Contribution of *GHR* and *IGFALS* mutations to growth hormone resistance
Identification of new variants and impact on the inheritance pattern

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Background

Bi-allelic *GHR* mutations are classically responsible for Laron syndrome, a severe growth hormone (GH) insensitivity syndrome. A few *GHR* missense mutations have also been implicated in mild dominant GH resistance or idiopathic short stature.

IGFALS mutations are responsible for recessive or semi-dominant short stature linked to a partial GH insensitivity. The moderate growth delay contrasts with extremely low IGF-I levels.

Objective

- to assess the contribution of *GHR* and *IGFALS* mutations to severe and mild non-syndromic GH insensitivity
- to study the correlation between the genotype and resistance severity

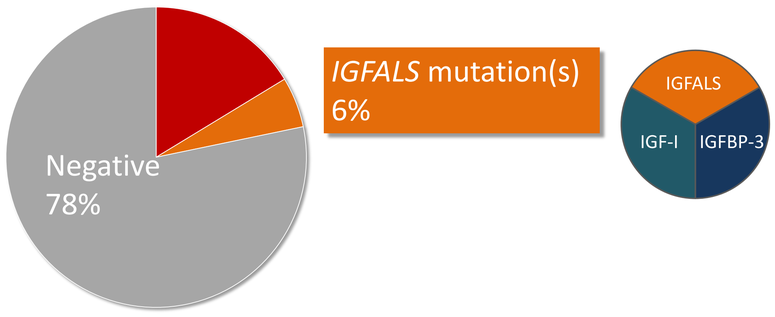
Method

All *GHR* and *IGFALS* coding regions and intronic boundaries were analyzed by Sanger sequencing in 92 independent patients with normal or high GH secretion test (>20mUI/L) associated with low IGF-I levels (<-2SD) and/or short stature.

1 *GHR* and *IGFALS* contribution

92 independent probands with GH insensitivity

GHR mutation(s) 16%



IGFALS mutation(s) 6%

2 Different inheritance/severity patterns

	GHR (n=15)		IGFALS (n=5)
	Recessive (n=11)	Dominant (n=4)	Recessive/semi-dominant
	Severe GH insensitivity Laron syndrome	Partial GH insensitivity	Partial GH insensitivity
	Normal		Normal or subnormal height
Stature at diagnosis, median [range]:	-6 SD [-9;-3]	-3 SD [-4;-2.5]	-2.5 SD [-4;-2.3]
GH provocation test, mean [range]:	150 mUI/L [42;278]	22 mUI/L [16;29]	44 mUI/L [19;58]

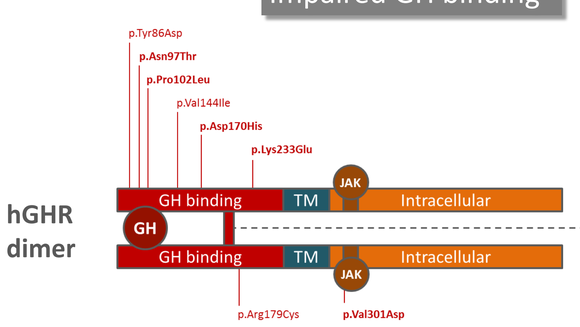
3 *GHR* mutations expected consequences

hGHR full length

Missense mutations:

Impaired GH binding

Recessive
Severe GH insensitivity

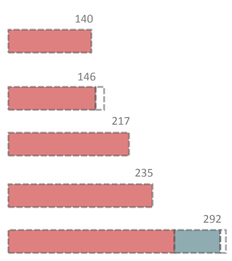


Impaired signal transduction

Dominant
Partial GH insensitivity

Truncating mutations:

p.(Leu141*)
p.(Val147Aspfs*18)
p.(Arg217*)
p.(Arg235*)
p.(Ile293Leufs*4)



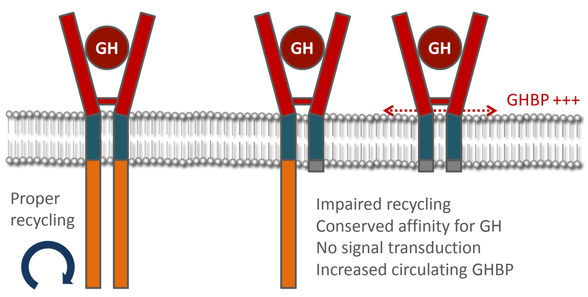
mRNA-decay: no protein

p.Arg292Serfs*7

No mRNA-decay:
dominant negative effect

In bold: newly described mutations

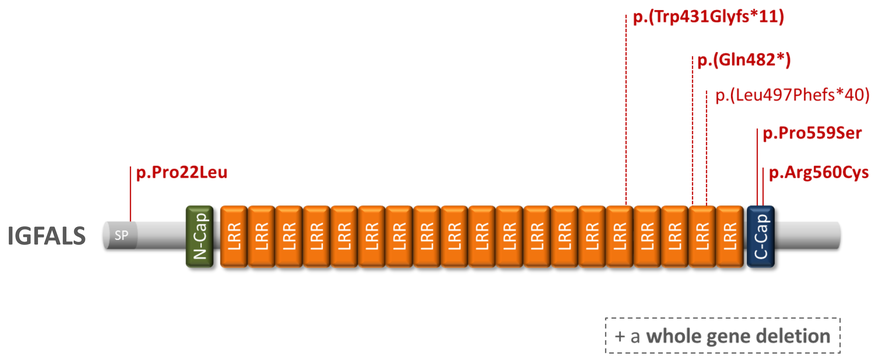
4 *GHR* mutation with dominant negative effect



Functional (minority)

Non-functional (majority)

5 *IGFALS* mutations



In bold: newly described mutations

Conclusion

In a large cohort of patients with GH resistance (n=92), we identified molecular defects in *GHR* or *IGFALS* in 22% of the independent probands.

Noteworthy, 2 neighboring *GHR* mutations, p.(Ile293Leufs*4) and p.Arg292Serfs*7 were respectively responsible for a recessive and a dominant form of GH resistance, underlining the impact of a complex alternative splicing pattern on nonsense-mediated mRNA decay.

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Growth: Mechanisms

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