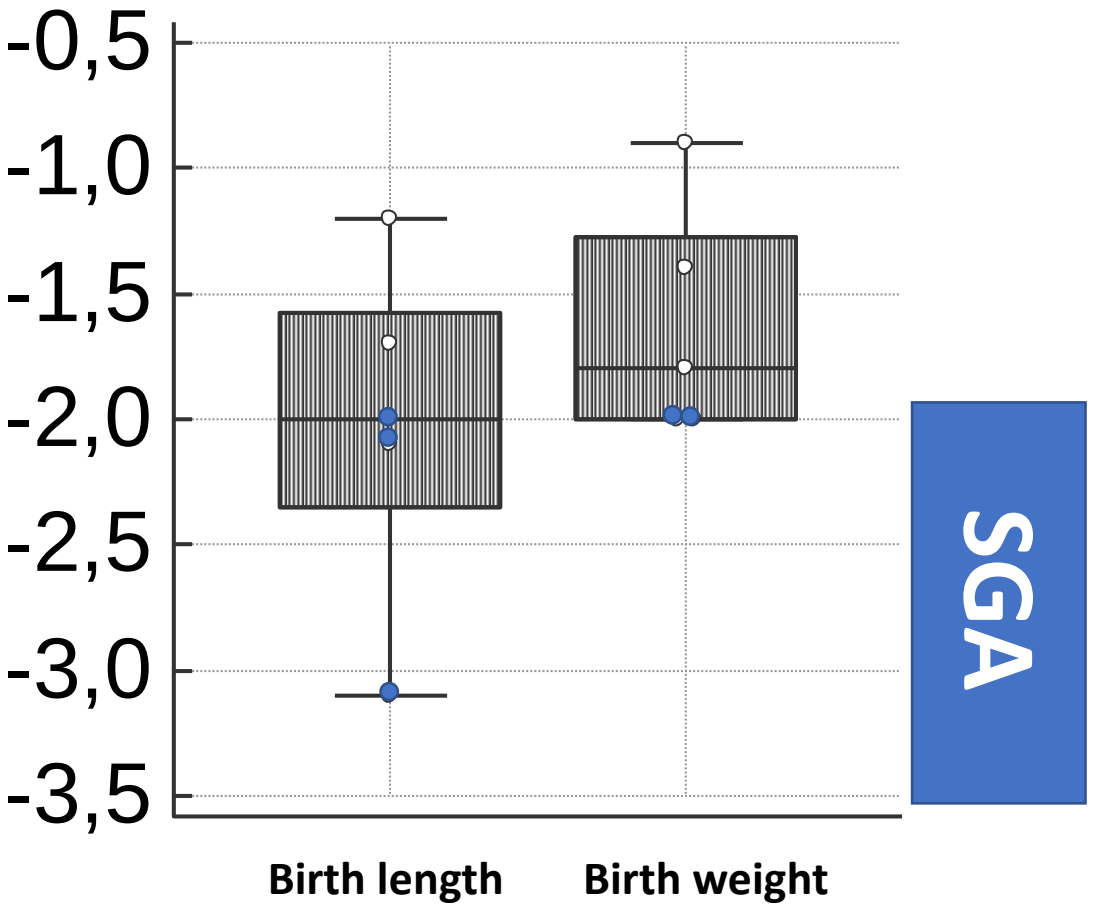


Children with heterozygous *NPR2* gene mutations have variable body proportionality



