

Authors: Quigley CA, Li YG, Brown MR, Pillai SG, Banerjee P, Scott RS, Blum WF, Parks JS

Title: Genetic Polymorphisms Associated with Idiopathic Short Stature and First-Year Response to Growth Hormone Treatment. *Hormone Research in Paediatrics*, 2019. DOI: 10.1159/000496989

Supplemental Table 1: Genetic Variants Analyzed

Table 1a: Genetic Variants Analyzed, Candidate Gene Group, Presented by Tier

Gene	Protein	RefSeq Locus	Alleles: Major/Minor	Alleles: Tall/Short	Location/Effect	Pathway	Association	Reference
Tier 1								
<i>CYP17A1</i>	17- α hydroxylase 1	rs17115144	C/T	C/T	Promoter -34	Sex hormone	Height	Lai
<i>ESR1</i>	Estrogen receptor α	rs9340799	A/G	G/A	Intron 1 XBA	Sex hormone	Height (male)	Parks
<i>ESR1</i>	Estrogen receptor α	rs2234693	T/C	C/T	Intron 1 PVUII	Sex hormone	Height (Fels)	Parks
<i>GHR</i>	Growth hormone receptor	N/A	FL/d3	d3/FL	Exon 3 deletion	Growth hormone	Height, GH response	Dos Santos; Wassenaar
Tier 2								
<i>ADRB2</i>	Adrenergic receptor- β 2	rs1042713	G/A	A/G	Arg16Gly	Catecholamine	Weight	Tafel
<i>COMT</i>	Catechol-o-methyl transferase	rs4680	G/A	G/A	Val158Met	Catecholamine	Weight	Gorai
<i>DRD2</i>	Dopamine D2 receptor	rs1799732	C+/C-	C-/C+	Promoter -141	Catecholamine	Height, ISS	Arinami
<i>DRD2/ANKK1</i>	Dopamine D2 receptor/ankyrin repeat and kinase domain containing-1	rs1800497	C/T	T/C	Upstream intron	Catecholamine	Obesity	Winkler; Lucht
<i>ESR1</i>	Estrogen receptor α	rs2179922	A/G	G/A	Intron 4	Sex hormone	Height (Fels)	Parks
<i>GHI</i>	Growth hormone 1	rs2011732	G/T	G/T	Promoter -362; transcription	Growth hormone	Height	Esteban
<i>GHI</i>	Growth hormone 1	N/A	G/T	G/T	Promoter -369; transcription	Growth hormone	Height	Esteban
<i>GHI</i>	Growth hormone 1	rs2665802	A/T	T/A	Intron 4	Growth hormone	Height	Esteban

Gene	Protein	RefSeq Locus	Alleles: Major/Minor	Alleles: Tall/Short	Location/Effect	Pathway	Association	Reference
HMGA2	High mobility group AT-hook 2	rs1042725	C/T	C/T	5' untranslated region	Chromatin	Tall stature	Tay; Hendriks 2011a
IGFBP3	IGF binding protein-3	rs2854744	A/C	C/A	Promoter -202	Growth hormone	Tall stature, GH response	Deal; Hendriks 2011b;
LHβ	Luteinizing hormone- β	N/A	T/C	T/C	Ile15Thr	Sex hormone	Height; puberty	Raivio; Hanevik
PTHr	Parathyroid hormone (PTH) and PTH-related protein receptor	N/A	(AAAG) ₅ / (AAAG) ₆	(AAAG) ₆ / (AAAG) ₅	Promoter	Skeletal	Skeletal dysplasia	Minagawa
SHOX	Short stature homeobox	rs2239401	A/G	G/A	5' untranslated (c. -372G>A)	Skeletal	Skeletal dysplasia	Solc

Footnotes: Fels = Fels Institute (<http://www.med.wright.edu/lhrc/fels>); ISS= idiopathic short stature; N/A = not applicable; rs# = National Center for Biotechnology Information Reference Sequence Number. Variants are listed alphabetically by gene name; variants are shown in the plus orientation. Additional variants included in the original genetic analyses that failed quality control and were excluded from the statistical analyses were: rs700518 (*CYP19A1*); rs10865710 (*PPARG*); rs1544410 (*VDR*) and rs2228570 (*VDR*), due to call rate <90%; rs2239402 (*SHOX*), due to MAF <5%.

