The American Journal of Human Genetics, Volume *92*

Supplemental Data

Mutations in *FGF17*, *IL17RD*, *DUSP6*, *SPRY4*, and *FLRT3*

Are Identified in Individuals with Congenital

Hypogonadotropic Hypogonadism

Hichem Miraoui, Andrew A. Dwyer, Gerasimos P. Sykiotis, Lacey Plummer, Wilson Chung, Bihua Feng, Andrew Beenken, Jeff Clarke, Tune H. Pers, Piotr Dworzynski, Kimberley Keefe, Marek Niedziela, Taneli Raivio, William F. Crowley, Jr., Stephanie B. Seminara, Richard Quinton, Virginia A. Hughes, Philip Kumanov, Jacques Young, Maria A. Yialamas, Janet E. Hall, Guy Van Vliet, Jean-Pierre Chanoine, John Rubenstein, Moosa Mohammadi, Pei-San Tsai, Yisrael Sidis, Kasper Lage, and Nelly Pitteloud

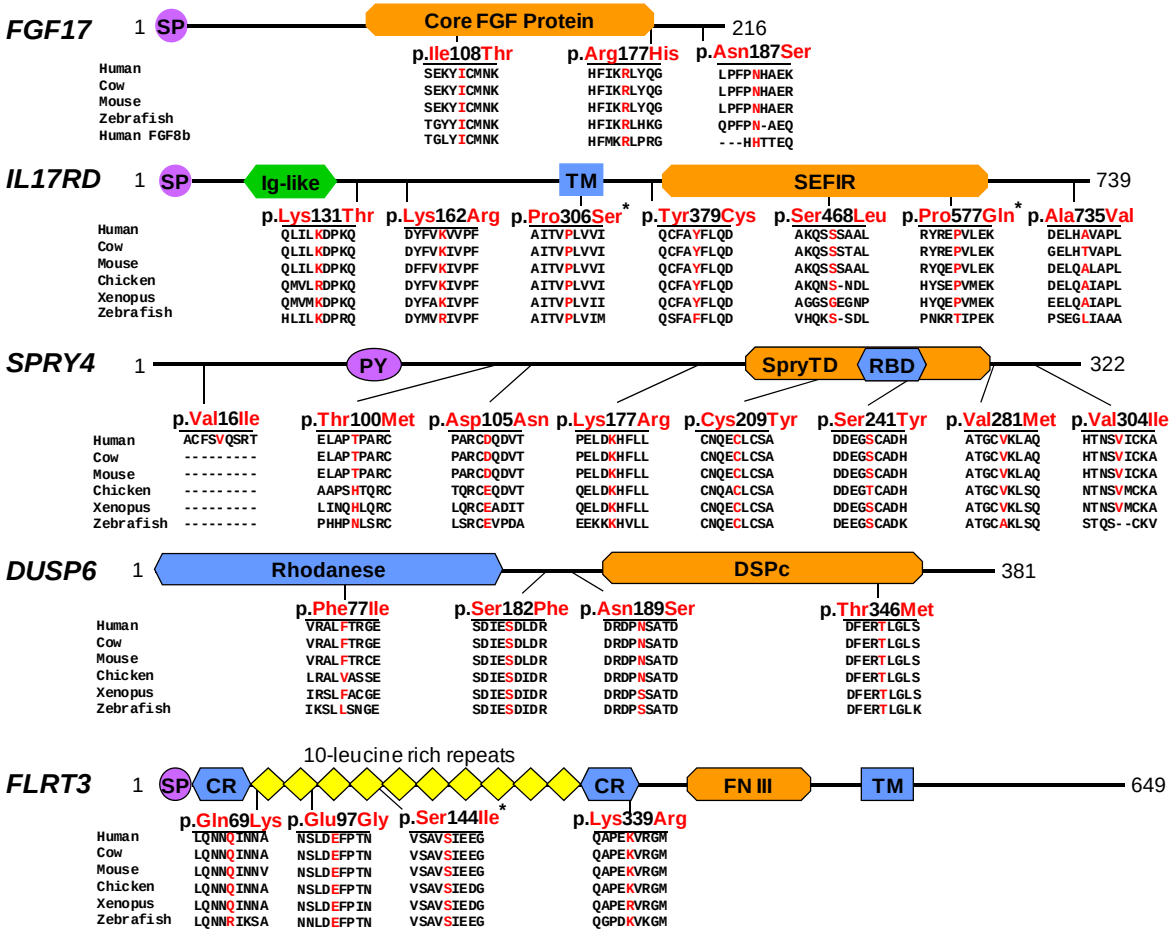

Figure S1. Schematics of *FGF17*, *IL17RD*, *SPRY4*, *DUSP6*, and *FLRT3* Depicting Structural Domains, Location of Mutations, and Conservation across Species

FGF17 : SP= signal peptide.
IL17RD : Ig-like = immunoglobulin-like, TM=transmembrane, SEFIR= SEF/IL-17R domain, * homozygous.
SPRY4 : PY=Phosphotyrosine-binding domain, SpryTD=Spry translocation domain, RBD=Raf1-binding domain.
DUSP6 : DSPc=Dual specificity phosphatases domain.
FLRT3 : CR=Cysteine rich domain, FN III=Fibronectin type-III domain, * homozygous.

The conservation across species was done using ClustalW2 software. The sequence for FGF17 has yet to be characterized in chicken and Xenopus.