Proportionate vs. disproportionate short limbed short stature

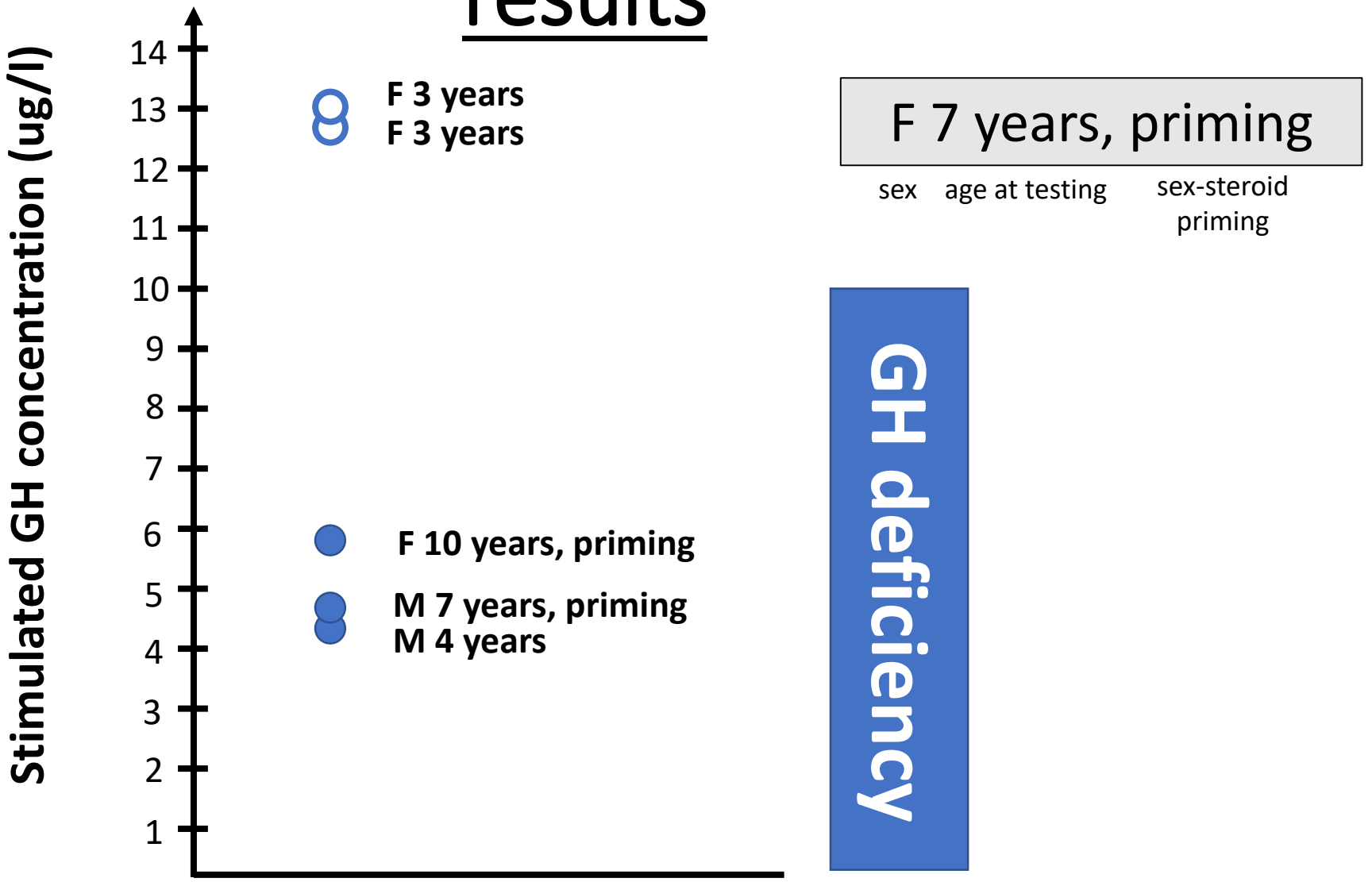
Birth parameters are affected in children with heterozygous *NPR2* gene mutations