Table 1b: Genetic Variants Analyzed, Genome-Wide Association Studies Polymorphism Group, Presented by Tier

Gene(s)	RefSeq Locus	Alleles: major/minor	Alleles: tall/short	Association	Reference(s)
Tier 1					
<i>ADAP2</i>	rs3760318	C/T	C/T	Adult height; pediatric height	Gudbjartsson; Zhao
<i>BFZB [UQCC1]</i>	rs6060369	T/C	C/T	Height	Lette; Sanna
<i>BMP2</i>	rs967417	C/T	C/T	Adult height; pediatric height	Gudbjartsson; Zhao
<i>CEP63</i>	rs10935120	G/A	G/A	Height (male)	Weedon
<i>DLEU7</i>	rs3116602	T/G	T/G	Height (male)	Weedon
<i>GPR126</i>	rs3748069	A/G	A/G	Adult height; pediatric height	Gudbjartsson; Zhao
<i>ZBTB38</i>	rs6440003	A/G	A/G	Height (male)	Weedon; Lei
<i>ZNF462</i>	rs4743034	G/A	A/G	Adult height; pediatric height	Gudbjartsson; Zhao
Tier 2					
<i>ACAN</i>	rs8041863	A/T	A/T	Height (male)	Weedon
<i>ANKS1</i>	rs4713858	G/A	G/A	Adult height; pediatric height	Gudbjartsson; Lei; Zhao
<i>ATXN3;TRIP11</i>	rs8007661	T/C	C/T	Height	Lette
<i>ATXN3; CPSF2; FBLN5; TRIP11</i>	rs7153027	A/C	A/C	Adult height; pediatric height	Gudbjartsson; Zhao
<i>BMP6</i>	rs12198986	G/A	A/G	Adult height; pediatric height	Gudbjartsson; Zhao
<i>C6orf106</i>	rs2814993	G/A	A/G	Height (male); pediatric height; frame size	Weedon; Zhao; Soranzo
<i>CABLES1</i>	rs4800148	G/A	A/G	Adult height; pediatric height	Gudbjartsson; Zhao
<i>DNM3</i>	rs678962	T/G	G/T	Adult height; pediatric height	Gudbjartsson; Zhao
<i>DOTIL</i>	rs12986413	A/T	T/A	Height	Lette
<i>DYM</i>	rs8099594	A/G	A/G	Height (male); linear growth in Crohn disease	Weedon; Lee
<i>EFEMPI</i>	rs3791679	T/C	T/C	Adult height; pediatric height	Gudbjartsson; Zhao
<i>GNAI2</i>	rs798544	G/A	G/A	Adult height; pediatric height	Gudbjartsson; Zhao
<i>HIST1H1D</i>	rs10946808	A/G	A/G	Adult height; pediatric height; frame size	Lette; Gudbjartsson; Zhao; Soranzo

Gene(s)	RefSeq Locus	Alleles: major/minor	Alleles: tall/short	Association	Reference(s)
<i>HLA class 3;</i> <i>NCR3; AIF1</i>	rs2844479	T/G	T/G	Pediatric height; obesity (China); SGA (New Zealand)	Zhao; Morgan
<i>Histone class 2A;</i> <i>MTMR11;</i> <i>SF3B4; SV2A</i>	rs11205277	A/G	G/A	Adult height; pediatric height	Gudbjartsson; Lango Allen; Zhao
<i>LCORL</i>	rs16896068	G/A	G/A	Height (male)	Weedon
<i>LCORL; NCAPG</i>	rs6830062	T/C	T/C	Adult height; frame size	Gudbjartsson; Soranzo
<i>LIN28B</i>	rs314277	C/A	A/C	Height: birth to adulthood; age at menarche; digit length ratio	Lettre; Widen; He; Sulem; Medland
<i>LOC387103</i>	rs4549631	C/T	C/T	Height (male)	Weedon
<i>NHEJ1</i>	rs6724465	G/A	G/A	Height (male)	Weedon
<i>PTCH1</i>	rs10512248	T/G	G/T	Height (male); cleft palate	Weedon; Letra
<i>PXMP3; ZFHX4</i>	rs7846385	T/C	C/T	Adult height; pediatric height	Gudbjartsson; Zhao
<i>SOCS2</i>	rs11107116	G/T	T/G	Height (male); growth in infancy	Weedon; Sovio
<i>SPAG17</i>	rs12735613	G/A	G/A	Height (male)	Weedon
<i>TSEN15</i>	rs2274432	C/T	T/C	Adult height; pediatric height	Gudbjartsson; Zhao
<i>UQCC1</i>	rs6060373	A/G	A/G	Height (male); vertebral size	Weedon; Deng
<i>ZNF768</i>	rs1390401	G/A	A/G	Height (male)	Weedon

