Supplemental Material

Short Stature is Progressive in Patients with Heterozygous *NPR2* Mutations

Short running title: *NPR2* mutations with progressive short stature

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Supplemental Material Legends:

Supplemental Table 1: In silico analysis of *NPR2* mutations.

Table with summary of *in silico* analysis done for two *NPR2* mutations. For the scaled C-score for CADD, a score equal to or greater than 10 indicates that these are predicted to be the 10% most deleterious substitutions in human genome, greater than or equal to 20 indicates that these are predicted to be the 1% most deleterious in the human genome. This continues to increase logarithmically with scoring and percentages. For SIFT as noted the range is from 0 to 1. The amino acid substitution is predicted damaging if the score is <= 0.05, and tolerated if the score is > 0.05. CADD = Complete Annotation Dependent Depletion. PolyPhen-2 = Polymorphism Phenotyping v2.

Supplemental Table 2: Bone age results for AMDM subjects III-1 and III-4.

* = BA read by outside endocrinologist. BA = bone age. GH = growth hormone. SD = standard deviation.

Supplemental Table 3: Growth factors for AMDM subjects III-1 and III-4.

IGF-1 = Insulin like growth factor 1. IGFBP-3 = Insulin like growth binding protein 3. GH = growth hormone.

Supplemental Figure 1: Hand and foot x-ray of child with AMDM.

Hand and foot radiographs of subject III-1 with AMDM. Panel A shows the left foot with early fusion of the physes of the phalanges and metatarsals, shortening of the second through fourth metatarsals, broadening of the ends of the proximal phalanges. And hallux valgus deformity of the first toe. Panel B shows the left hand with shortening of the metacarpals, mild broadening of the phalanges, and early fusion of the most of the physes of the phalanges and metacarpals. AMDM = acromesomelic dysplasia Maroteaux type.

Supplemental Figure 2: Growth charts for siblings in family A.

Growth charts of wild type, heterozygous, and compound heterozygous *NPR2* mutations in children from family A, demonstrating dose effect of *NPR2* mutations on height. Growth chart for subject III-6 in family A not included because he was an infant. Panel A = subject III-3. Panel B = subject III-2. Panel C = subject III-5. Panel D = subject III-1. Panel E = subject III-4. Panel D depicts treatments used for subject III-1 including the duration of GH and Lupron treatments. Panel E depicts GH treatment used for subject III-4. Black solid line = GH treatment. Black arrow line = Lupron treatment. GH = growth hormone.

Supplemental Table 1.

In silico analysis of *NPR2* mutations					
Mutation	**p.P93S**		**p.R989L**		
	Score	**Comment**	**Score**	**Comment**	**Reference range**
CADD Scaled C-score	24.3	See legend	34	See legend	See legend
SIFT	0.23	Tolerated	0.01	Damaging	0.0 - 1.0
PolyPhen-2 (HumDiv)	0.993	Probably damaging	1.000	Probably damaging	0.00 - 1.00
PolyPhen-2 (HumVar)	0.815	Possibly damaging	0.995	Probably damaging	0.00 - 1.00
MutationTaster	X	Prediction disease causing	X	Prediction disease causing	X

Supplemental Table 2.

