Supplemental Table 1: *ACAN* clinical data form

Name:	**DOB:**	**Age:**
Gestational age (weeks + days)		
Birth weight (kg)		
Birth length (cm)		
Birth head circumference (cm)		
FHx (each family member)		
Recent weight (kg) [measured]		
Recent height (cm) [measured]		
Puberty (age Menarche? Early/late/average?)		
Age at growth cessation?		
Joint disease? Back problems? Surgeries?		
Physical examination		
Growth chart (Y/N)?		
Current Measurements		
Weight		
Height		
Head circumference		
Arm span		
Sitting height		
Upper arm, forearm length		
Hand length		
Craniofacial features		
Flat nasal bridge		
Midface hypoplasia		
Prognathism		
Dental development		
Other dental abnormalities		
Hands		
Brachydactyly (short hands)		
Short thumbs		
Camptodactyly		
Short metacarpals? Other?		
Skeletal manifestations		
Exaggerated lumbar lordosis		
Other		
Puberty		
Tanner stage		
Gynecomastia		
Radiology		
Bone age x-ray		
Skeletal survey		
Patient photos		
Face, front & side		
Whole body front & side		
Hands & feet		
Comments:		

Supplemental Table 2: Genetic details of the *ACAN* variants including in silico analysis of the *ACAN* missense variants.

Family	cDNA	Exon/ Intron	Amino acid	GerpN	CADD V1.3	SIFT	Polyphen	Mutation Taster	Splicing prediction	Frequency in ExAc
18	c.61G>T	2	p.Glu21*	-	-	-	-	-	-	Absent
12	c.223T>C	3	p.Trp75Arg	5.36	23.5	Del (0)	Prob dam (1.0)	Dis caus (1.0)	-	Absent
1	c.272delA	3	p.Arg93Alafs*41	-	-	-	-	-	-	Absent
20	c.492C>G	4	p.Tyr164*	-	-	-	-	-	-	Absent
10	c.532A>T	4	p.Asn178Tyr	5.79	23.8	Del (0)	Prob dam (1.0)	Dis caus (1.0)	-	Absent
16	c.903G>C	6	p.Trp301Cys	5.56	24.7	Del (0)	Prob dam (1.0)	Dis caus (1.0)	-	Absent
15	c.916A>T	6	p.Ser306Cys	5.56	23.5	Del (0)	Prob dam (1.0)	Dis caus (1.0)	-	Absent
13	c.1047_1048delinsAC	6	p.Tyr349*	-	-	-	-	-	-	Absent
8	c.1443G>T	7	p.Glu415*	-	-	-	-	-	-	Absent
14	c.1425delA	8	p.Val478Serfs*14	-	-	-	-	-	-	Absent
11	c.1526C>A	8	p.Ser509*	-	-	-	-	-	-	Absent
2	c.2026+1G>A	int10	-	-	-	-	-	-	Destroys acceptor site and predicted to cause exon 10 skipping	Absent
9	c.4657G>T	12	p.Glu1553*		-	-	-	-	-	Absent
4	c.5391delG	12	p.Gly1797Glyfs*52		-	-	-	-	-	Absent
3	c.7064T>C	14	p.Leu2355Pro	5.59	31	Del (0)	Prob dam (1.0)	Dis caus (1.0)	-	Absent
7	c.7153G>A	15	p.Glu2385Lys	5.66	34	Del (0)	Prob dam (0.998)	Dis caus (1.0)	-	Absent
19	c.7203G>A	16	p.Trp2401*		-	-	-	-	-	Absent
5,6	c.7429G>A	16	p.Val2417Met	5.26	32	Del (0)	Prob dam (1.0)	Dis caus (1.0)	-	Absent
17	c.7276G>T	16	p.Glu2426*		-	-	-	-	-	Absent

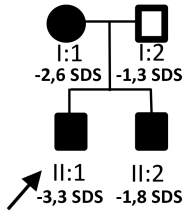
The coordinates are according to *ACAN* transcript NM_013227.3. SIFT Del = deleterious; Polyphen Prob dam = probably damaging; MutationTaster Dis caus = disease causing; ExAc = Exome aggregation consortium.

Supplemental Files – *ACAN* patients Pedigrees

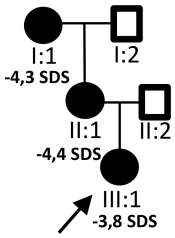
Supplemental Figure 1.

Pedigrees of families 1 - 20. The arrows indicate the proband. Individuals carrying heterozygous *ACAN* mutations are indicated by solid symbols while unaffected individuals are indicated as open symbols. Height SD scores are indicated under the individuals.