Genes listed are those reported at SNPedia or in cited references to be associated with the particular RefSeq locus. However, these loci may be some distance from the associated gene. RefSeq = National Center for Biotechnology Information Reference Sequence Database (<http://www.ncbi.nlm.nih.gov/refseq/>); data accessed from SNPedia 11 Jan2015. Allelic variants are shown in the plus orientation. One additional assayed SNP (rs6842303, associated with *NCAPG* gene; reference Zhao et al.) was excluded from analysis because it failed the 90% call rate criterion.

Table 1c: Candidate Gene Polymorphisms that Failed Predefined Quality Control Criteria

Gene	Protein	RefSeq Locus	Alleles: major/minor	Alleles: tall/short	Location/ Effect	Pathway (associations)	Reason for failure	Reference
<i>CYP19A1</i>	Aromatase	rs700518	G/A	G/A	Val80Val	Sex hormone (height; bone mass)	Call rate	Kiel
<i>PPARG</i>	Peroxisome proliferator- activated receptor γ -3	rs10865710	C/G	G/C	Promoter -681	Insulin (weight)	Call rate	Luo
<i>SHOX</i>	Short stature homeobox	rs2239402	G/T	U/U	Intron 2	Skeletal (skeletal dysplasia)	MAF < 5%	Hirschfeldova
<i>VDR</i>	Vitamin D receptor	rs1544410	G/A	G/A	Intron 8	Skeletal (height)	Call rate	Kitagawa
<i>VDR</i>	Vitamin D receptor	rs2228570	C/T	T/C	Exon 2	Skeletal (height)	Call rate	Tao

MAF = minor allele frequency; U = unknown

References for Supplemental Table 1

Arinami T, Iijima Y, Yamakawa-Kobayashi K, Ishiguro H, Ohtsuki T, Yanagi H, Shimakura Y, Ishikawa H, Hamaguchi H: Supportive evidence for contribution of the dopamine D2 receptor gene to heritability of stature: linkage and association studies. *Ann Hum Genet* 1999;63:147-151. Deng FY, Dong SS, Xu XH, Liu YJ, Liu YZ, Shen H, Tian Q, Li J, Deng HW. Genome-wide association study identified UQCC locus for spine bone size in humans. *Bone* 2013;53:129-133.

Deal C, Ma J, Wilkin F, Paquette J, Rozen F, Ge B, Hudson T, Stampfer M, Pollak M: Novel promoter polymorphism in insulin-like growth factor-binding protein-3: correlation with serum levels and interaction with known regulators. *J Clin Endocrinol Metab* 2001;86:1274-1280.

Deng FY, Dong SS, Xu XH, Liu YJ, Liu YZ, Shen H, Tian Q, Li J, Deng HW: Genome-wide association study identified UQCC locus for spine bone size in humans. *Bone* 2013;53:129-133.

Dos Santos C, Essioux L, Teinturier C, Tauber M, Goffin V, Bougnères P: A common polymorphism of the growth hormone receptor is associated with increased responsiveness to growth hormone. *Nature Genet* 2004;36:720-724.

Esteban C, Audí L, Carrascosa A, Fernández-Cancio M, Pérez-Arroyo A, Ulied A, Andaluz P, Arjona R, Albisu M, Clemente M, Gussinyé M, Yeste D: Human growth hormone (GH1) gene polymorphism map in a normal-statured adult population. *Clin Endocrinol (Oxf)* 2007;66:258-268.