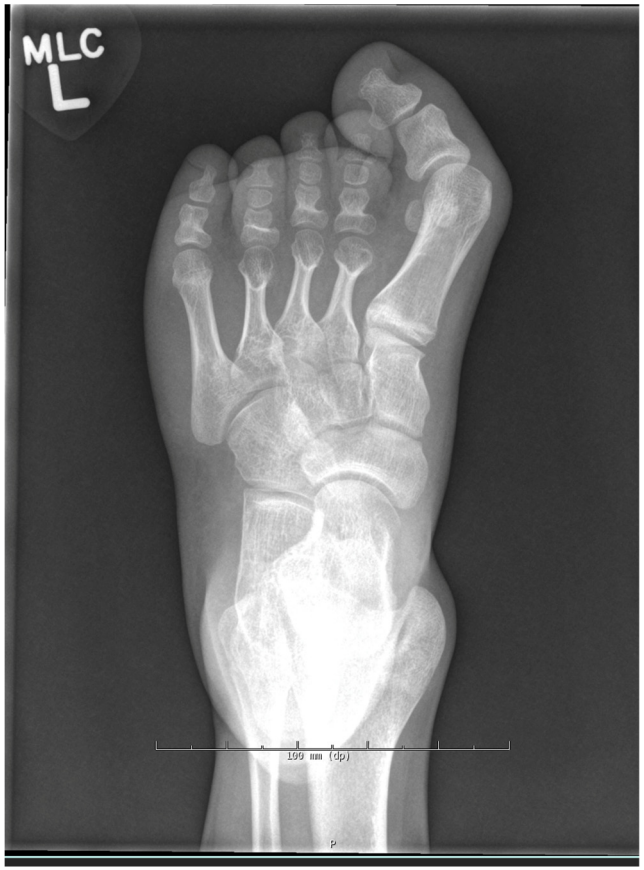
Bone age results for AMDM subjects III-1 and III-4			
Subject	**Chronological Age**	**Bone Age**	**Comments**
III-1	8 yrs 5 mo	7 yrs 10 mo*	GH started
III-1	9 yrs 9 mo	8 yrs 10 mo (wrist 10 yr)*	
III-1	10 yrs 7 mo	12 yrs 6 mo*	Lupron started
III-1	11 yrs 8 mo	14 yrs*	> 2 SD advanced, Lupron stopped
III-1	13 years 2 mo	15 years	GH stopped at 13 yrs 9 mo
Subject	**Chronological Age**	**Bone Age**	**Comments**
III-4	5 yrs 2 mo	3 yrs 6 mo to 4 yrs 2 mo*	
III-4	6 yrs 6 mo	7 yrs 10 mo	On GH
III-4	8 yrs 5 mo	10 yrs	> 2 SD advanced, GH stopped at time of BA

Supplemental Table 3.

Growth factors for AMDM subjects III-1 and III-4			
Subject	**IGF-1 level (ng/mL)**	**IGFBP-3 (mg/L)**	**Comments**
III-1	531	3.7	On GH
III-4	107	1.8	2 months before starting GH
III-4	241 (+2.5 SD)		On GH
III-4	183 (+0.7 SD)	3.7	Off GH before repeat GH provocative testing

Supplemental Figures

A



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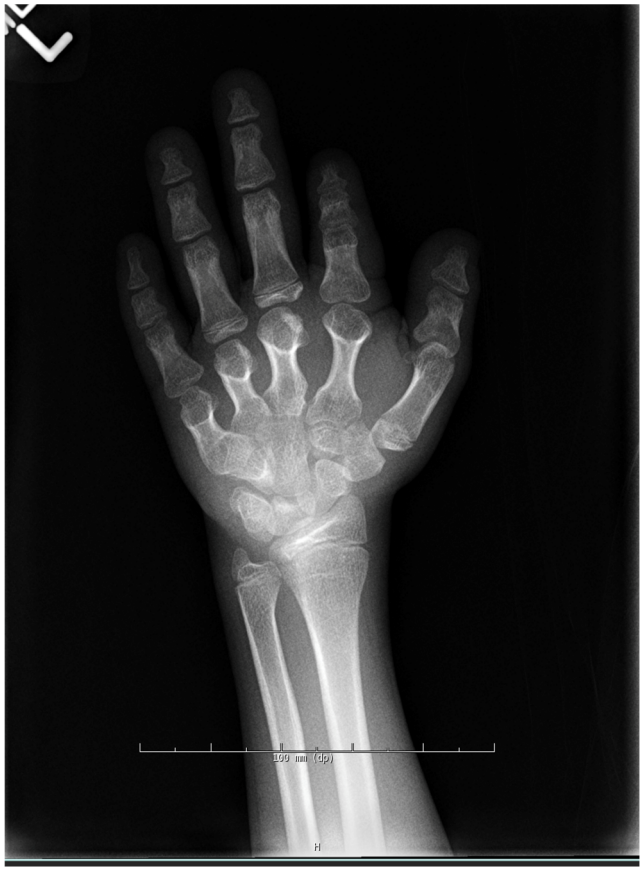

