Contribution of GHR and IGFALS mutations to growth hormone resistance
Identification of new variants and impact of 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 (>20mIU/L) associated with low IGF-I levels (<25D) and/or short stature.

1 GHR and IGFALS contribution

92 independent probands with GH insensitivity

GHR mutation(s) 16%
IGFALS mutation(s) 6%

IGFALS (IGF1-SF)
GHR

GHR (n=15)
Recessive (n=11)
Dominant (n=4)

Severe GH insensitivity
Laron syndrome
Partial GH insensitivity
Normal

Partial GH sensitivity
Normal or subnormal height

Stature at diagnosis, median [range]: -6 SD [-9; -3]
150 mUI/L [42;278]
22 mUI/L [16;29]

GH provocation test, mean [range]: -3 SD [-4; -2.5]

2 Different inheritance/severity patterns

IGFALS (n=5)
Recessive/semi-dominant

Normal or subnormal height

GHR full length

mRNA-decay: no protein

Truncating mutations:
p.(Leu141*)
p.(Val147Glufs*18)
p.(Arg217*)
p.(Arg235*)
p.(Ile293Leufs*4)
p.Arg292Serfs*7

In bold: newly described mutations

3 GHR mutations expected consequences

Missense mutations:
- Impaired GH binding
- Impaired signal transduction

In bold: newly described mutations

4 GHR mutation with dominant negative effect

5 IGFALS 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.

In bold: newly described mutations