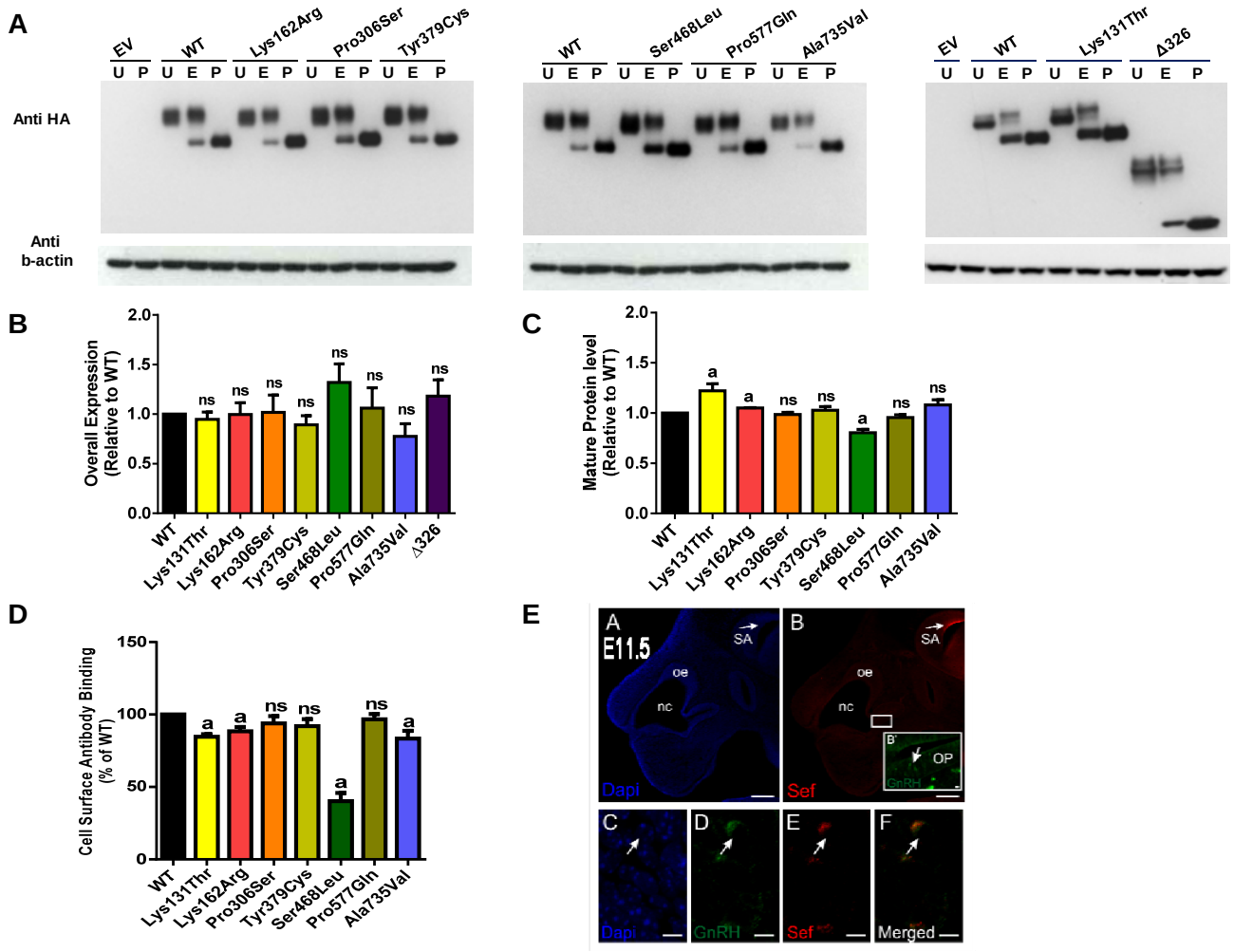

Figure S2. Expression of WT and Mutant IL17RD In Vitro and Expression of Il17rd in the Nasal Region of WT Mouse Embryos (E 11.5)

Panels (A)–(C) depict the overall expression and maturation levels of IL17RD mutants.

(A) A representative western blot analysis of whole cell lysate of HEK293T cells transfected with IL17RD mutants. U = Untreated, E = EndoHf , P = PNGaseF.

(B and C) Quantification of overall expression (B) and maturation level (C) of three independent experiments. Data were normalized to IL17RD WT and are plotted as means +/- SEM. All IL17RD mutants had overall protein expression similar to WT. The p.Ser468Leu mutant had decreased maturation level; Pro306Ser, Tyr379Cys, Pro577Gln and Ala735Val were similar to the WT. The Lys131Thr and Lys162Arg had a small increases compare to the WT.

(D) Cell surface expression of IL17RD mutants in COS7 cells. Data were normalized to IL17RD WT and are plotted as means +/- SEM. Experiments were performed in quadruplets and repeated four times. Lys131Thr, Lys162Arg, Ser468Leu and Ala735Val mutants showed decreased expression levels while Pro306Ser, Tyr379Cys and Pro577Gln were similar to WT. ns, not significant. a, $P < 0.05$ using t-test.

(E) IL17RD (Sef)- and GnRH-immunoreactive (IR) cells in E11.5 WT mouse nasal region (sagittal view).