Gorai I, Tanaka K, Inada M, Morinaga H, Uchiyama Y, Kikuchi R, Chaki O, Hirahara F: Estrogen-metabolizing gene polymorphisms, but not estrogen receptor-alpha gene polymorphisms, are associated with the onset of menarche in healthy postmenopausal Japanese women. *J Clin Endocrinol Metab* 2003;88:799-803.

Gudbjartsson DF, Walters GB, Thorleifsson G, Stefansson H, Halldorsson BV, Zusmanovich P, Sulem P, Thorlacius S, Gylfason A, Steinberg S, Helgadóttir A, Ingason A, Steinthorsdóttir V, Olafsdóttir EJ, Olafsdóttir GH, Jonsson T, Borch-Johnsen K, Hansen T, Andersen G, Jorgensen T,

- Pedersen O, Aben KK, Witjes JA, Swinkels DW, den Heijer M, Franke B, Verbeek ALM, Becker DM, Yanek LR, Becker LC, Tryggvadottir L, Rafnar T, Gulcher J, Kiemenev LA, Kong A, Thorsteinsdottir U, Stefansson K: Many sequence variants affecting diversity of adult human height. *Nature Genet* 2008;40:609–615.
- Hanevik HI, Hilmarsen HT, Skjelbred CF, Tanbo T, Kahn JA: Variant-beta luteinizing hormone is not associated with poor ovarian response to controlled ovarian hyperstimulation. *Reprod Biol Endocrinol.* 2014;12:20.
- He C, Kraft P, Chen C, Buring JE, Paré G, Hankinson SE, Chanock SJ, Ridker PM, Hunter DJ, Chasman DI: Genome-wide association studies identify loci associated with age at menarche and age at natural menopause. *Nat Genet* 2009;41:724-728.
- Hendriks AEJ, Brown MR, Boot AM, Oostra BA, de Jong FH, Drop SL, Parks JS: Common polymorphisms in the GH/IGF-1 axis contribute to growth in extremely tall subjects. *Growth Horm IGF Res* 2011a;21:318–324.
- Hendriks AEJ, Brown MR, Boot AM, Oostra BA, Drop SLS, Parks JS. Genetic variation in candidate genes like the HMGA2 gene in the extremely tall: *Horm Res Paed* 2011b;76:307–313.
- Hirschfeldova K, Florianova M, Kebrdlova V, Urbanova M, Stekrova J: Detection of SHOX gene aberrations in routine diagnostic practice and evaluation of phenotype scoring form effectiveness. *J Hum Genet* 2017;62:253–257
- Kiel DP, Demissie S, Dupuis J, Lunetta KL, Murabito JM, Karasik D: Genome-wide association with bone mass and geometry in the Framingham Heart Study. *BMC Med Genet* 2007;8 (Suppl 1):S14.
- Kitagawa I, Kitagawa Y, Nagaya T, Tokudome S: Interplay of physical activity and vitamin D receptor gene polymorphism on bone mineral density. *J Epidemiol* 2001;11:229-232.
- Lai J, Vesprini D, Chu W, Jernstrom H, Narod SA: CYP gene polymorphisms and early menarche. *Mol Genet Metab* 2001;74:449–457.
- Lango Allen H, Estrada K, Lettre G, Berndt SI, Weedon MN, Rivadeneira F, et al. Hundreds of variants clustered in genomic loci and biological pathways affect human height. *Nature.* 2010 Oct;467(7317):832–8. Lee JJ, Essers JB, Kugathasan S, Escher JC, Lettre G, Butler JL, Stephens MC, Ramoni MF, Grand RJ, Hirschhorn J: Association of linear growth impairment in pediatric Crohn's disease and a known height locus: a pilot study. *Ann Hum Genet* 2010;74:489-497.
- Lei S-F, Tan L-J, Liu X-G, Wang L, Yan H, Guo Y-F, Liu Y-Z, Xiong D-H, Li J, Yang T-L, Chen X-D, Guo Y, Deng F-Y, Zhang Y-P, Zhu X-Z, Levy S, Papasian CJ, Hamilton JJ, Recker RR, Deng H-W: Genome-wide association study identifies two novel loci containing FLNB and SBF2 genes underlying stature variation. *Hum Molec Genet* 2009;18:1661-1669.
- Letra A, Menezes R, Govil M, Fonseca RF, McHenry T, Granjeiro JM, Castilla EE, Orioli IM, Marazita ML, Vieira AR: Follow-up association studies of chromosome region 9q and nonsyndromic cleft lip/palate. *Am J Med Genet A* 2010;152A:1701-1710.
- Lettre G, Jackson AU, Gieger C, Schumacher FR, Berndt SI, Sanna S, Eyheramendy S, Voight BF, Butler JL, Guiducci C, Illig T, Hackett R, Heid IM, Jacobs KB, Lyssenko V, Uda M; The Diabetes Genetics Initiative; FUSION; KORA; The Prostate, Lung Colorectal and Ovarian Cancer Screening Trial; The Nurses' Health Study; SardiNIA; Boehnke M, Chanock SJ, Groop LC, Hu FB, Isomaa B, Kraft P, Peltonen L, Salomaa V, Schlessinger D, Hunter DJ, Hayes RB, Abecasis GR, Wichmann H-E, Mohlke KL, Hirschhorn JN: Identification of ten loci associated with height highlights new biological pathways in human growth: *Nature Genet* 2008;40:584–591.