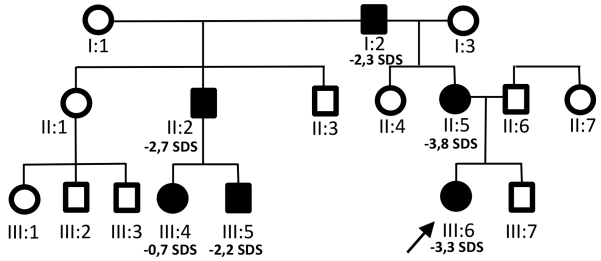
Family 1_ACAN Mutation p.Arg93Alafs*



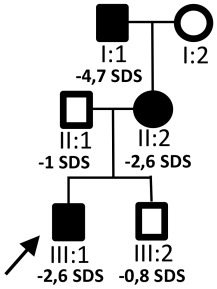
Family 2_ ACAN Mutation c.2026+1 G>A



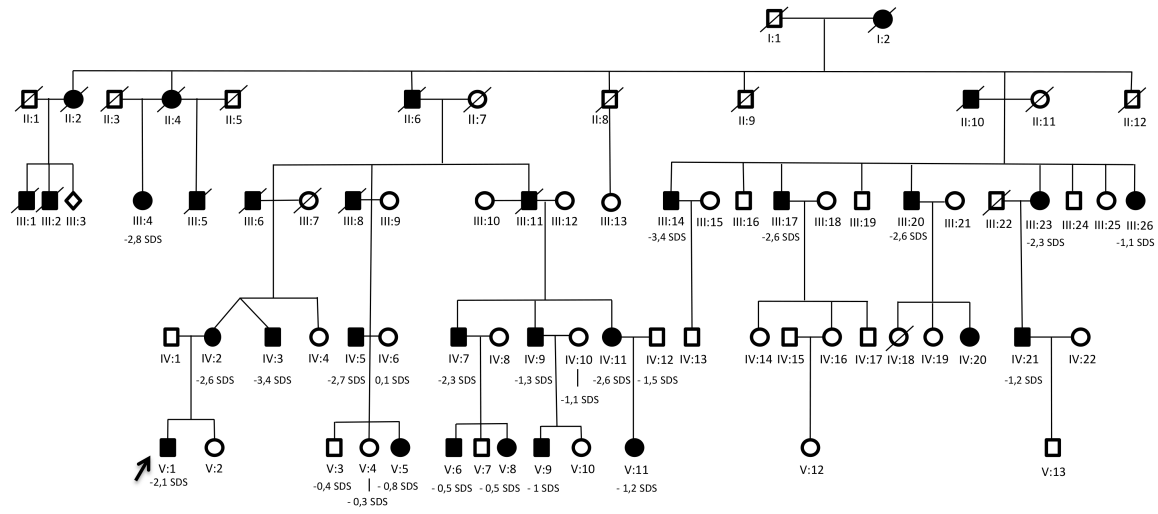
Family 3_ ACAN Mutation p.Leu2355Pro



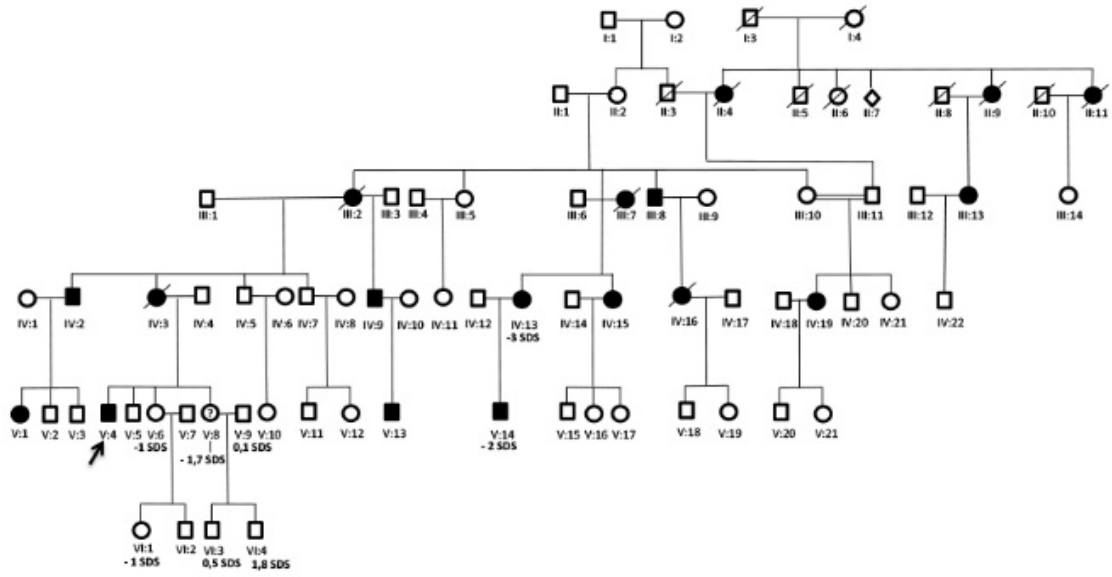
Family 4_ ACAN Mutation p.Gly1797Glyfs*



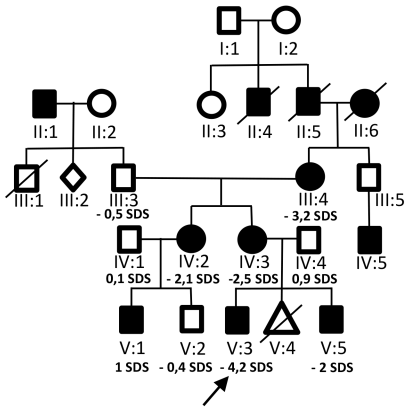
Family 5_ACAN Mutation p.Val2417Met



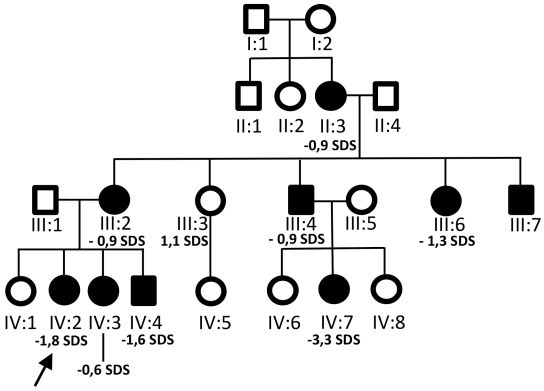
Family 6_ACAN Mutation p.Val2417Met



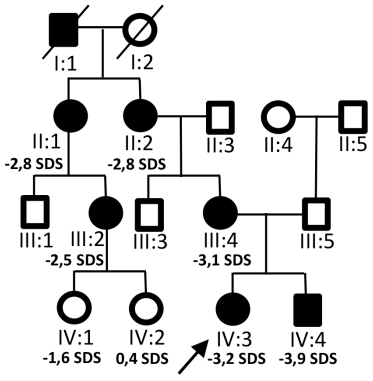
Family 7_ACAN Mutation p.Glu2385Lys



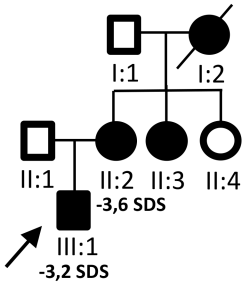
Family 8_ ACAN Mutation p.Glu415*



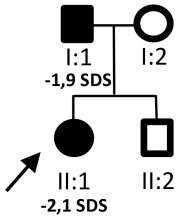
Family 9_ ACAN Mutation p.Glu1553*



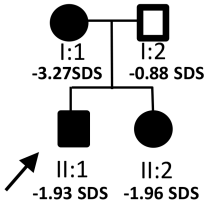
Family 10_ ACAN Mutation p.Asn178Tyr



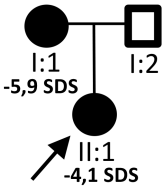
Family 11_ ACAN Mutation p.Ser509*



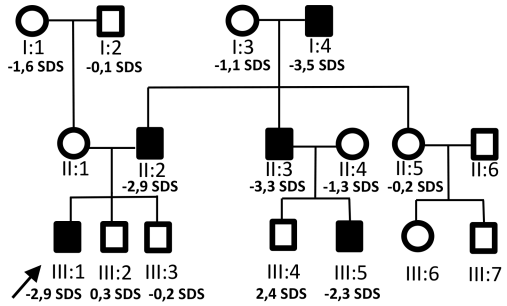
Family 12_ ACAN Mutation p.Trp75Arg



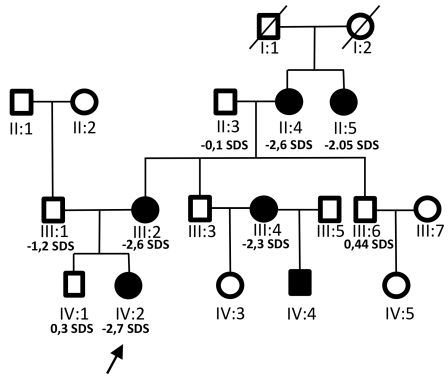
Family 13_ ACAN Mutation p.Tyr349*



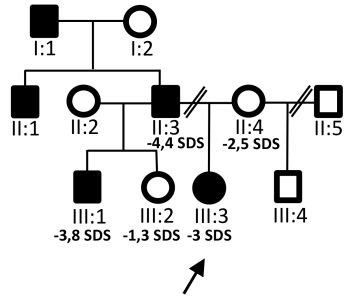
Family 14_ ACAN Mutation p.Val478Serfs*



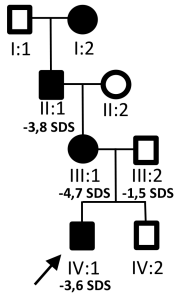