Birth length more affected than birth weight

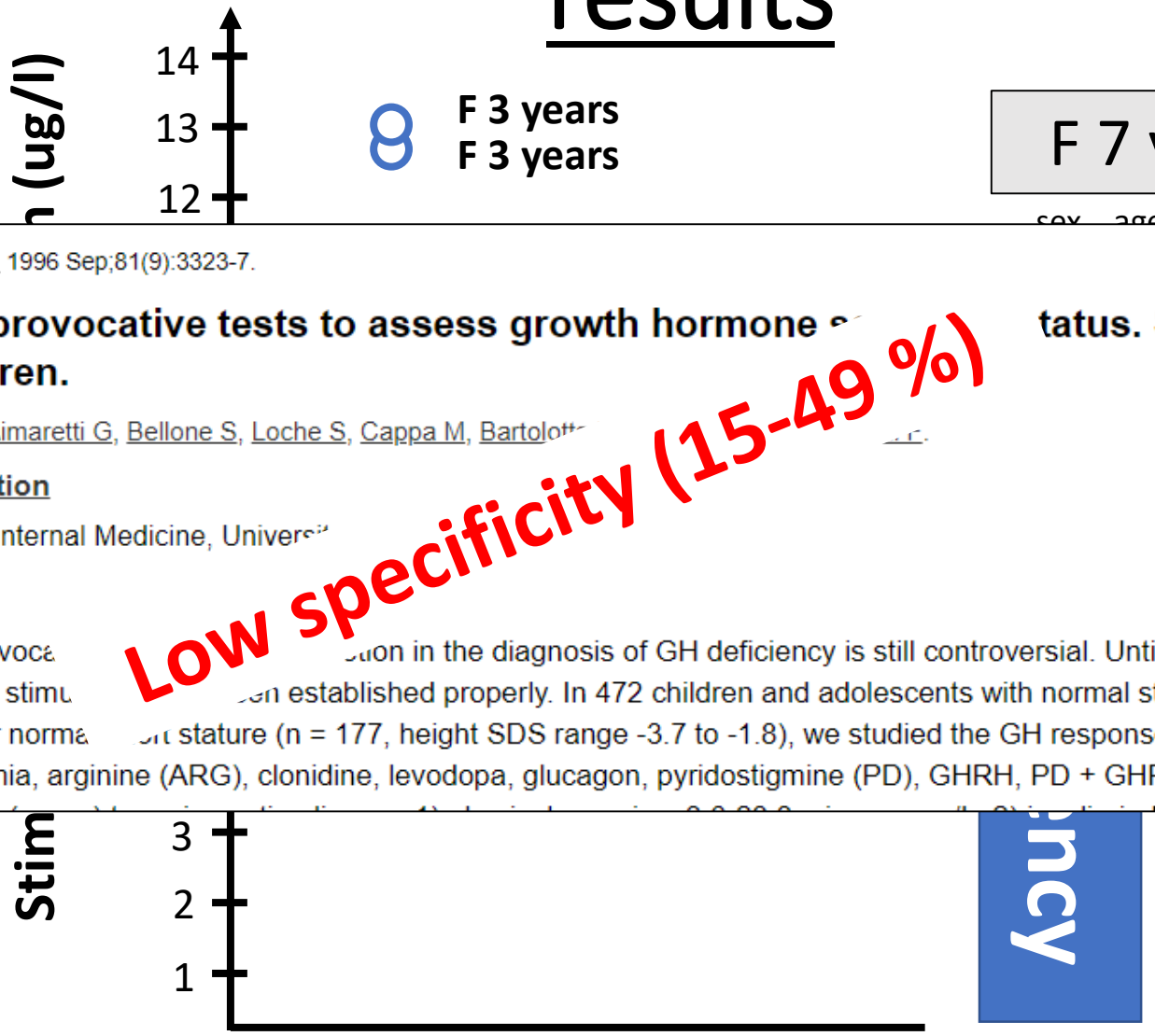
3/5 children were born SGA

GH deficiency testing