Table S1. Variants in FGF8 Network Genes in CHH Individuals

	Gene	Nucleotide change	Amino acid change	Exon	Domain	Prediction Programs					Annotated SNP	MAF (%)			Ethnicity	References
						Polyphen	SIFT	PMut	Mutation Taster	NNSplice		Controls	1000 Genome	Individuals		
genes reported here to be mutated in CHH	*FGF17*	c.323T>C	p.Ile108Thr	4	FGF Core	probably damaging	not tolerated	neutral	disease causing	--	--	0	0	0.1	European	This study
	FGF17	c.530G>A	p.Arg177His	5	FGF Core	probably damaging	not tolerated	pathological	disease causing	--	--	0	0	0.1	European	This study
	FGF17	c.560A>G	p.Asn187Ser	5	CT	possibly damaging	tolerated	neutral	disease causing	--	--	0	0	0.1	European	This study
	IL17RD	c.392A>C	p.Lys131Thr	6	link b/w Ig-like & TM	probably damaging	not tolerated	pathological	disease causing	--	rs184758350	0.3	0.3	0.2	European	This study
	IL17RD	c.485A>G	p.Lys162Arg	7	Ig-like	benign	tolerated	neutral	disease causing	--	--	0	0	0.1	European	This study
	IL17RD	c.916C>T	p.Pro306Ser [A]	12	TM	probably damaging	not tolerated	pathological	disease causing	--	--	0	0	0.2	Asian	This study
	IL17RD	c.1136A>G	p.Tyr379Cys	13	SEFIR	probably damaging	tolerated	pathological	disease causing	--	--	0	0	0.1	European	This study
	IL17RD	c.1403C>T	p.Ser468Leu	14	SEFIR	possibly damaging	tolerated	pathological	disease causing	--	--	0	0	0.1	European	This study
	IL17RD	c.1730C>A	p.Pro577Gln [A]	14	SEFIR	possibly damaging	not tolerated	pathological	disease causing	--	--	0	0	0.2	Asian	This study
	IL17RD	c.2204C>T	p.Ala735Val	15	CT	benign	not tolerated	pathological	disease causing	--	--	0	0	0.1	European	This study
	DUSP6	c.229T>A	p.Phe77Ile	1	Rhodanese	benign	tolerated	neutral	disease causing	--	--	0	0	0.1	European	This study
	DUSP6	c.545C>T	p.Ser182Phe	2	link b/w Rhodanese & DSPc	probably damaging	not tolerated	pathological	disease causing	--	--	0	0	0.1	European	This study
	DUSP6	c.566A>G	p.Asn189Ser	2	link b/w Rhodanese & DSPc	benign	tolerated	neutral	disease causing	--	--	0	0	0.2	European	This study
	DUSP6	c.1037C>T	p.Thr346Met	3	DSPc	possibly damaging	not tolerated	pathological	disease causing	--	--	0	0	0.1	European	This study
	SPRY4	c.46G>A	p.Val16Ile	3	NT	benign	not tolerated	neutral	polymorphism	--	--	0	0	0.1	European	This study
	SPRY4	c.299C>T	p.Thr100Met	3	link b/w PY & SpryTD	benign	tolerated	pathological	polymorphism	--	--	0	0	0.1	European	This study
	SPRY4	c.313G>A	p.Asp105Asn	3	link b/w PY & SpryTD	possibly damaging	tolerated	neutral	polymorphism	--	--	0	0	0.1	European	This study
	SPRY4	c.530A>G	p.Lys177Arg	3	link b/w PY & SpryTD	possibly damaging	tolerated	neutral	polymorphism	--	rs78310959	0	0.3	0.5	European	This study
	SPRY4	c.626G>A	p.Cis209Tyr	3	SpryTD	benign	not tolerated	pathological	disease causing	--	--	0.3	0	0.1	European	This study
	SPRY4	c.722C>A	p.Ser241Tyr	3	SpryTD	probably damaging	not tolerated	neutral	disease causing	--	rs139512218	0.6	0.8	0.5	European	This study
	SPRY4	c.841G>A	p.Val281Met	3	SpryTD	probably damaging	not tolerated	neutral	disease causing	--	--	0	0	0.1	European	This study
	SPRY4	c.910G>A	p.Val304Ile	3	CT	benign	not tolerated	neutral	polymorphism	--	--	0	0	0.1	Black/African American	This study