Family 15_ACAN Mutation p.Ser306Cys



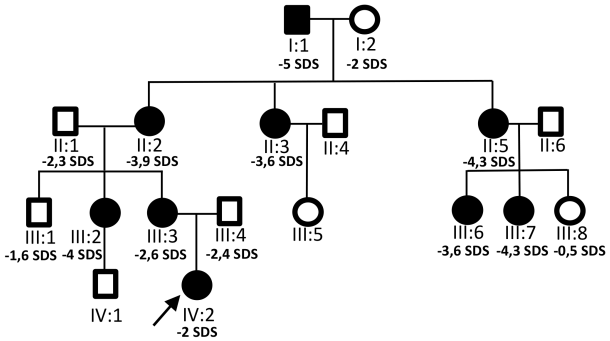
Family 16_ACAN Mutation p.Trp301Cys



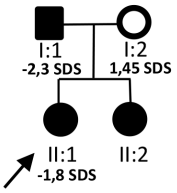
Family 17_ACAN Mutation p.Glu2426*



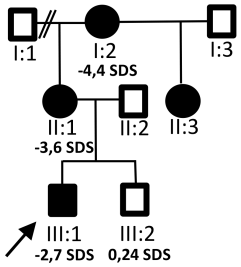
Family 18_ ACAN Mutation p.Glu21*



Family 19_ ACAN Mutation p.Trp2401*



Family 20_ ACAN Mutation p.Tyr164*

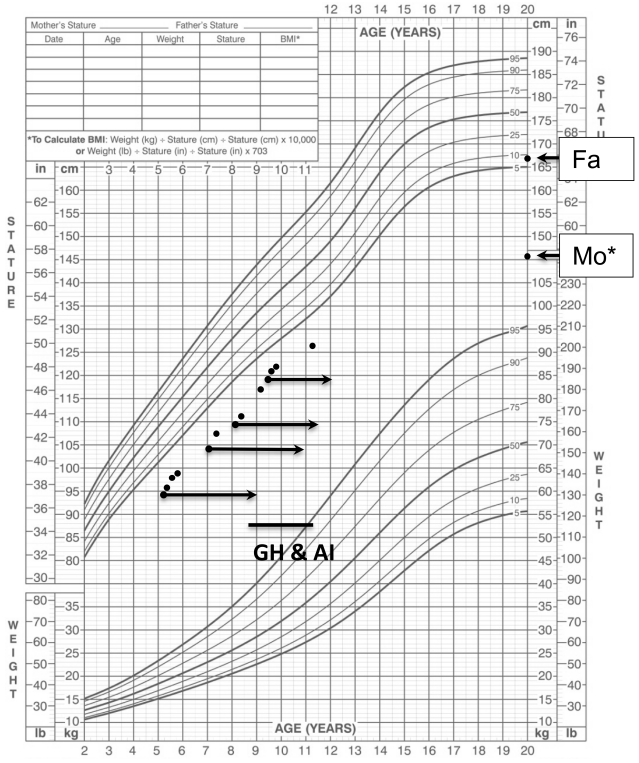


Supplemental Files – ACAN patients Growth Charts

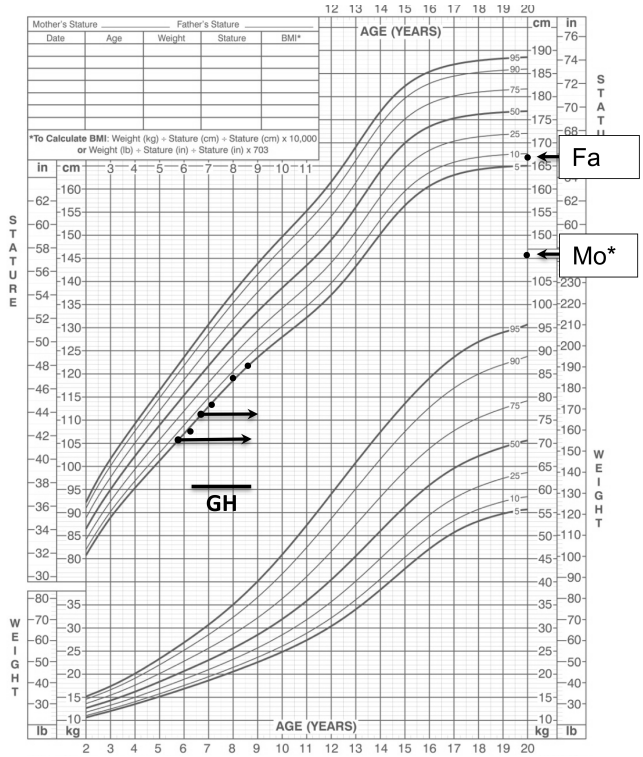
Supplemental Figure 2.

Growth (height) charts of individuals with heterozygous *ACAN* mutations. The left end of each arrow represents the subject's chronological age (CA) and height and the right end represents the bone age. Lines indicate periods with GH or GnRH analogue (GnRHa) or GH and GnRHa or GH and aromatase inhibitor letrozole (AI) treatment. Fa, father's height; Mo, mother's height; Asterix indicates parent carrying the mutation.

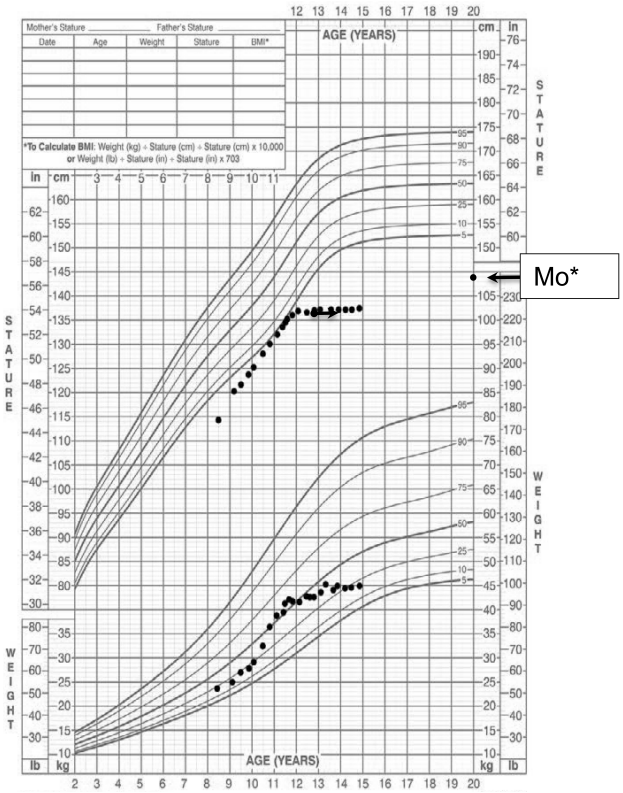
Family 1_Patient II-1_ACAN Mutation p.Arg93Alafs*_Male_GH & AI Treatment



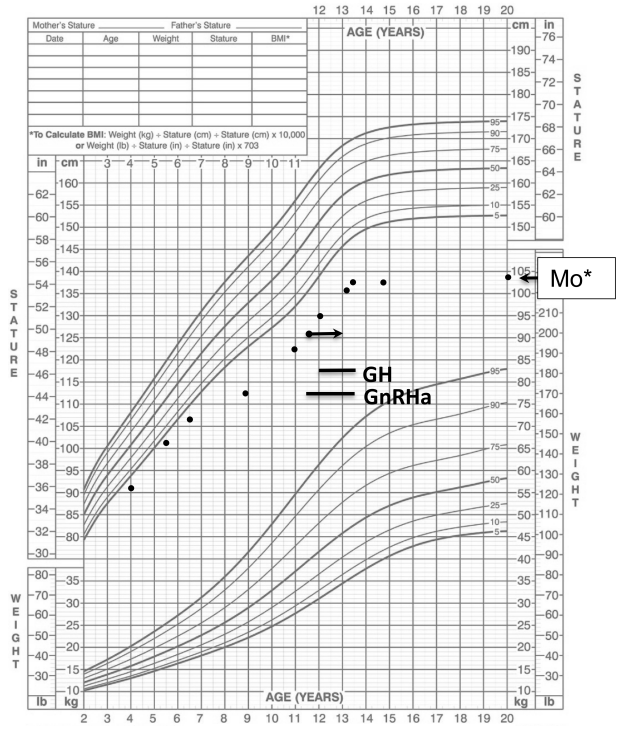
Family 1_Patient II-2_ACAN Mutation p.Arg93Alafs*_Male_GH Treatment



