

**Supplementary Materials for Digenic Variants in the FGF21 Signaling Pathway Associated with Severe Insulin Resistance and Pseudoacromegaly.**

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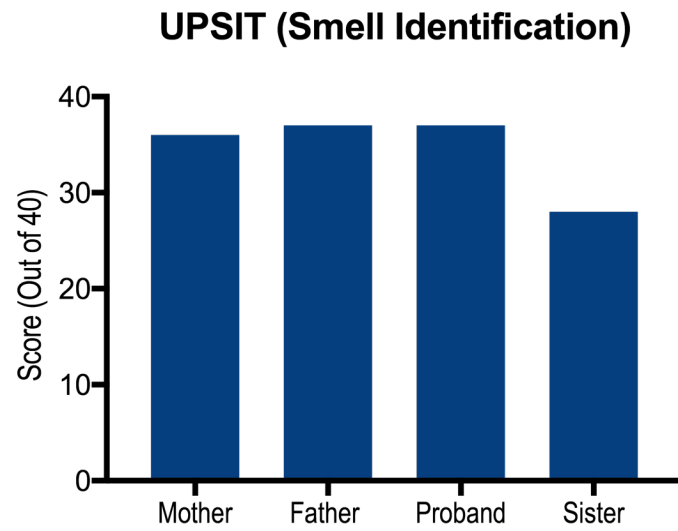
**Supplementary Figure 1. Additional photographs of proband and family.**

Additional photographs taken demonstrate central adiposity with relative sparing of fat from the extremities (A-C). Photographs taken with the proband's mother (D) and father (E).



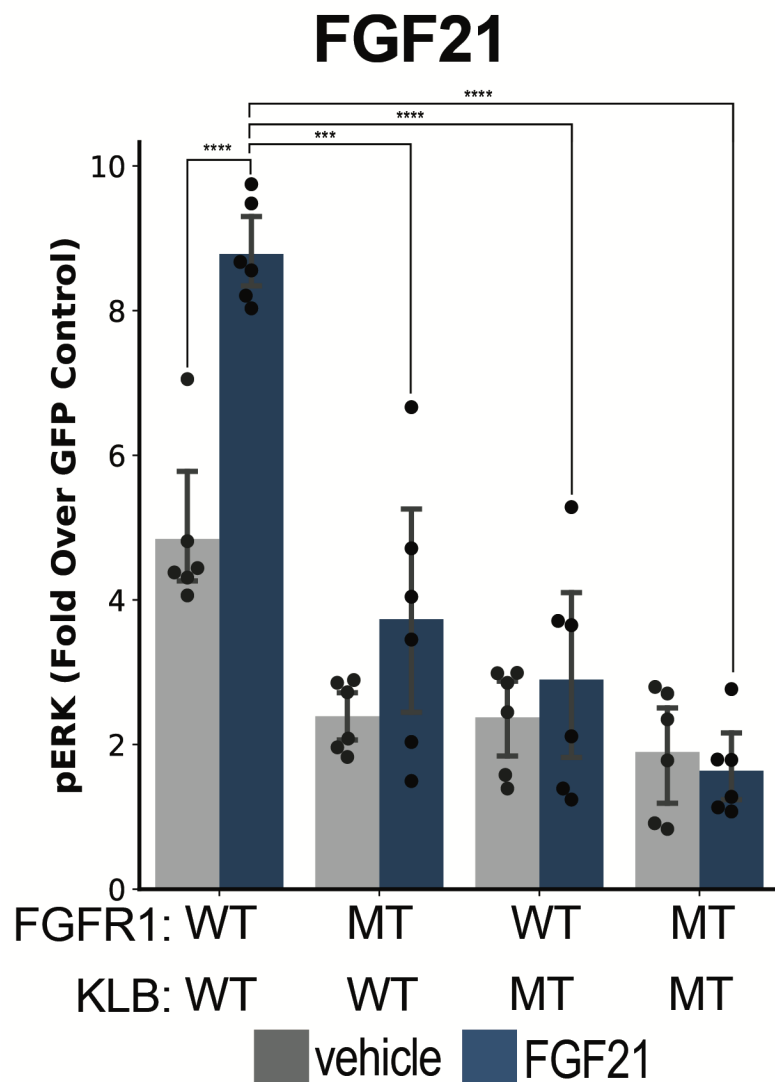
**Supplementary Figure 2. Bone age x-ray.**

Bone age x-ray is closest to 14 years demonstrating near closure of the epiphyses.



**Supplementary Figure 3: Smell identification testing.**

The affected relatives demonstrated normal smell identification.



**Supplementary Figure 4. ERK phosphorylation in HeLa Cells.**

HeLa cells were transfected with either wild type (WT) or mutant (MT) FGFR1 / KLB alone and in combination. A GFP expressing plasmid was used as a negative control. Transfected cells were treated with 100 nM recombinant human FGF21 for 10 min. PhosphoERK (pERK) was measured via ELISA. The results are demonstrated as fold over GFP control.



Gene	Amino Acid Change	gnomAD AF	gnomAD Latino	gnomAD African	CADD Score	Inheritance
<i>ELK1</i>	G144S	0.0027	0.0012	0.0232	0.293	Father
<i>GRB10</i>	P36L	0.0063	0.0035	0.0652	9.552	Father
<i>FASN</i>	V2005A	0.0155	0.0079	0.0714	18.79	Father
<i>FBP2</i>	R158C	0.00004	0.00003	0.00008	14.47	Father
<i>PRKAG3</i>	L153V	0.0118	0.0066	0.1212	9.892	Father
<i>TSC1</i>	K536R	0.0239	0.1742	0.0020	18.82	Mother
<i>CACNA1B</i>	G177R	0.00004	0.0002	0	23.9	Mother
<i>CACNA1C</i>	T1795M	0.0011	0.0008	0.0119	16.31	Mother
<i>FGFR1</i>	V102I	0.00039	0.00045	0	16.81	Mother
<i>KLB</i>	S9Y	0.0020	0.0012	0.02	23.5	Father

**Supplementary Table 1. Candidate genes from research exome.**

Candidate genes based on in silico analysis.

## Full Plasmid Sequences

Sequence of FGFR1-P2A-KLB Plasmids used in this study.

>FL6731 (FGFR1 WT; KLB WT)

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