	FLRT3	c.205C>A	p.Gln69Lys	3	Leucine-Rich	possibly damaging	tolerated	neutral	disease causing	--	--	0	0	0.1	European	This study
	FLRT3	c.290A>G	p.Glu97Gly	3	Leucine-Rich	probably damaging	not tolerated	neutral	disease causing	--	--	0	0	0.1	European	This study
	FLRT3	c.431G>T	p.Ser144Ile [A]	3	Leucine-Rich	probably damaging	tolerated	neutral	disease causing	--	--	0	0	0.2	European	This study
	FLRT3	c.1016A>G	p.Lys339Arg	3	CR	benign	tolerated	neutral	disease causing	--	--	0	0	0.1	European	This study
genes known to be mutated in CHH	*FGFR1*	c.232C>T	p.Arg78Cys	3	D1	probably damaging	not tolerated	pathological	disease causing	--	--	0	0	0.1	European	1
	FGFR1	c.296A>G	p.Tyr99Cys	3	D1	probably damaging	not tolerated	pathological	disease causing	--	--	0	0	0.1	European	1, 2, 3
	FGFR1	c.304G>A	p.Val102Ile	3	D1	benign	tolerated	neutral	polymorphism	--	--	0	0	0.1	European	4
	FGFR1	c.350A>G	p.Asn117Ser	3	D1	benign	tolerated	neutral	disease causing	--	--	0	0	0.1	European	3
	FGFR1	c.682T>G	p.Tyr228Asp	6	D2	probably damaging	not tolerated	pathological	disease causing	--	--	0	0	0.1	European	3
	FGFR1	c.710G>A	p.Gly237Asp	6	D2	probably damaging	not tolerated	pathological	disease causing	--	--	0	0	0.1	European	1
	FGFR1	c.709G>A	p.Gly237Ser	6	D2	probably damaging	not tolerated	pathological	disease causing	--	--	0	0	0.1	European	5
	FGFR1	c.716T>C	p.Ile239Thr	6	D2	possibly damaging	not tolerated	neutral	disease causing	--	--	0	0	0.1	European	3
	FGFR1	c.749G>A	p.Arg250Gln	7	link b/w D2 & D3	possibly damaging	not tolerated	pathological	disease causing	--	--	0	0	0.4	European	This study, 3
	FGFR1	c.761G>A	p.Arg254Gln	7	link b/w D2 & D3	benign	not tolerated	pathological	disease causing	--	--	0	0	0.1	European	1
	FGFR1	c.817G>A	p.Val273Met	7	D3	probably damaging	not tolerated	neutral	disease causing	--	--	0	0	0.1	European	6
	FGFR1	c.821A>G	p.Glu274Gly	7	D3	possibly damaging	not tolerated	pathological	disease causing	--	--	0	0	0.1	European	1
	FGFR1	c.1016A>G	p.Tyr339Cys	8b	D3	probably damaging	not tolerated	pathological	disease causing	--	--	0	0	0.1	European	1
	FGFR1	c.1025T>C	p.Leu342Ser	8b	D3	probably damaging	not tolerated	neutral	disease causing	--	--	0	0	0.1	European	7
	FGFR1	c.1037C>G	p.Ser346Cys	8b	D3	probably damaging	not tolerated	pathological	disease causing	--	--	0	0	0.1	European	1
	FGFR1	c.1038_1039insT	p.Ile347fs	8b	D3	--	--	--	disease causing	--	--	0	0	0.1	European	4
	FGFR1	c.1042G>A	p.Gly348Arg	8b	D3	probably damaging	not tolerated	pathological	disease causing	--	--	0	0	0.1	European	This study
	FGFR1	c.1063T>C	p.Trp355Arg	8b	D3	probably damaging	not tolerated	pathological	disease causing	--	--	0	0	0.1	Asian	This study
	FGFR1	c.1097C>T	p.Pro366Leu	9	link b/w D3 & TM	possibly damaging	tolerated	pathological	disease causing	--	--	0	0	0.1	Asian	8
	FGFR1	c.1279G>T	p.Val427Leu	9	FRS2 binding domain	possibly damaging	tolerated	neutral	disease causing	--	--	0	0	0.1	European	4
	FGFR1	c.1286T>A	p.Val429Glu [A]	10	FRS2 binding domain	probably damaging	not tolerated	pathological	disease causing	--	--	0	0	0.2	European	4
	FGFR1	c.1409G>T	p.Arg470Leu	10	TK	benign	tolerated	pathological	disease causing	--	--	0	0	0.1	European	7
	FGFR1	c.1447C>A	p.Pro483Thr	11	TK	probably damaging	tolerated	pathological	disease causing	--	--	0	0	0.1	European	This study