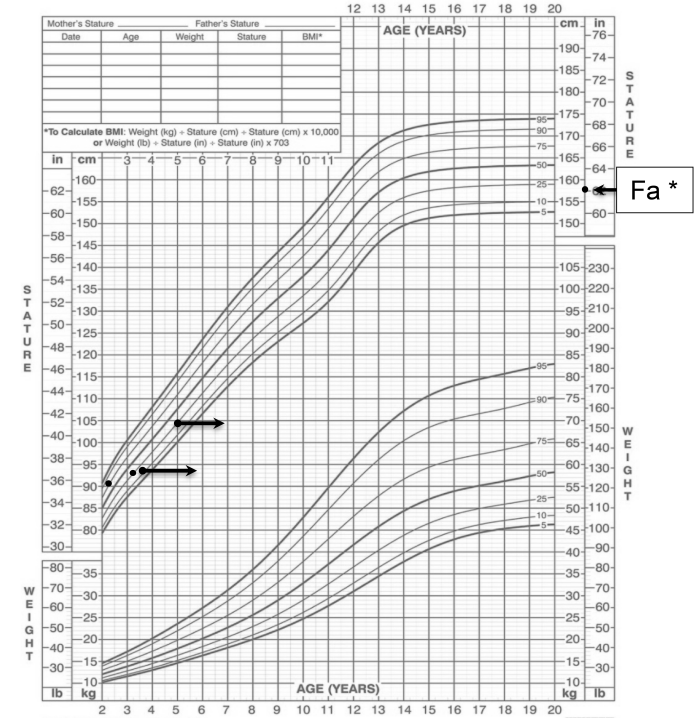
Family 2_Patient III-1_ACAN Mutation c.2026+1 G>A _Female_No GH Treatment



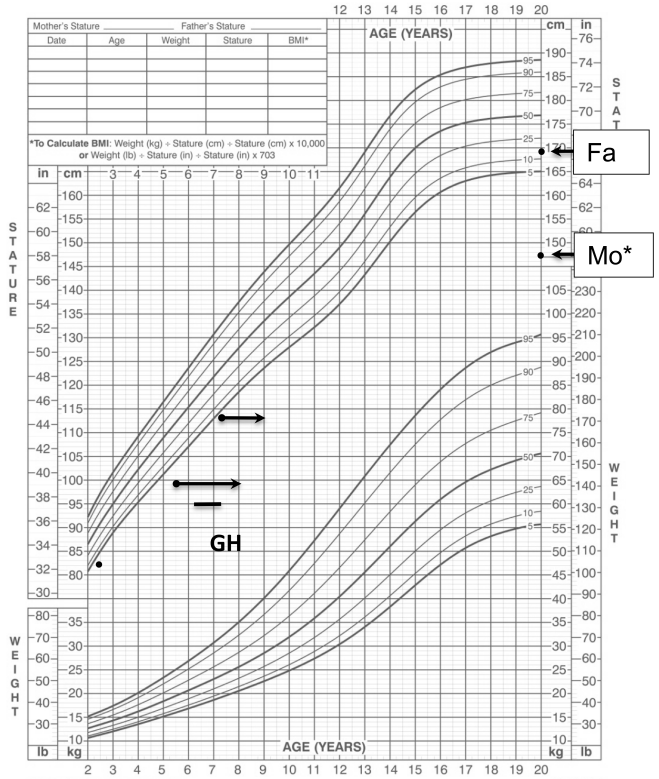
Family 3_Patient III-6_ACAN Mutation p.Leu2355Pro_Female_GH & GnRHa Treatment



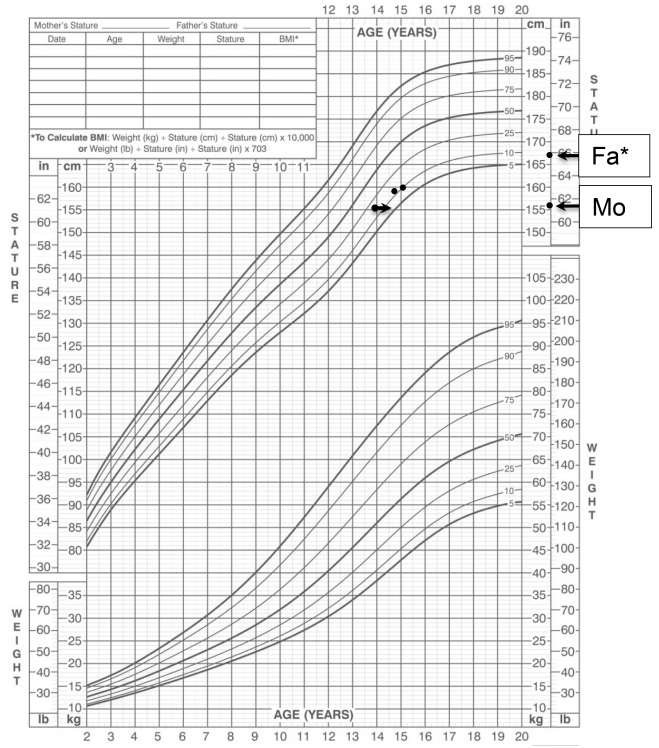
Family 3_Patient III-4_ACAN Mutation p.Leu2355Pro_Female_No GH Treatment



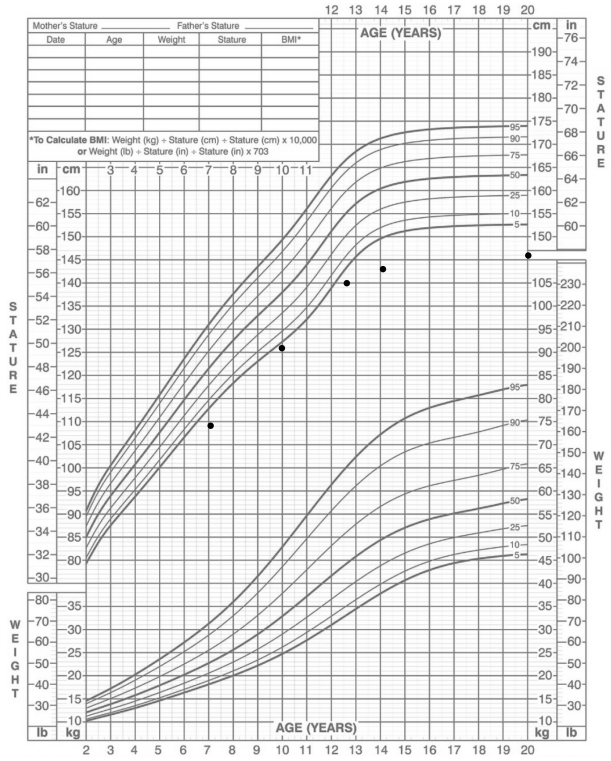
Family 4_Patient III-1_ACAN Mutation p.Gly1797Glyfs*_Male_GH Treatment