might have false positive results



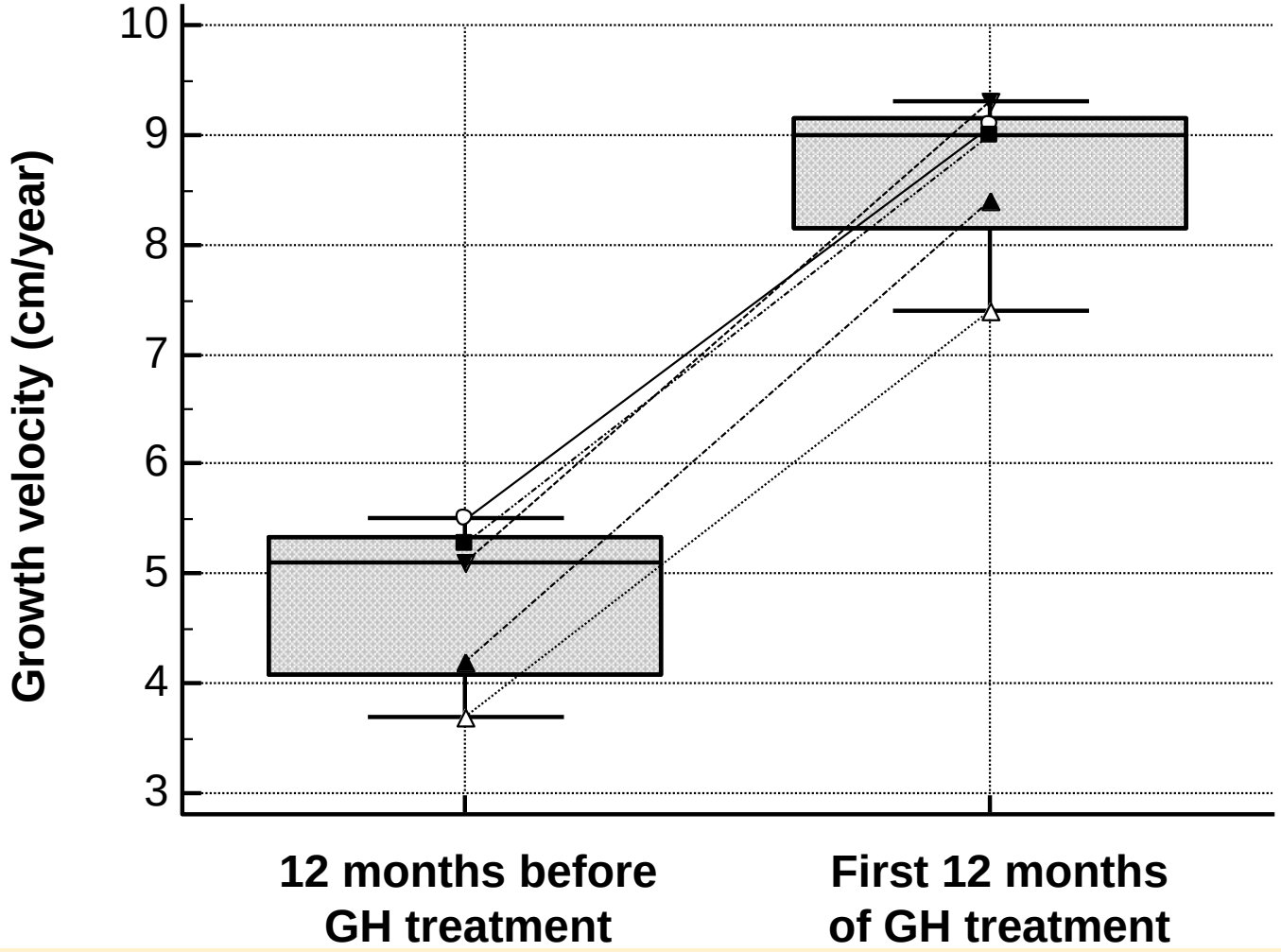
3/5 children were (apparently incorrectly) diagnosed with GHD

