A Rare Form of Insulin Resistance with Pseudoacromegaly

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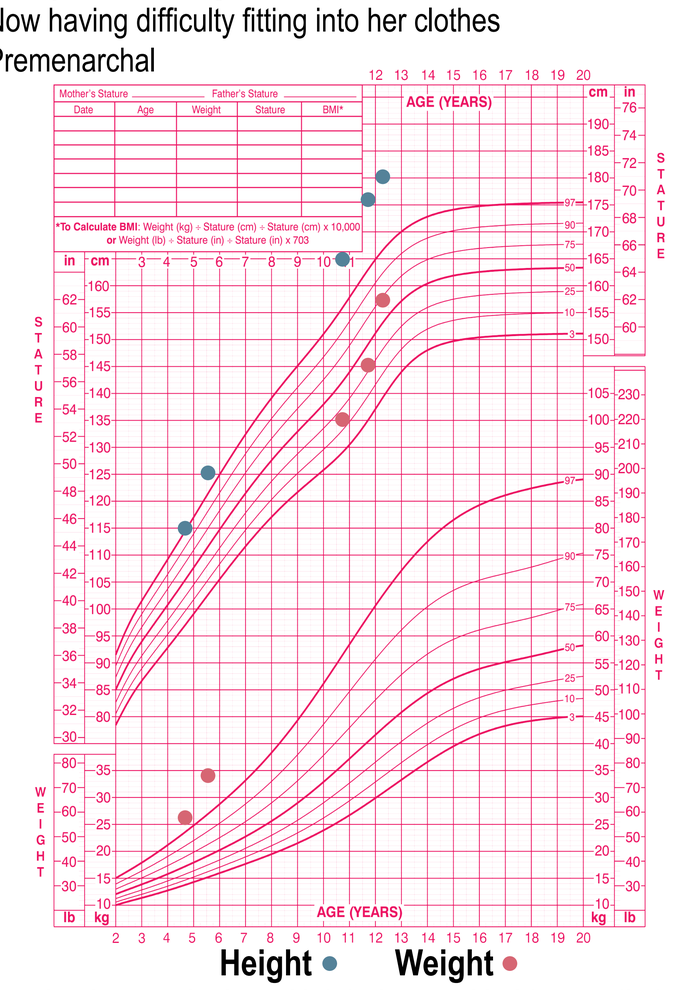
Background

Insulin resistance occurs in a variety of common endocrine disorders including obesity, type 2 diabetes, polycystic ovarian syndrome, and metabolic syndrome. Additionally, rare syndromes exist that result in extreme insulin resistance. These conditions help contribute to our knowledge of the mechanisms of insulin signaling and resistance.

Case

12-year-old girl referred to pediatric endocrine clinic for evaluation of new onset diabetes. She was found to have an elevated random glucose in her pediatrician's office 3 months before. Subsequently she was started on metformin and lisinopril prior to the referral.

- Birth weight: 6lb 7oz (2920 g)
- Obese since kindergarten age
- Extreme weight gain in the last 2 years
- Nearly continuous growth spurt
- Now having difficulty fitting into her clothes
- Premenarchal



The patient's growth chart. Height is noted in blue, well above the 97th percentile. Weight is shown in red, and is extremely elevated. Weight is out of proportion to height.

Photos

Patient photographs: A) Whole body B) Facial features C) Axilla D) Left Hand E) Left Foot F) Profile

Genetics

Low Pass (10x) Genome

↓

No Significant Copy Number Gain/Loss

Whole Exome Sequencing

McDonnell Genome Institute	Cole-Wambach Lab
SIFT/PolyPhen/Condel	SIFT/PolyPhen2/LRT MutTaster/GERP/PhyloP