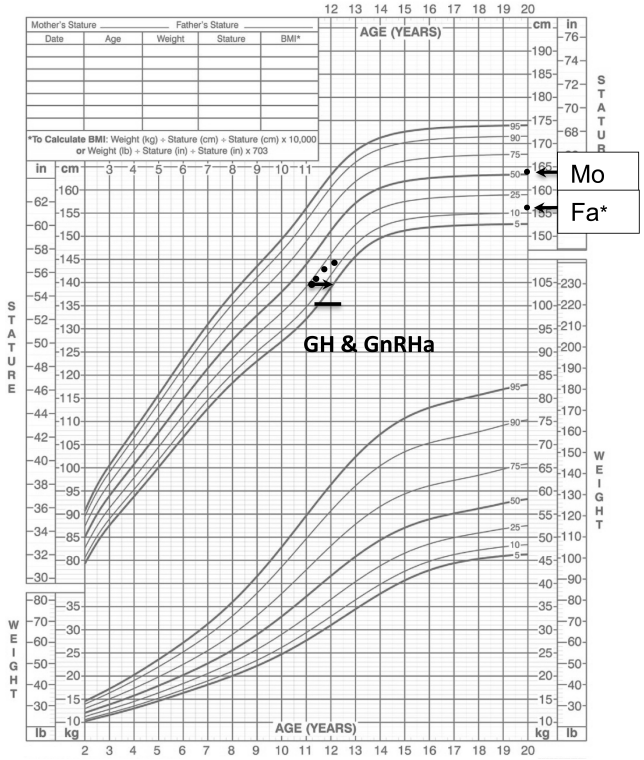
Family 5_Patient V:9_ACAN Mutation p.Val2417Met_Male_No GH Treatment



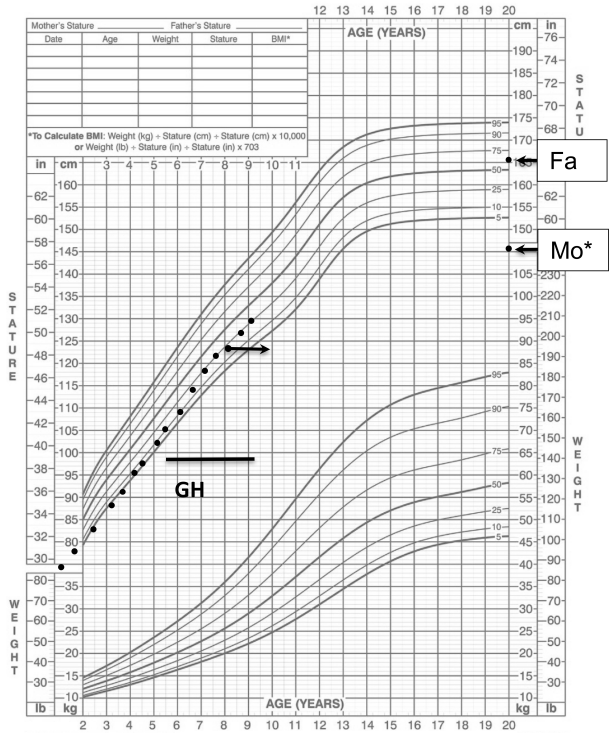
Family 5_Patient IV:12_ACAN Mutation p.Val2417Met_Female_No GH Treatment



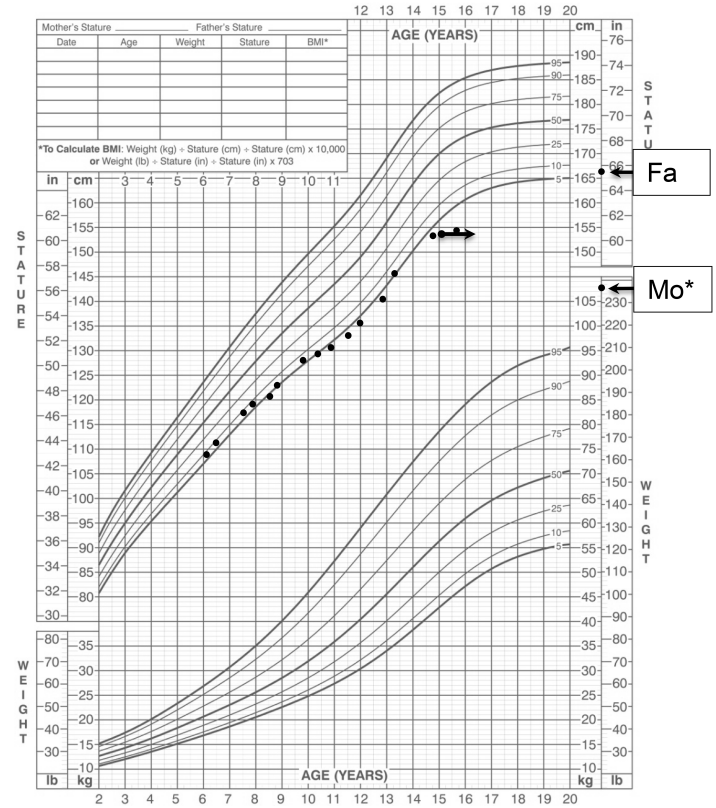
Family 5_Patient V:5_ACAN Mutation p.Val2417Met_Female_GH & GnRHa Treatment



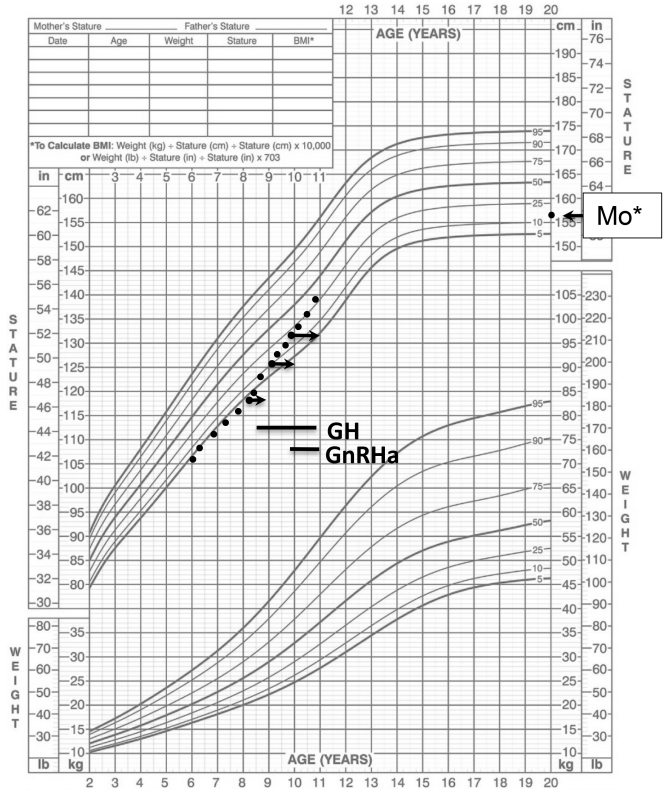
Family 5_Patient V:11_ACAN Mutation p.Val2417Met_Female_GH Treatment