GH deficiency testing might have false positive results



3/5 children were (apparently incorrectly) diagnosed with GHD

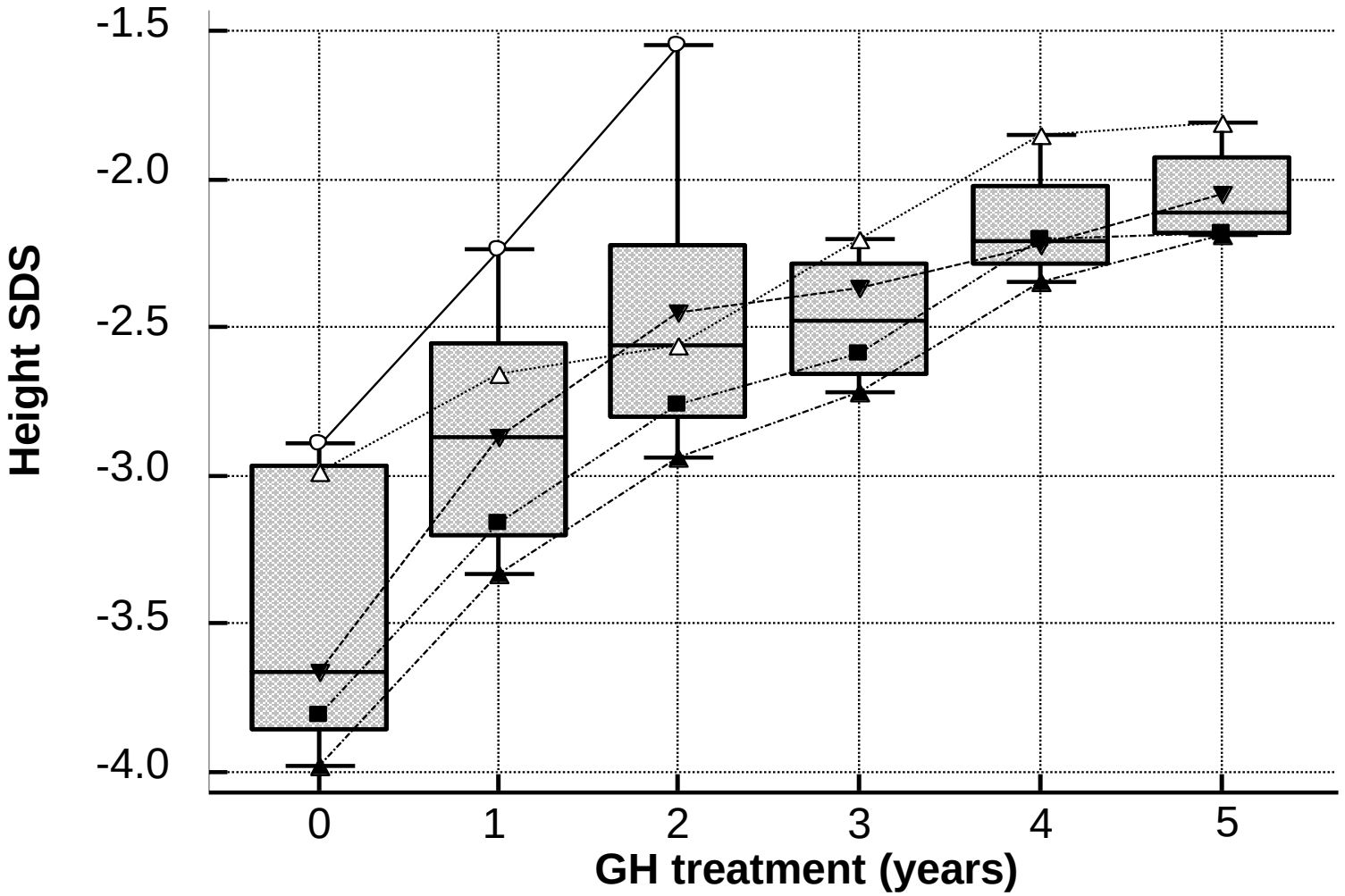
Good response to GH treatment in children with heterozygous *NPR2* gene mutations



Growth velocity increased from 5.1 cm/year to 9.0 cm/year (p<0.0001*)

*Paired sample T-test

Good response to GH treatment in children with heterozygous *NPR2* gene mutations



Height improved from -3.7 SD to -2.1 SD after 5 years of therapy ($p<0.001^{*}$)

*ANOVA repeated measures analysis of variants

1) **Monogenic causes** of familial short stature are frequent
2) The etiology is heterogeneous, **growth plate disorders** play a key role
3) In the **homogeneous groups of children** with the same genetic etiology of short stature, detailed phenotype including GH treatment outcomes may be evaluated

Supported by Ministry of Health, Czech Republic, grant number 16-31211A and by research project of Grant Agency of Charles University of Prague, GAUK 976718.