genes known to be mutated in CHH																
	FGFR1	c.1553-2A>G	--	Intron b/w exon 11,12	--	--	--	--	disease causing	Loss splice acceptor site	--	0	0	0.1	European	4
	FGFR1	c.1755C>A	p.Tyr585*	13	TK	--	--	--	disease causing	--	--	0	0	0.1	European	1
	FGFR1	c.1854G>T	p.Lys618Asn	13	TK	probably damaging	not tolerated	pathological	disease causing	Loss splice donor site	--	0	0	0.1	European	3
	FGFR1	c.1864C>T	p.Arg622*	14	TK	--	--	--	disease causing	--	--	0	0	0.2	European	2
	FGFR1	c.2008G>A	p.Glu670Lys	15	TK	probably damaging	not tolerated	pathological	disease causing	--	--	0	0	0.1	European	This study
	FGFR1	c.2011G>C	p.Ala671Pro	15	TK	probably damaging	not tolerated	pathological	disease causing	--	--	0	0	0.1	European	3
	FGFR1	c.2038C>T	p.Gln680*	15	TK	--	--	--	disease causing	--	--	0	0	0.1	European	5
	FGFR1	c.2059G>A	p.Gly687Arg	16	TK	probably damaging	not tolerated	pathological	disease causing	--	--	0	0	0.1	European	9
	FGFR1	c.2075A>G	p.Glu692Gly	16	TK	probably damaging	not tolerated	pathological	disease causing	--	--	0	0	0.1	European	10
	FGFR1	c.2107G>C	p.Gly703Arg	16	TK	probably damaging	not tolerated	pathological	disease causing	--	--	0	0	0.1	European	1
	FGFR1	c.2165C>A	p.Pro722His	16	TK	probably damaging	not tolerated	pathological	disease causing	--	--	0	0	0.1	European	5
	FGFR1	c.2172C>G	p.Asn724Lys	16	TK	possibly damaging	not tolerated	pathological	disease causing	--	--	0	0	0.1	European	5
	FGFR1	c.2302G>T	p.Asp768Tyr	18	CT	probably damaging	not tolerated	pathological	disease causing	--	--	0	0	0.1	European	11
	FGF8	c.40C>A	p.His14Asn	1b	NT	possibly damaging	not tolerated	neutral	disease causing	--	--	0	0	0.1	European	12
	FGF8	c.77C>T	p.Pro26Leu	1c	NT	benign	not tolerated	neutral	polymorphism	--	rs137852660	0.3	0.1	0.1	European	12
	FGF8	c.118T>C	p.Phe40Leu [A]	1c	NT	benign	tolerated	neutral	polymorphism	--	--	0	0	0.2	European	12
	FGF8	c.298A>G	p.Lys100Glu	1d	core FGF binding	possibly damaging	tolerated	pathological	disease causing	--	--	0	0	0.1	European	12
	FGF8	c.379C>G	p.Arg127Gly	2	core FGF binding	probably damaging	tolerated	pathological	disease causing	--	--	0	0	0.1	European	12
	KAL1	c.113C>A	p.Ser38* [B]	1	CR	--	--	--	disease causing	--	--	0	0	0.2	European	4
	KAL1	c.161T>G	p.Leu54Arg [B]	1	CR	possibly damaging	not tolerated	neutral	polymorphism	--	--	0	0	0.2	European	4
	KAL1	c.393G>T	p.Gln131His [A]	2	CR	probably damaging	not tolerated	neutral	disease causing	--	--	0	0	0.4	European	4
	KAL1	c.514T>C	p.Cys172Arg [B]	4	WAP	probably damaging	tolerated	pathological	disease causing	--	--	0	0	0.2	European	13
	KAL1	c.555G>C	p.Lys185Asn	5	FnIII-1	probably damaging	tolerated	neutral	disease causing	--	--	0	0	0.2	European	4
	KAL1	c.571C>T	p.Arg191* [B]	5	FnIII-1	--	--	--	disease causing	--	--	0	0	0.2	European	14, 6, 13
	KAL1	c.769C>T	p.Arg257* [B]	6	FnIII-1	--	--	--	disease causing	--	--	0	0	0.2	European	15
	KAL1	c.814C>T	p.Arg272*	6	FnIII-1	--	--	--	disease causing	--	--	0	0	0.2	European	This study
	KAL1	c.829C>A	p.Pro277Thr	6	FnIII-1	probably damaging	not tolerated	neutral	disease causing	--	--	0	0	0.2	European	4
	KAL1	c.1201_12011del	p.Asn400fs [B]	8	FnIII-2	--	--	--	disease causing	--	--	0	0	0.2	European	4
	KAL1	c.1267C>T	p.Arg423* [B]	9	FnIII-3	--	--	--	disease causing	--	--	0	0	0.2	European	6, 16
	KAL1	c.1369C>T	p.Arg457* [B]	10	FnIII-3	--	--	--	disease causing	--	--	0	0	0.2	European	6, 13
	KAL1	c.1424C>A	p.Ser475* [B]	10	FnIII-3	--	--	--	disease causing	--	--	0	0	0.2	European	4
	KAL1	c.1627G>A	p.Val543Ile [B]	12	FnIII-4	benign	tolerated	neutral	polymorphism	--	--	0	0	0.6	European	4
	KAL1	c.1627G>A	p.Val543Ile	12	FnIII-4	benign	tolerated	neutral	polymorphism	--	--	0	0	0.6	European	4
	KAL1	c.1756C>T	p.Gln586* [B]	12	FnIII-4	--	--	--	disease causing	--	--	0	0	0.2	European	This study
	KAL1	c.1759G>T	p.Val587Leu	12	FnIII-4	probably damaging	tolerated	pathological	disease causing	--	rs137900287	0.4	0.2	0.2	European	4
	KAL1	c.1800del	p.Leu601fs [B]	12	FnIII-4	--	--	--	disease causing	--	--	0	0	0.2	European	4
	KAL1	c.1887_1888del	p.Leu629fs [B]	13	FnIII-4	--	--	--	disease causing	--	--	0	0	0.2	European	4
	HS6ST1	c.916C>T	p.Arg306Trp [A]	2	Sulfotransferase	probably damaging	not tolerated	pathological	disease causing	--	--	0	0	0.2	European	17
	HS6ST1	c.917G>A	p.Arg306Gln	2	Sulfotransferase	probably damaging	tolerated	neutral	disease causing	--	--	0	0	0.1	European	17
	HS6ST1	c.968G>A	p.Arg323Gln	2	Sulfotransferase	probably damaging	not tolerated	pathological	disease causing	--	--	0	0	0.1	European	17
	HS6ST1	c.1144C>T	p.Arg382Trp	2	CT	probably damaging	not tolerated	pathological	disease causing	--	--	0	0	0.4	European & Asian	17
	HS6ST1	c.1210A>G	p.Met404Val	2	CT	benign	tolerated	neutral	disease causing	--	--	0	0	0.1	European	17