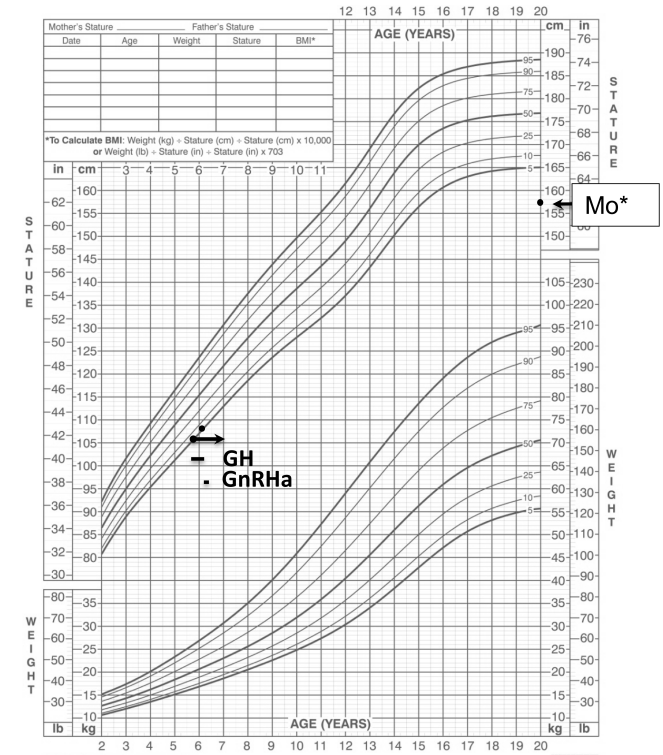
Family 6_Patient V:14_ACAN Mutation p.Val2417Met_Male_ No GH Treatment



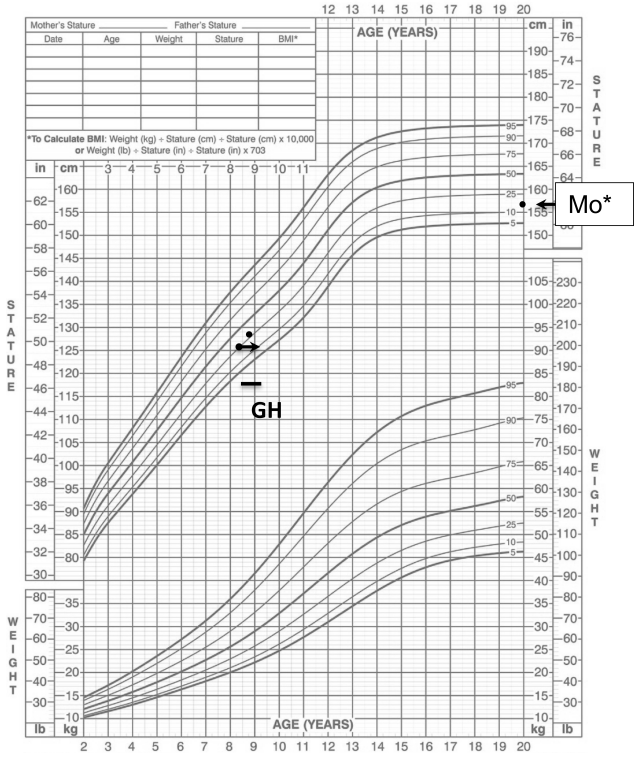
Family 8_Patient IV-2_ACAN Mutation p.Glu415*_Female_GH & GnRHa Treatment



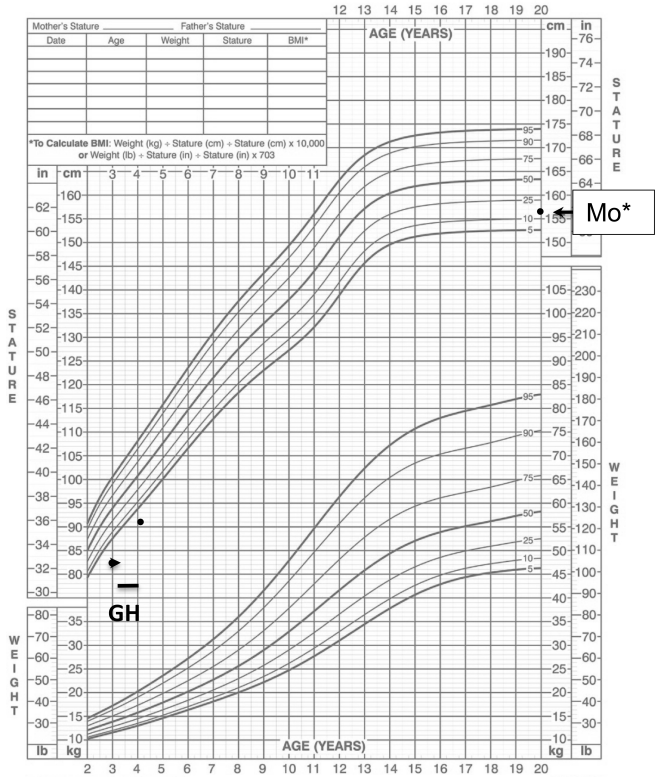
Family 8_Patient IV-4_ACAN Mutation p.Glu415*_Male_GH & GnRHa Treatment



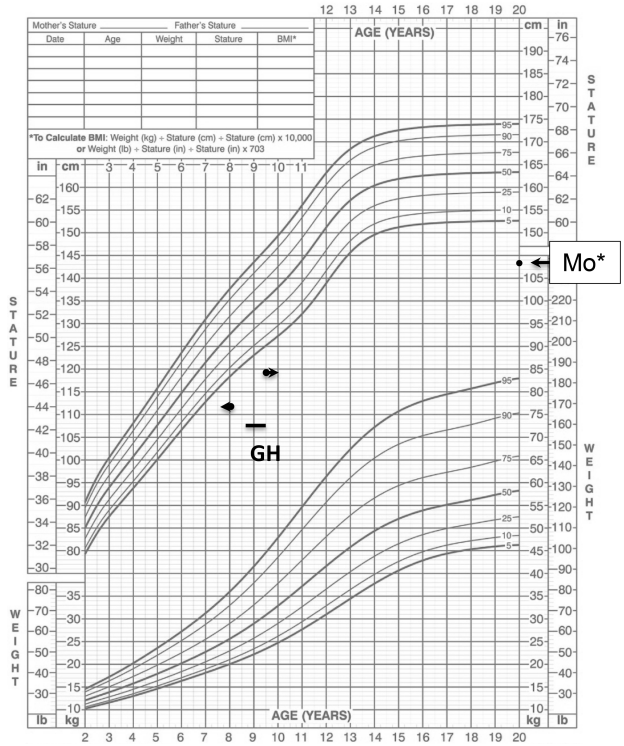
Family 8_Patient IV-3_ACAN Mutation p.Glu415*_Female_GH Treatment