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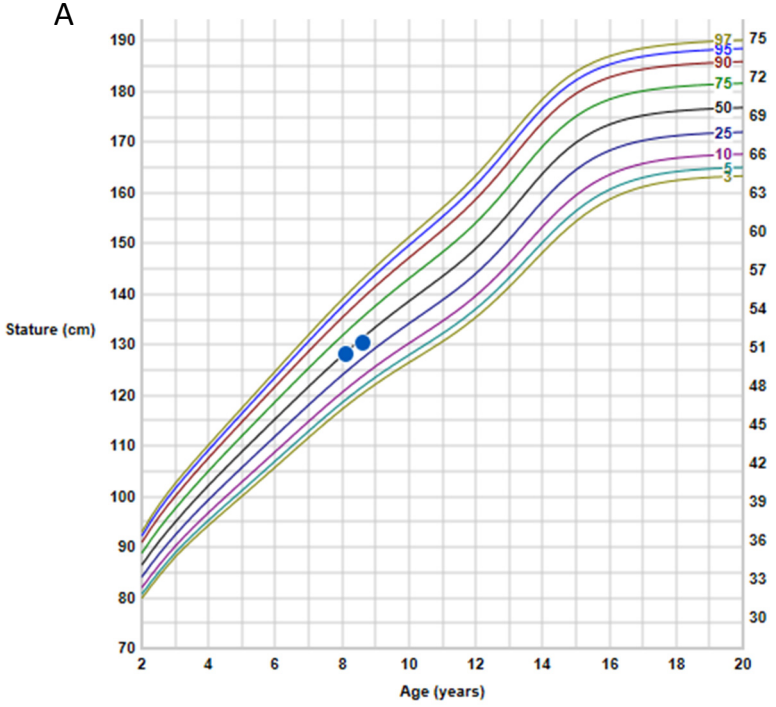
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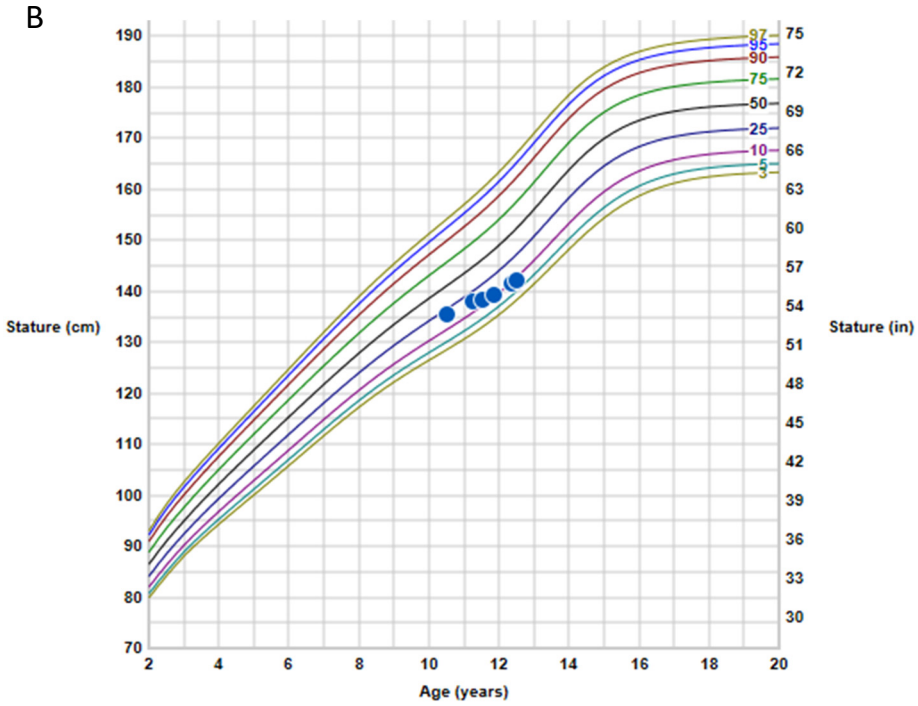
Age (years)

B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Age (years)