Autosomal Dominant
1108 Shared Variants
11 Candidates*
5 Damaging**

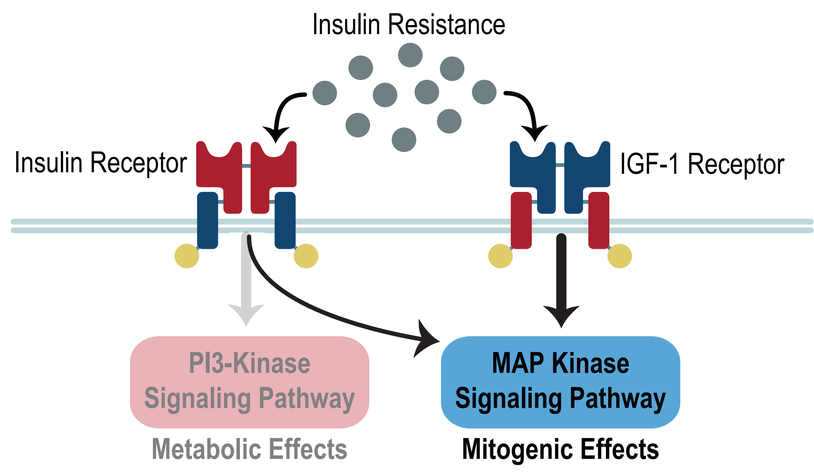
No DeNovo Mutations

Autosomal Recessive Analysis: No Candidate Variants

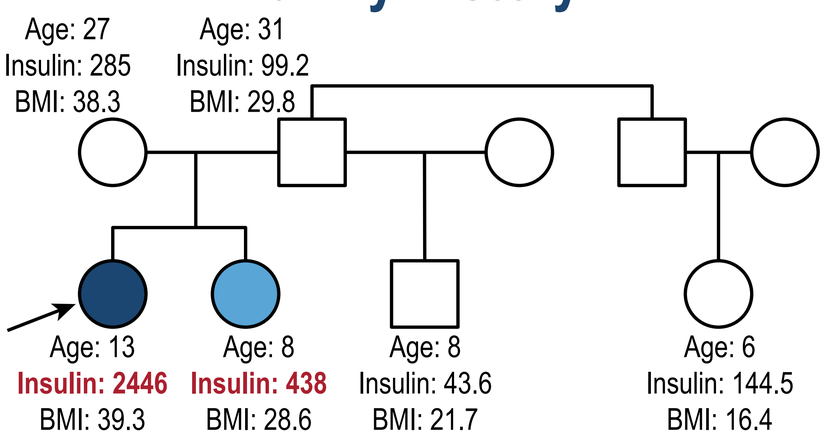
*Molecular Signatures Database (Broad Institute): Insulin

**Combined Annotation Dependent Depletion(CADD) Score >14

Model



Family History



Radiology

Bone Age x-ray was consistent with 14 yr. This provides a predicted adult height of 72 inches (1.83 m, +3.23 SDS).

Laboratory Assessments

HbA1c 6.6% (49 mmol/mol)

Cholesterol 141 mg/dL (3.64 mmol/L)
Triglycerides 189 mg/dL (2.13 mmol/L)
HDL 29 mg/dL (0.75 mmol/L)
LDL 74 mg/dL (1.91 mmol/L)

AST 31 U/L (0.52 ukat/L)
ALT 72 U/L (1.20 ukat/L)

Chromosomal Microarray: No significant duplications or deletions.

DHEA-S 99 mcg/dL (2.67 umol/L)
Total Testosterone 66 ng/dL (2.29 nmol/L)
Free Testosterone 16 pg/mL (55.5 pmol/L)
17-OH Progesterone 69 ng/dL (2.09 (nmol/L)
Estradiol 29 pg/mL (106.46 pmol/L)
LH 7.7 mIU/mL (IU/L)
FSH 5.4 mIU/mL (IU/L)

Glucose 186 mg/dL (10.32 mmol/L)
IGF-1 331 ng/mL (43.6 nmol/L)
IGFBP-3 5.3 ug/mL (16038.2 nmol/L)
Insulin 1279 uIU/mL (8882.66 pmol/L)

Leptin 19.0 ng/mL (1.19 mmol/L)

2 Hour Oral Glucose Tolerance Test

Time (minutes)	0	30	60	90	120
Glucose (mg/dL)	85	142	127	128	120
Insulin (mIU/mL)	27.7*	752*	799	488	390
Growth Hormone (ng/mL)	0.55	0.24	0.1	<0.1	0.49

The subject was brought in for a 75g oral glucose tolerance test. Glucose, insulin, and growth hormone were measured at serial time points. This test demonstrated severe insulin resistance, however she appropriately suppressed growth hormone at 90 minutes. *Sample hemolyzed, insulin may be falsely lowered.

Discussion

- We are reporting on an extremely rare form of severe insulin resistance.
- Most insulin resistance syndromes are associated with short stature.
- This syndrome is unique as it is associated with overgrowth.
- Likely represents downstream defect in insulin signaling:
  - **Impaired metabolic effects.**
  - **Enhanced mitogenic effects.**
- Genetic and functional studies may reveal a causative gene(s).
- Potential to teach us about novel aspects of insulin signaling.

Author Disclosures

The authors have no relevant financial disclosures or conflicts of interest.

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