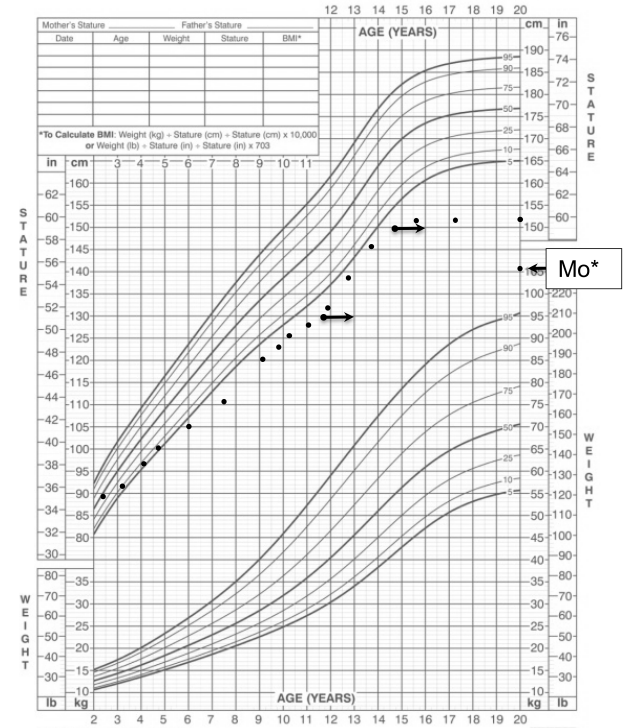
Family 8_Patient IV-7_ACAN Mutation p.Glu415*_Female_GH Treatment



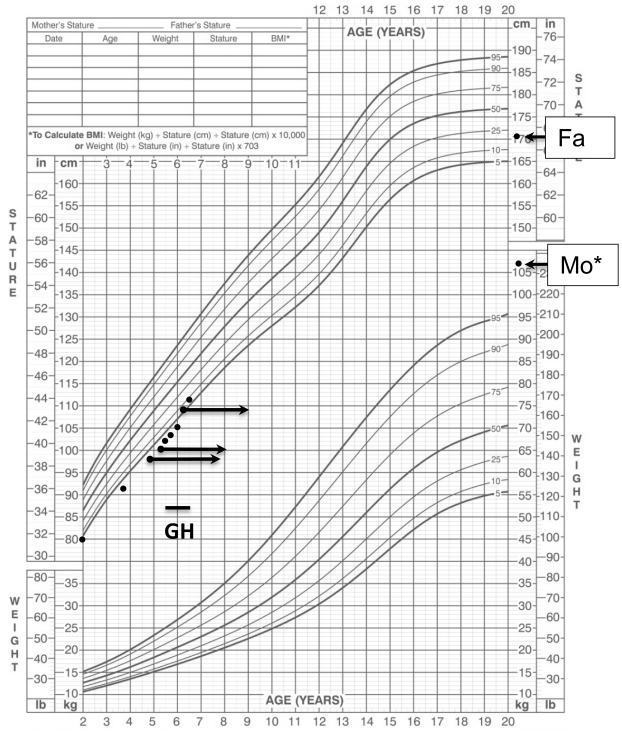
Family 9_Patient IV-3_ACAN Mutation p.Glu1553*_Female_GH Treatment



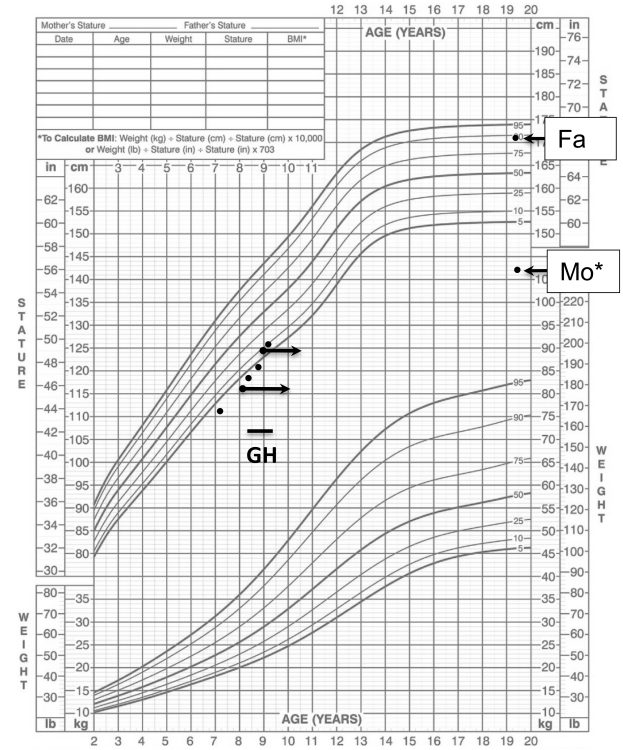
Family 10_Patient III-1_ACAN Mutation p.Asn178Tyr_Male_No GH Treatment



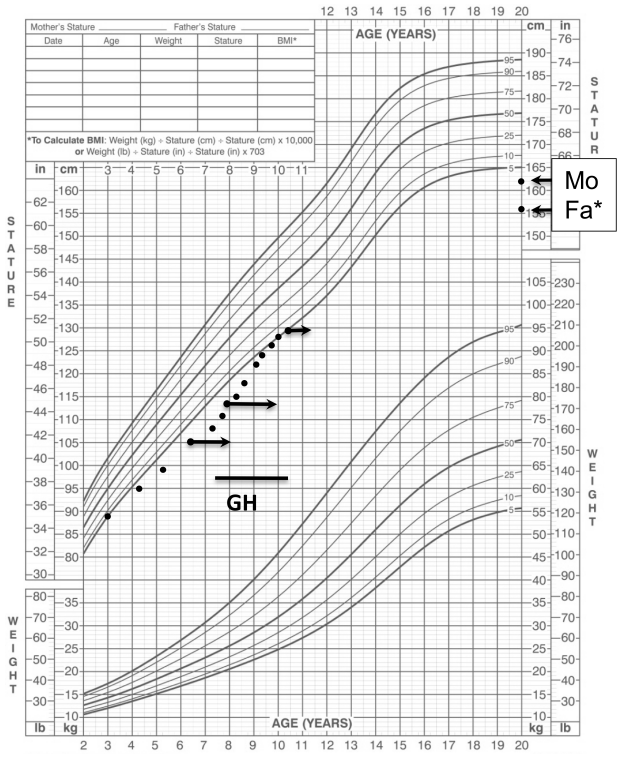
Family 12_Patient II-1_ACAN Mutation p.Trp75Arg_Male_GH Treatment



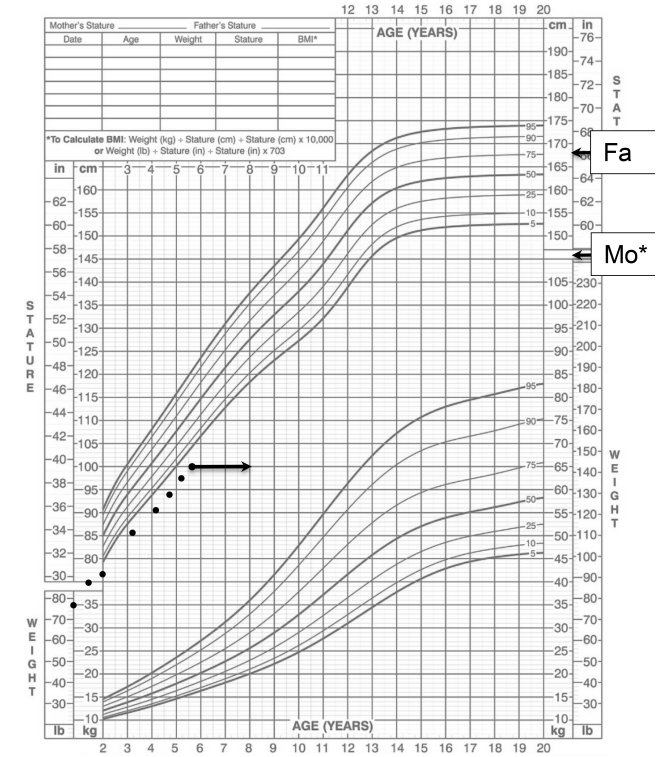
Family 12_Patient II-2_ACAN Mutation p.Trp75Arg_Female_GH Treatment