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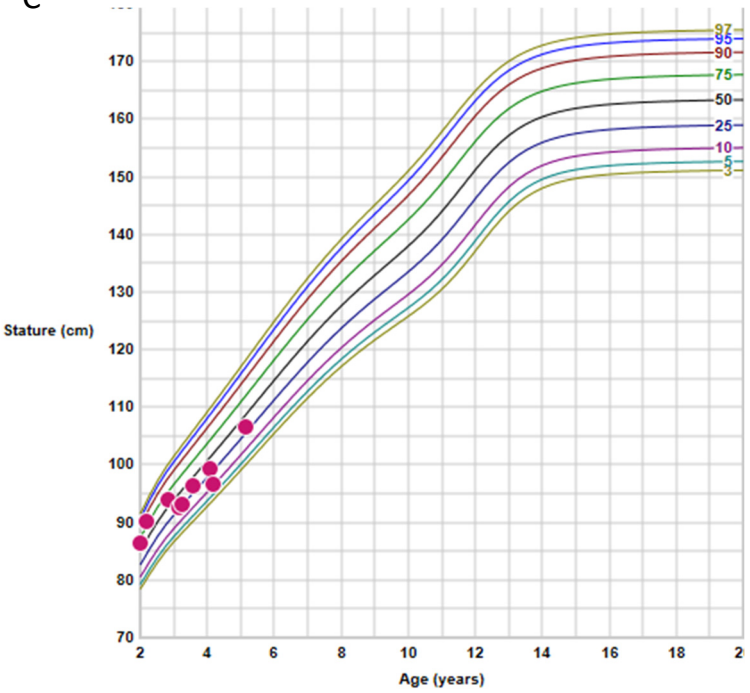
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Age (years)
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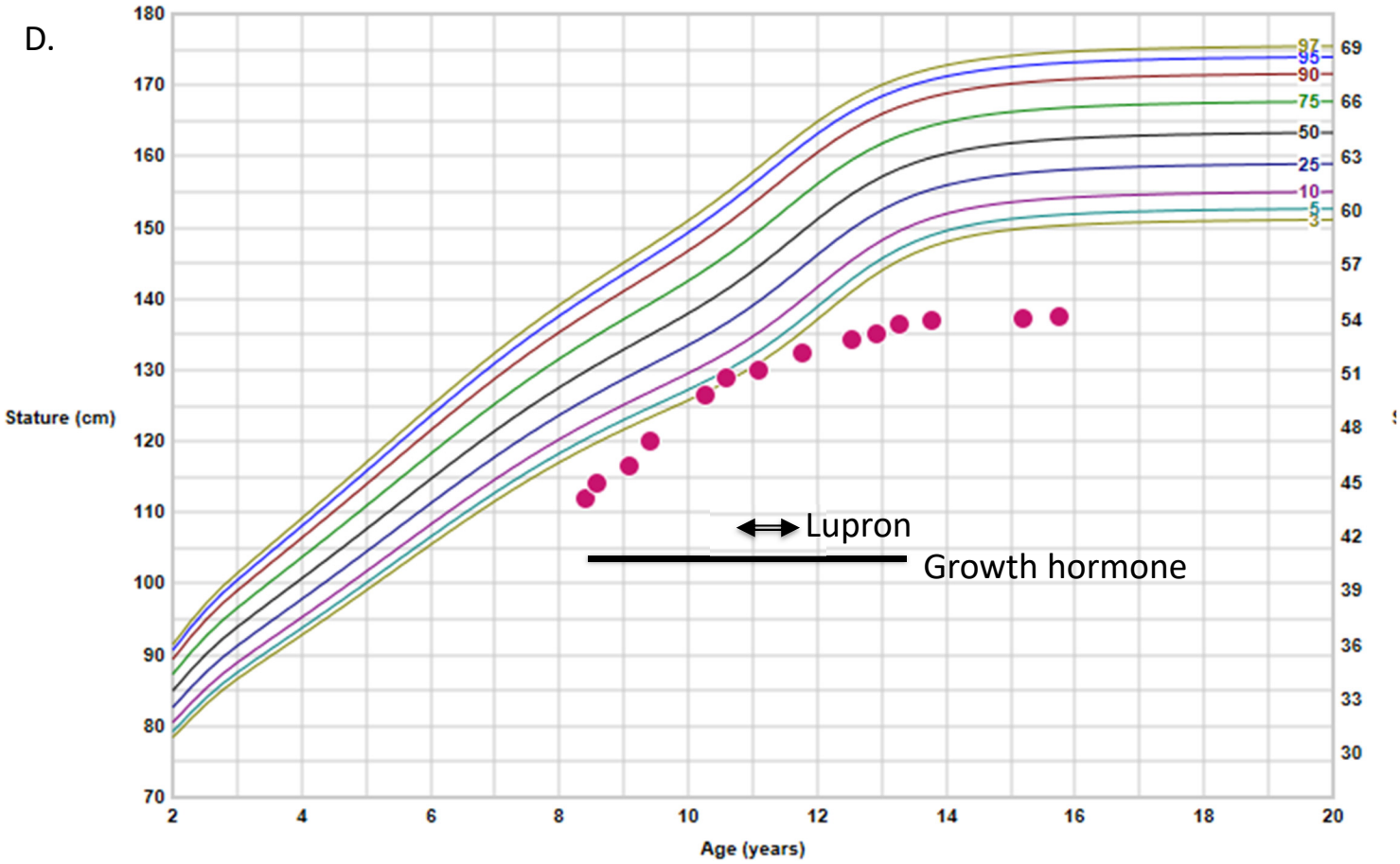