- Lucht M, Samochowiec A, Samochowiec J, Jasiewicz A, Grabe HJ, Geissler I, Rimmbach C, Roskopf D, Grzywacz A, Wysiecka JP, Tybura P, Brzuchalski B, Bieńkowski P: Influence of DRD2 and ANKK1 genotypes on apomorphine-induced growth hormone (GH) response in alcohol-dependent patients. *Prog Neuropsychopharmacol Biol Psychiatry* 2010;34:45-49.
- Luo W, Guo Z, Wu M, Hao C, Hu X, Zhou Z, Zhou Z, Yao X, Zhang L, Liu J: Association of peroxisome proliferator-activated receptor $\alpha/\delta/\gamma$ with obesity, and gene-gene interaction, in the Chinese Han population. *J Epidemiol* 2013;23:187-194.
- Medland SE, Zayats T, Glaser B, Nyholt DR, Gordon SD, Wright MJ, Montgomery GW, Campbell MJ, Henders AK, Timpson NJ, Peltonen L, Wolke D, Ring SM, Deloukas P, Martin NG, Smith GD, Evans DM: A variant in LIN28B is associated with 2D:4D finger-length ratio, a putative retrospective biomarker of prenatal testosterone exposure. *Am J Hum Genet* 2010;86:519-525.
- Minagawa M, Yasuda T, Watanabe T, Minamitani K, Takahashi Y, Goltzman D, White JH, Hendy GN, Kohno Y: Association between AAAG repeat polymorphism in the P3 promoter of the human parathyroid hormone (PTH)/PTH-related peptide receptor gene and adult height, urinary pyridinoline excretion and promoter activity. *J Clin Endocrinol Metab* 2002;87:1791-1796.
- Morgan AR, Thompson JM, Murphy R, Black PN, Lam WJ, Ferguson LR, Mitchell EA: Obesity and diabetes genes are associated with being born small for gestational age: results from the Auckland Birthweight Collaborative study. *BMC Med Genet* 2010;11:125.
- Parks JS, Brown MR, Siervogel RM, Towne B: Variation in the estrogen receptor gene and the timing of pubertal growth; in Gilli G, Schell L, Benso L (eds): *Human Growth from Conception to Maturity*. London, Smith-Gordon, 2002, pp 140–144.
- Raivio T, Huhtaniemi I, Anttila R, Siimes MA, Hagenäs L, Nilsson C, Pettersson K, Dunkel L: The role of luteinizing hormone-beta gene polymorphism in the onset and progression of puberty in healthy boys. *J Clin Endocrinol Metab* 1996;81:3278-3282.
- Sanna S, Jackson AU, Nagaraja R, Willer CJ, Chen WM, Bonnycastle LL, Shen H, Timpson N, Lettre G, Usala G, Chines PS, Stringham HM, Scott LJ, Dei M, Lai S, Albai G, Crisponi L, Naitza S, Doherty KF, Pugh EW, Ben-Shlomo Y, Ebrahim S, Lawlor DA, Bergman RN, Watanabe RM, Uda M, Tuomilehto J, Coresh J, Hirschhorn JN, Shuldiner AR, Schlessinger D, Collins FS, Davey Smith G, Boerwinkle E, Cao A, Boehnke M, Abecasis GR, Mohlke KL: Common variants in the GDF5-UQCC region are associated with variation in human height. *Nat Genet* 2008;40:198–203.
- Solc R, Hirschfeldova K, Kebrdlova V, Baxova A: Analysis of common **SHOX** gene sequence variants and ~4.9-kb PAR1 deletion in ISS patients *J Genet*. 2014 Aug;93(2):505-8.
- Soranzo N, Rivadeneira F, Chinappan-Horsley U, Malkina I, Richards JB, Hammond N, Stolk L, Nica A, Inouye M, Hofman A, Stephens J, Wheeler E, Arp P, Gwilliam R, Jhamai PM, Potter S, Chaney A, Ghori MJ, Ravindrarajah R, Ermakov S, Estrada K, Pols HA, Williams FM, McArdle WL, van Meurs JB, Loos RJ, Dermitzakis ET, Ahmadi KR, Hart DJ, Ouwehand WH, Wareham NJ, Barroso I, Sandhu MS, Strachan DP, Livshits G, Spector TD, Uitterlinden AG, Deloukas P: Meta-analysis of genome-wide scans for human adult stature identifies novel Loci and associations with measures of skeletal frame size. *PLoS Genet* 2009;5:e1000445. DOI: 10.1371/journal.pgen.1000445.
- Sovio U, Bennett AJ, Millwood IY, Molitor J, O'Reilly PF, Timpson NJ, Kaakinen M, Laitinen J, Haukka J, Pillas D, Tzoulaki I, Molitor J, Hoggart C, Coin LJ, Whittaker J, Pouta A, Hartikainen AL, Freimer NB, Widen E, Peltonen L, Elliott P, McCarthy MI, Jarvelin MR: Genetic determinants of height growth assessed longitudinally from infancy to adulthood in the Northern Finland Birth Cohort 1966. *PLoS Genet* 2009;5: e1000409. DOI:10.1371/journal.pgen.1000409.