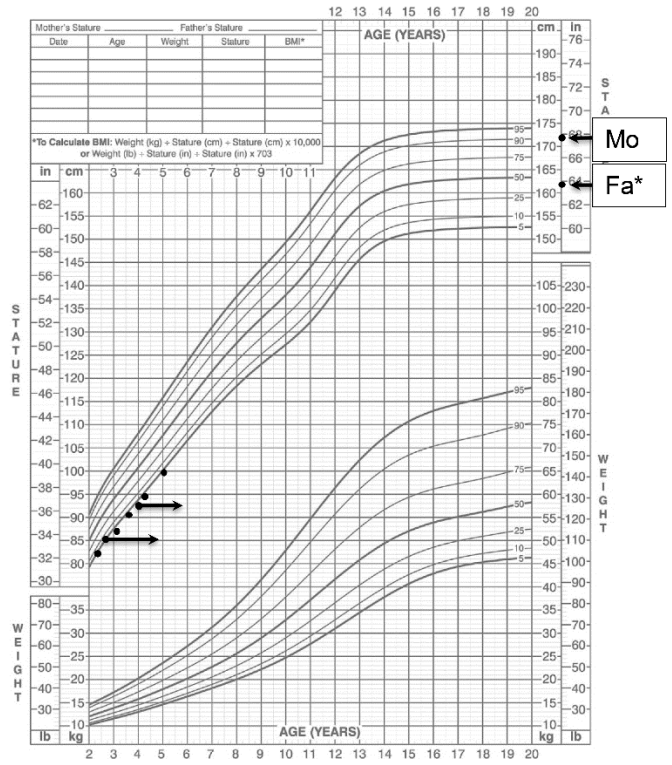
Family 14_Patient III-1_ACAN Mutation p.Val478Serfs*_Male_GH Treatment



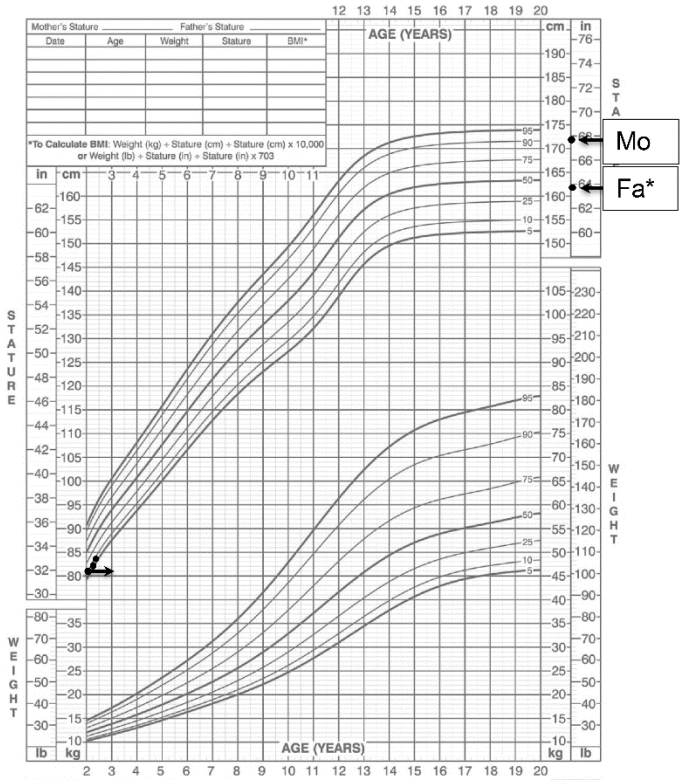
Family 15_Patient IV-2_ACAN Mutation p.Ser306Cys_Female_No GH Treatment



Family 19_Patient II-1_ACAN Mutation p. Trp2401*_Female_No GH Treatment

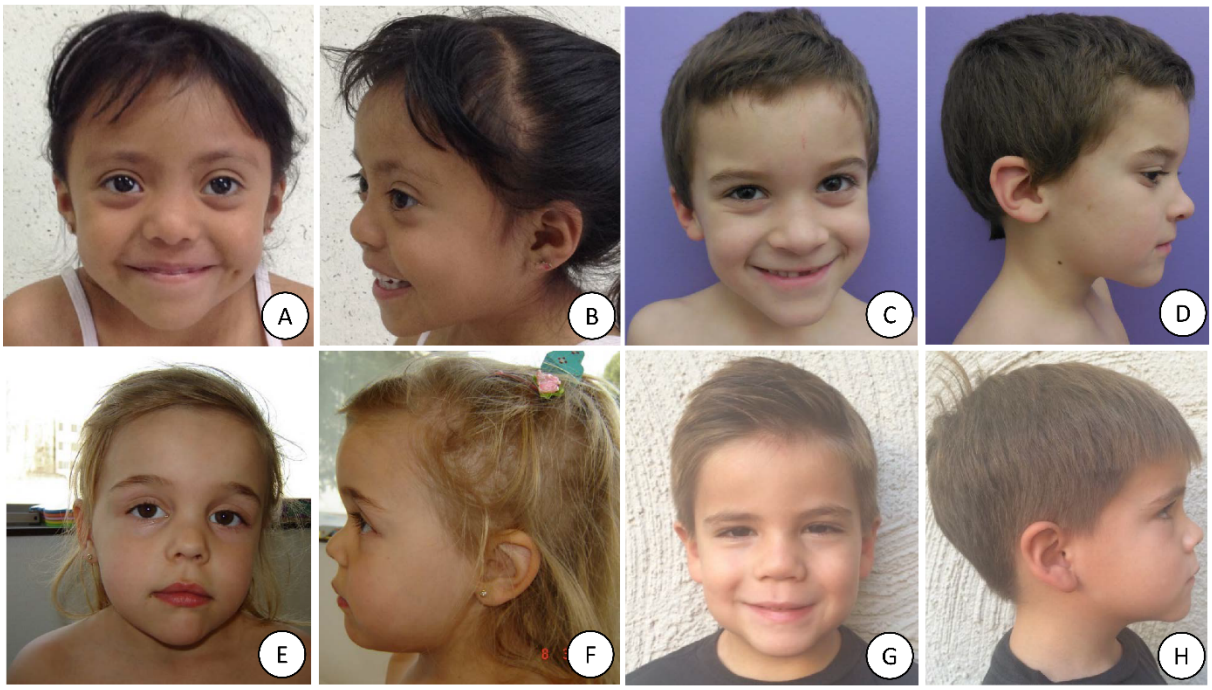


Family 19_Patient II-2_ACAN Mutation p. Trp2401*_Female_No GH Treatment



Supplemental Figure 3.

Aggrecan patient's photos: A and B) Proband of Family 13 (II:1), Female, *ACAN* mutation p.Tyr349*; C and D) Proband of Family 9 (IV:4), Male, *ACAN* mutation p.Glu1553*; E and F) Proband of Family 16 (III:3), Female, *ACAN* mutation p.Trp301Cys and G and H) Proband of Family 8 (IV:4), Male, *ACAN* mutation p.Glu415*.



Supplemental Figure 4.

Radiographs from skeletal survey of female cousin of Family 3, proband (III:4), *ACAN* mutation p.Leu2355Pro, at the age of 3 years and 7 months.