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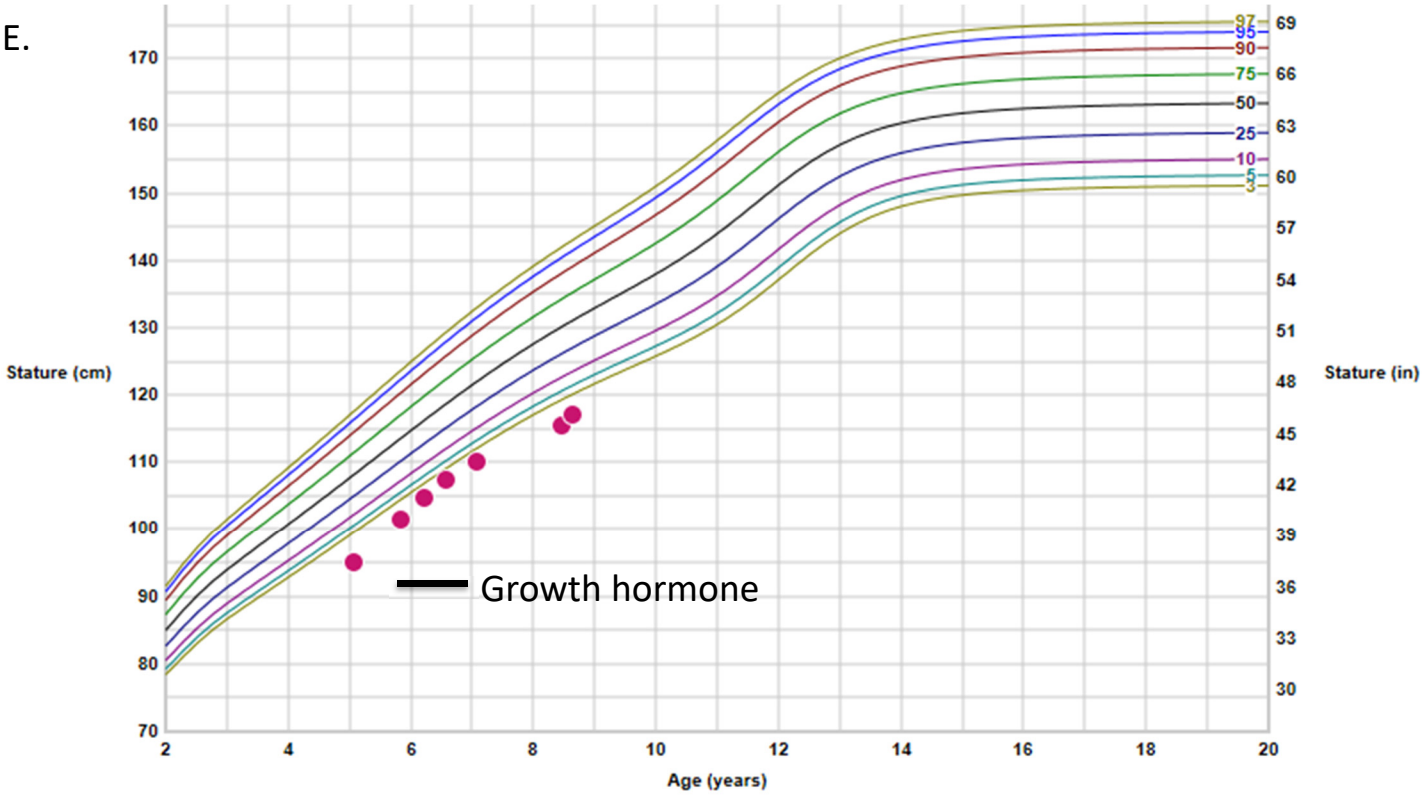
E.



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