Sulem P, Gudbjartsson DF, Rafnar T, Holm H, Olafsdottir EJ, Olafsdottir GH, Jonsson T, Alexandersen P, Feenstra B, Boyd HA, Aben KK, Verbeek AL, Roeleveld N, Jonasdottir A, Styrkarsdottir U, Steinthorsdottir V, Karason A, Stacey SN, Gudmundsson J, Jakobsdottir M, Thorleifsson G, Hardarson G, Gulcher J, Kong A, Kiemenev LA, Melbye M, Christiansen C, Tryggvadottir L, Thorsteinsdottir U, Stefansson K: Genome-wide association study identifies sequence variants on 6q21 associated with age at menarche. *Nat Genet* 2009;41:734-738.

Tafel J, Branscheid I, Skwarma B, Schlimme M, Morcos M, Algenstaedt P, Hinney A, Hebebrand J, Nawroth P, Hamann A: Variants in the human beta 1-, beta 2-, and beta 3-adrenergic receptor genes are not associated with morbid obesity in children and adolescents. *Diabetes Obes Metab* 2004;6:452-455.

Tao C, Yu T, Garnett S, Briody J, Knight J, Woodhead H, Cowell CT: Vitamin D receptor alleles predict growth and bone density in girls. *Arch Dis Child* 1998;79:488-493.

Tay Y, Peter S, Rigoutsos I, Barahona P, Ahmed S, Dröge P: Insights into the regulation of a common variant of HMGA2 associated with human height during embryonic development. *Stem Cell Rev* 2009;5:328-333.

Wassenaar MJE, Dekkers OM, Pereira AM, Wit JM, Smit JW, Biermasz NR, Romijn JA: Impact of the exon 3-deleted growth hormone (GH) receptor polymorphism on baseline height and the growth response to recombinant human GH therapy in GH-deficient (GHD) and non-GHD children with short stature: a systematic review and meta-analysis. *J Clin Endocrinol Metab* 2009;94:3721-3730.