SNP= single-nucleotide polymorphism, MAF= minor allele frequency, A= homozygous, B= hemizygous, b/w= between, CT= C-terminus, NT= N-terminus, TM= Transmembrane domain, Ig-like= Immunoglobulin-like domain, SEFIR= SEF/IL-17R domain, DSPc= Dual Specificity Phosphatases domain, PY= Phosphotyrosine-binding domain, SpryTD= Spry Translocation domain, CR= Cysteine rich domain, D1= Domain 1, D2= Domain 2, D3=Domain 3, TK= Tyrosine Kinase domain, WAP= whey acidic protein, FN III= Fibronectin type-III domain.

Table S2. Synonymous Changes in FGF8 Network Genes in CHH Individuals

	Gene	Nucleotide change	Amino acid change	Exon	Domain	NN Splice	Annotated SNP	MAF (%)			Ethnicity	References
								Controls	1000 Genomes	Individuals		
reported here to be mutated in CHH genes	*FGF17*	c.87G>T	p.Pro29Pro	3	link b/w SP & FGF Core	--	--	0	0	0.2	European	This study
	FGF17	c.255G>A	p.Lys85Lys	4	FGF Core	--	--	0	0	0.1	European	This study
	FGF17	c.294C>T	p.Arg98Arg	4	FGF Core	--	--	0	0	0.1	European	This study
	FGF17	c.429C>T	p.Asn143Asn	5	FGF Core	--	--	0	0	0.1	European	This study
	FGF17	c.597C>T	p.Gly199Gly	5	CT	--	rs147413881	0.3	0.4	0.1	European	This study
	IL17RD	c.1209G>A	p.Gly403Gly	14	SEFIR	--	--	0	0	0.1	European	This study
	DUSP6	c.957C>T	p.Ala319Ala	3	DSPc	--	rs148295375	0	0	0.1	Black/African American	This study
	SPRY4	c.300G>A	p.Thr100Thr	3	link b/w PY & SpryTD	--	rs143709567	0	0.1	0.5	European	This study
	SPRY4	c.306C>T	p.Ala102Ala	3	link b/w PY & SpryTD	--	--	0	0	0.1	European	This study
	SPRY4	c.459C>T	p.Arg153Arg	3	link b/w PY & SpryTD	--	--	0	0	0.1	European	This study
	SPRY4	c.735C>T	p.His245His	3	SpryTD	--	--	0	0	0.1	European	This study
	FLRT3	c.831T>C	p.Asp277Asp	3	Leucine-Rich	--	rs149124349	0	0.5	0.2	European	This study
genes known to be mutated in CHH	*FGFR1*	c.273C>T	p.Ser91Ser	3	D1	--	--	0	0	0.1	European	4
	FGFR1	c.336C>T	p.Thr112Thr	3	D1	--	rs148480919	0	0	0.1	European	This study
	FGFR1	c.1098G>A	p.Pro366Pro	9	link b/w D3 & TM	--	rs56174879	0	0	0.1	European	This study
	FGFR1	c.1134C>T	p.Ile378Ile	9	TM	--	--	0.3	0	0.1	European	5
	FGFR1	c.2067C>T	p.Leu689Leu	16	TK	--	--	0	0	0.1	European	This study
	FGF8	c.336C>T	p.Phe112Phe	1D	NT	--	--	0	0	0.1	European	4
	FGF8	c.379C>A	p.Arg127Arg	2	NT	--	--	0	0	0.1	European	4
	FGF8	c.402C>A	p.Gly134Gly	2	NT	--	--	0	0	0.1	European	4
	FGF8	c.582G>A	p.Thr194Thr	3	NT	--	--	0.3	0	0.1	European	4
	FGF8	c.681C>T	p.Pro227Pro	3	CT	--	--	0	0	0.1	European	4
	KAL1	c.231C>T	p.Cys77Cys	2	CR	--	--	0	0	0.2	European	4
	KAL1	c.666A>G	p.Arg222Arg	5	FnIII-1	--	--	0	0	0.2	European	4
	KAL1	c.1953G>A	p.Arg651Arg	13	FnIII-4	--	--	0	0	0.2	European	4
	HS6ST1	c.549G>A	p.Leu183Leu	2	Sulfotransferase	--	--	0	0	0.1	European	This study
	HS6ST1	c.882C>T	p.Thr294Thr	2	Sulfotransferase	--	--	0.3	0	0.1	European	This study

SNP= single-nucleotide polymorphism, MAF= minor allele frequency, b/w= between, SP= Signal Peptide, CT= C-terminus, SEFIR= SEF/IL-17R domain, DSPc= Dual Specificity Phosphatases domain, PY= Phosphotyrosine-binding domain, SpryTD= Spry Translocation domain, D1= Domain 1, D2= Domain 2, D3=Domain 3, TM= Transmembrane domain, TK= Tyrosine Kinase domain, NT= N-terminus, CR= Cysteine Rich domain, FN III= Fibronectin type-III domain.