Weedon MN, Lango H, Lindgren CM, Wallace C, Evans DM, Mangino M, Freathy RM, Perry JR, Stevens S, Hall AS, Samani NJ, Shields B, Prokopenko I, Farrall M, Dominiczak A; Diabetes Genetics Initiative; Wellcome Trust Case Control Consortium, Johnson T, Bergmann S, Beckmann JS, Vollenweider P, Waterworth DM, Mooser V, Palmer CN, Morris AD, Ouwehand WH; Cambridge GEM Consortium, Zhao JH, Li S, Loos RJ, Barroso I, Deloukas P, Sandhu MS, Wheeler E, Soranzo N, Inouye M, Wareham NJ, Caulfield M, Munroe PB, Hattersley AT, McCarthy MI, Frayling TM: Genome-wide association analysis identifies 20 loci that influence adult height. *Nat Genet* 2008;40:575-583.

Widén E, Ripatti S, Cousminer DL, Surakka I, Lappalainen T, Järvelin MR, Eriksson JG, Raitakari O, Salomaa V, Sovio U, Hartikainen AL, Pouta A, McCarthy MI, Osmond C, Kajantie E, Lehtimäki T, Viikari J, Kähönen M, Tyler-Smith C, Freimer N, Hirschhorn JN, Peltonen L, Palotie A: Distinct variants at LIN28B influence growth in height from birth to adulthood. *Am J Hum Genet* 2010;86:773-782.

Winkler JK, Woehning A, Schultz JH, Brune M, Beaton N, Challa TD, Minkova S, Roeder E, Nawroth PP, Friederich HC, Wolfrum C, Rudofsky G: TaqIA polymorphism in dopamine D2 receptor gene complicates weight maintenance in younger obese patients. *Nutrition* 2012;28:996-1001.

Zhao J, Li M, Bradfield JP, Zhang H, Mentch FD, Wang K, Sleiman PM, Kim CE, Glessner JT, Hou C, Keating BJ, Thomas KA, Garris ML, Deliard S, Frackelton EC, Otieno FG, Chiavacci RM, Berkowitz RI, Hakonarson H, Grant SFA: The role of height-associated loci identified in genome wide association studies in the determination of pediatric stature. *BMC Med Genet* 2010;11:96.

Supplemental Table 2: Baseline Demographics by Genotype for Genetic Variants Associated with Idiopathic Short Stature in Case-control Analysis

	Gene	<i>GHR</i>	<i>ESR1</i>	<i>BMP2</i>	<i>ZNF462</i>	<i>IGFBP3</i> ^{&}
Variant rs Number		None	rs2234693	rs967417	rs4743034	rs2854744
Alleles Major/Minor		FL/d3	T/C	C/T	G/A	A/C
Alleles Tall/Short		d3/FL	T/C	C/T	A/G	C/A
	Genotype	Mean±SD (n)	Mean±SD (n)	Mean±SD (n)	Mean±SD (n)	Mean±SD (n)
Birth Weight SDS	AA	-0.30±1.00 (46)	-0.08±1.00 (30)	-0.49±0.63 (19)	-0.50±0.82 (44)	-0.42±0.94 (26)
	AB	-0.45±0.71 (25)	-0.45±0.66 (39)	-0.34±1.09 (38)	0.01±0.97 (25)	-0.29±0.99 (33)
	BB	-0.02±0.90 (10)	-0.40±1.34 (11)	-0.11±0.69 (15)	-0.32±1.61 (2)	-0.21±0.77 (22)
Birth Length SDS	AA	-0.24±1.25 (39)	-0.26±1.12 (25)	-0.13±0.81 (18)	-0.40±1.25 (37)	-0.42±1.35 (21)
	AB	-0.49±1.00 (22)	-0.50±1.15 (34)	-0.50±1.32 (34)	-0.27±1.04 (24)	-0.46±1.15 (31)
	BB	-0.51±1.35 (9)	-0.03±1.41 (10)	-0.59±1.01 (11)	-1.57 (1)	-0.10±1.03 (18)
Chronological Age (y)	AA	11.48±2.60 (54)	11.30±2.80 (34)	11.71±2.95 (23)	11.47±2.55 (50)	11.89±2.06 (32)
	AB	11.68±2.54 (27)	11.39±2.74 (46)	11.59±2.64 (44)	11.42±2.72 (31)	11.38±2.97 (36)
	BB	10.41±2.90 (13)	11.58±1.95 (13)	10.68±1.94 (17)	12.38±4.11 (2)	10.78±2.71 (26)
Bone Age (y)	AA	10.48±2.38 (42)	10.09±2.41 (28)	11.07±2.35 (18)	10.41±2.29 (38)	11.06±2.01 (26)
	AB	10.17±2.73 (24)	10.28±2.89 (35)	10.26±2.67 (39)	10.33±2.88 (28)	9.83±2.85 (30)
	BB	9.65±3.01 (9)	10.67±1.98 (11)	9.74±2.09 (11)	10.37±3.01 (2)	9.92±2.61 (19)
Height SDS	AA	-2.37±0.48 (54)	-2.21±0.39 (34)	-2.37±0.38 (23)	-2.43±0.55 (50)	-2.26±0.44 (32)
	AB	-2.33±0.42 (27)	-2.56±0.51* (46)	-2.37±0.52 (44)	-2.27±0.42 (31)	-2.42±0.49 (36)
	BB	-2.58±0.59 (13)	-2.24±0.45 (13)	-2.45±0.65 (17)	-2.22±0.18 (2)	-2.50±0.51 (26)
Target Height SDS	AA	-0.36±0.64 (48)	-0.35±0.48 (31)	-0.35±0.72 (19)	-0.43±0.75 (46)	-0.21±0.49 (28)
	AB	-0.68±0.75 (27)	-0.55±0.71 (43)	-0.52±0.67 (41)	-0.44±0.66 (27)	-0.44±0.70 (33)
	BB	-0.15±0.56** (11)	-0.03±0.72* (11)	-0.34±0.78 (16)	-0.04±0.65 (2)	-0.67±0.79* (25)
Weight SDS	AA	-1.91±1.08 (53)	-1.82±0.79 (34)	-1.90±1.06 (23)	-2.21±1.05 (50)	-1.96±1.07 (32)
	AB	-1.78±1.02 (27)	-2.04±1.25 (45)	-1.87±1.06 (43)	-1.52±0.95* (30)	-1.88±0.99 (36)
	BB	-2.24±1.17 (13)	-1.86±1.14 (13)	-2.19±1.21 (17)	-2.27±0.19 (2)	-1.93±1.23 (25)
BMI SDS	AA	-0.77±1.39 (53)	-0.76±1.09 (34)	-0.75±1.34 (23)	-1.12±1.30 (50)	-0.93±1.39 (32)
	AB	-0.58±1.38 (27)	-0.76±1.56 (45)	-0.70±1.39 (43)	-0.26±1.19* (30)	-0.66±1.20 (36)
	BB	-1.03±1.36 (13)	-0.81±1.44 (13)	-1.05±1.44 (17)	-1.42±1.14 (2)	-0.66±1.60 (25)
IGF-I SDS	AA	-2.83±1.52 (24)	-2.46±1.27 (16)	-2.70±1.90 (10)	-2.50±1.56 (22)	-2.65±1.72 (18)
	AB	-2.41±1.34 (13)	-2.96±1.53 (15)	-2.52±1.33 (20)	-2.47±1.15 (13)	-2.59±1.14 (13)
	BB	-2.34±0.99 (3)	-2.48±1.54 (9)	-2.39±1.06 (6)	-4.66 (1)	-2.77±1.24 (9)

AA=major allele homozygous; AB=heterozygous; BB=minor allele homozygous; n for individual variables is provided in parentheses after mean±SD. BMI=body mass index; d3=exon 3 deleted allele of *GHR*; FL= full length allele of *GHR*; IGF-I=insulin-like growth factor-I; rs=reference sequence; SDS=standard deviation score; yr=year; *p<0.05; **p=0.051 by ANOVA; [&]IGFBP3 failed to retain significance after adjustment for multiplicity, but is presented for completeness.