Table S3. Variants in the Cohort of 350 CHH Individuals of European Descent

Case #	Dx	Sex	# of genes with variants	# of alleles with variants	Gene	Nucleotide change	Amino acid change	Variant type	Genotype	MAF in controls (%)	MAF in individuals (%)
1	KS	F	4	6	*FGFR1*	c.749G>A	p.Arg250Gln	missense	heterozygous	0	0.4
					FGF17	c.323T>C	p.Ile108Thr	missense	heterozygous	0	0.1
					FLRT3	c.290A>G	p.Glu97Gly	missense	heterozygous	0	0.1
					FLRT3	c.431G>T	p.Ser144Ile	missense	homozygous	0	0.2
					HS6ST1	c.916C>T	p.Arg306Trp	missense	homozygous	0	0.2
2	nIHH	F	3	3	*FGFR1*	c.716T>C	p.Ile239Thr	missense	heterozygous	0	0.1
					PROKR2	c.604A>G	p.Ser202Gly	missense	heterozygous	0	0.1
					GNRH1	c.91C>T	p.Arg31Cys	missense	heterozygous	0	0.1
3	nIHH	F	2	3	*FGFR1*	c.1409G>T	p.Arg470Leu	missense	heterozygous	0	0.1
					GNRHR	c.317A>G	p.Gln106Arg	missense	heterozygous	0.3	1.8
					GNRHR	c.785G>A	p.Arg262Gln	missense	heterozygous	0	0.5
4	nIHH	F	2	3	*FGFR1*	c.350A>G	p.Asn117Ser	missense	heterozygous	0	0.1
					GNRHR	c.247C>G	p.Leu83Val	missense	heterozygous	0	0.1
					GNRHR	c.317A>G	p.Gln106Arg	missense	heterozygous	0.3	1.8
5	nIHH	F	2	3	*FGFR1*	c.2165C>A	p.Pro722His	missense	heterozygous	0	0.1
					FGFR1	c.2172C>G	p.Asn724Lys	missense	heterozygous	0	0.1
					TACR3	c.857A>G	p.Lys286Arg	missense	heterozygous	0.3	0.4
6	nIHH	M	2	3	*FGFR1*	c.2302G>T	p.Asp768Tyr	missense	heterozygous	0	0.1
					FGF8	c.118T>C	p.Phe40Leu	missense	homozygous	0	0.2
7	nIHH	M	2	2	*FGFR1*	c.749G>A	p.Arg250Gln	missense	heterozygous	0	0.4
					FGF8	c.298A>G	p.Lys100Glu	missense	heterozygous	0	0.1
8	nIHH	M	2	2	*FGFR1*	c.1854G>T	p.Lys618Asn	missense	heterozygous	0	0.1
					GNRHR	c.785G>A	p.Arg262Gln	missense	heterozygous	0	0.5
9	nIHH	F	2	2	*FGFR1*	c.682T>G	p.Tyr228Asp	missense	heterozygous	0	0.1
					KISS1R	c.565G>A	p.Ala189Thr	missense	heterozygous	0	0.1
10	KS	M	2	2	*FGFR1*	c.1025T>C	p.Leu342Ser	missense	heterozygous	0	0.1
					NSMF	c.1165-14_22del	-	splice site	heterozygous	0	0.1
11	KS	M	2	2	*FGFR1*	c.1864C>T	p.Arg622*	nonsense	heterozygous	0	0.2
					NSMF	c.587G>A	p.Arg196His	missense	heterozygous	0	0.1
12	KS	M	2	2	*FGFR1*	c.1447C>A	p.Pro483Thr	missense	heterozygous	0	0.1
					SPRY4	c.722C>A	p.Ser241Tyr	missense	heterozygous	0.6	0.5
13	KS	F	2	2	*FGFR1*	c.1042G>A	p.Gly348Arg	missense	heterozygous	0	0.1
					IL17RD	c.1136A>G	p.Tyr379Cys	missense	heterozygous	0	0.1
14	KS	F	2	2	*FGFR1*	c.2008G>A	p.Glu670Lys	missense	heterozygous	0	0.1
					FLRT3	c.205C>A	p.Gln69Lys	missense	heterozygous	0	0.1
15	nIHH	F	2	2	*FGFR1*	c.1553-2A>G	-	splice site	heterozygous	0	0.1
					KAL1	c.1759G>T	p.Val587Leu	missense	heterozygous	0.4	0.2
16	KS	M	2	2	*FGFR1*	c.2075A>G	p.Glu692Gly	missense	heterozygous	0	0.1
					DUSP6	c. 545C>T	p.Ser182Phe	missense	heterozygous	0	0.1
17	KS	F	2	2	*FGFR1*	c.1755C>A	p.Tyr585*	nonsense	heterozygous	0	0.1
					TACR3	c.1091G>A	p.Arg364Gln	missense	heterozygous	0	0.1
18	KS	F	2	2	*DUSP6*	c.566A>G	p.Asn189Ser	missense	heterozygous	0	0.2
					SPRY4	c.722C>A	p.Ser241Tyr	missense	heterozygous	0.6	0.5
19	KS	F	2	2	*DUSP6*	c.1037C>T	p.Thr346Met	missense	heterozygous	0	0.1
					SPRY4	c.722C>A	p.Ser241Tyr	missense	heterozygous	0.6	0.5
20	nIHH	F	2	2	*SPRY4*	c.722C>A	p.Ser241Tyr	missense	heterozygous	0.6	0.5
					TACR3	c.1345G>A	p.Ala449Thr	missense	heterozygous	0.6	0.5
21	KS	M	2	2	*IL17RD*	c.2204C>T	p.Ala735Val	missense	heterozygous	0	0.1
					KISS1R	c.581C>A	p.Ala194Asp	missense	heterozygous	0	0.1
22	nIHH	F	2	2	*HS6ST1*	c.1144C>T	p.Arg382Trp	missense	heterozygous	0	0.2
					TAC3	c.238C>A	p.Arg80Ser	missense	heterozygous	0	0.1
23	KS	M	2	2	*KAL1*	c.571C>T	p.Arg191*	nonsense	hemizygous	0	0.2
					TACR3	c.1345G>A	p.Ala449Thr	missense	heterozygous	0.6	0.5
24	KS	F	2	2	*PROK2*	c.70G>C	p.Ala24Pro	missense	heterozygous	0	0.1
					PROKR2	c.343G>A	p.Val115Met	missense	heterozygous	0	0.1
25	nIHH	F	1	2	*GNRHR*	c.30T>A	p.Asn10Lys	missense	heterozygous	0	0.1
					GNRHR	c.31C>A	p.Gln11Lys	missense	heterozygous	0	0.1
					GNRHR	c.959C>T	p.Pro320Leu	missense	heterozygous	0	0.1
26	nIHH	M	1	2	*GNRHR*	c.317A>G	p.Gln106Arg	missense	homozygous	0.2	1.8
					GNRHR	c.651C>A	p.Ser217Arg	missense	heterozygous	0	0.1
27	KS	M	1	2	*GNRHR*	c.286C>T	p.Pro96Ser	missense	heterozygous	0	0.1
					GNRHR	c.317A>G	p.Gln106Arg	missense	heterozygous	0.2	1.8
28	KS	F	1	2	*KAL1*	c.393G>T	p.Gln131His	missense	homozygous	0	0.4
					KAL1	c.829C>A	p.Pro277Thr	missense	heterozygous	0	0.2

29	nIHH	M	1	2	*GNRHR*	c.317A>G	p.Gln106Arg	missense	homozygous	0.2	1.8
30	KS	F	1	2	*GNRHR*	c.317A>G	p.Gln106Arg	missense	homozygous	0.2	1.8
31	nIHH	F	1	2	*GNRHR*	c.785G>A	p.Arg262Gln	missense	homozygous	0	0.5
32	KS	M	1	2	*FGFR1*	c.1286T>A	p.Val429Glu	missense	homozygous	0	0.2
33	nIHH	M	1	2	*KISS1R*	c.443T>C	p.Leu148Ser	missense	homozygous	0	0.2
34	KS	M	1	2	*PROK2*	c.163del	p.Ile55fs	frameshift	homozygous	0	0.2
35	nIHH	M	1	2	*TACR3*	c.80C>A	p.Ser27*	nonsense	homozygous	0	0.2
36	nIHH	M	1	2	*TACR3*	c.1057C>T	p.Pro353Ser	missense	homozygous	0	0.2
37	nIHH	M	1	2	*TACR3*	c.824G>A	p.Trp275*	nonsense	homozygous	0	0.7
38	nIHH	M	1	2	*TACR3*	c.766T>C	p.Tyr256His	missense	homozygous	0	0.2
39	KS	M	1	1*	*KAL1*	c.113C>A	p.Ser38*	nonsense	hemizygous	0	0.2
40	KS	M	1	1*	*KAL1*	c.161T>G	p.Leu54Arg	missense	hemizygous	0	0.2
41	KS	M	1	1*	*KAL1*	c.514T>C	p.Cys172Arg	missense	hemizygous	0	0.2
42	KS	M	1	1*	*KAL1*	c.769C>T	p.Arg257*	nonsense	hemizygous	0	0.2
43	KS	M	1	1*	*KAL1*	c.814C>T	p.Arg272*	nonsense	hemizygous	0	0.2
44	KS	M	1	1*	*KAL1*	c.1201_12011del	p.Asn400fs	frameshift	hemizygous	0	0.2
45	KS	M	1	1*	*KAL1*	c.1267C>T	p.Arg423*	nonsense	hemizygous	0	0.2
46	KS	M	1	1*	*KAL1*	c.1369C>T	p.Arg457*	nonsense	hemizygous	0	0.2
47	KS	M	1	1*	*KAL1*	c.1369C>T	p.Arg457*	nonsense	hemizygous	0	0.2
48	KS	M	1	1*	*KAL1*	c.1424C>A	p.Ser475*	nonsense	hemizygous	0	0.2
49	KS	M	1	1*	*KAL1*	c.1627G>AI	p.Val543Ile	missense	hemizygous	0	0.4
50	KS	M	1	1*	*KAL1*	c.1627G>AI	p.Val543Ile	missense	hemizygous	0	0.4
51	KS	M	1	1*	*KAL1*	c.1756C>T	p.Gln586*	nonsense	hemizygous	0	0.2
52	KS	M	1	1*	*KAL1*	c.1800del	p.Leu601fs	frameshift	hemizygous	0	0.2
53	KS	M	1	1*	*KAL1*	c.1887_1888del	p.Leu629fs	frameshift	hemizygous	0	0.2
54	nIHH	F	1	1	*FGF8*	c.40C>A	p.His14Asn	missense	heterozygous	0	0.1
55	KS	M	1	1	*FGF8*	c.77C>T	p.Pro26Leu	missense	heterozygous	0.3	0.1
56	KS	F	1	1	*FGF8*	c.379C>G	p.Arg127Gly	missense	heterozygous	0	0.1
57	nIHH	M	1	1	*FGF17*	c.530G>A	p.Arg177His	missense	heterozygous	0	0.1
58	KS	M	1	1	*FGF17*	c.560A>G	p.Asn187Ser	missense	heterozygous	0	0.1
59	KS	M	1	1	*FGFR1*	c.232C>T	p.Arg78Cys	missense	heterozygous	0	0.1
60	nIHH	M	1	1	*FGFR1*	c.296A>G	p.Tyr99Cys	missense	heterozygous	0	0.1
61	KS	M	1	1	*FGFR1*	c.304G>A	p.Val102Ile	missense	heterozygous	0	0.1
62	KS	F	1	1	*FGFR1*	c.710G>A	p.Gly237Asp	missense	heterozygous	0	0.1
63	KS	M	1	1	*FGFR1*	c.709G>A	p.Gly237Ser	missense	heterozygous	0	0.1
64	nIHH	F	1	1	*FGFR1*	c.749G>A	p.Arg250Gln	missense	heterozygous	0	0.4
65	KS	M	1	1	*FGFR1*	c.761G>A	p.Arg254Gln	missense	heterozygous	0	0.1
66	KS	M	1	1	*FGFR1*	c.817G>A	p.Val273Met	missense	heterozygous	0	0.1
67	KS	M	1	1	*FGFR1*	c.821A>G	p.Glu274Gly	missense	heterozygous	0	0.1
68	KS	M	1	1	*FGFR1*	c.1016A>G	p.Tyr339Cys	missense	heterozygous	0	0.1
69	KS	M	1	1	*FGFR1*	c.1037C>G	p.Ser346Cys	missense	heterozygous	0	0.1
70	KS	M	1	1	*FGFR1*	c.1038_1039insT	p.Ile347fs	frameshift	heterozygous	0	0.1
71	nIHH	F	1	1	*FGFR1*	c.1279G>T	p.Val427Leu	missense	heterozygous	0	0.1
72	nIHH	F	1	1	*FGFR1*	c.1864C>T	p.Arg622*	nonsense	heterozygous	0	0.2
73	nIHH	M	1	1	*FGFR1*	c.2011G>C	p.Ala671Pro	missense	heterozygous	0	0.1
74	nIHH	M	1	1	*FGFR1*	c.2038C>T	p.Gln680*	nonsense	heterozygous	0	0.1
75	KS	M	1	1	*FGFR1*	c.2059G>A	p.Gly687Arg	missense	heterozygous	0	0.1
76	KS	M	1	1	*FGFR1*	c.2107G>C	p.Gly703Arg	missense	heterozygous	0	0.1
77	KS	F	1	1	*KAL1*	c.555G>C	p.Lys185Asn	missense	heterozygous	0	0.2
78	KS	F	1	1	*KAL1*	c.1627G>A	p.Val543Ile	missense	heterozygous	0	0.4
79	nIHH	F	1	1	*DUSP6*	c.229T>A	p.Phe77Ile	missense	heterozygous	0	0.1
80	KS	M	1	1	*DUSP6*	c.566A>G	p.Asn189Ser	missense	heterozygous	0	0.2
81	KS	M	1	1	*FLRT3*	c.1016A>G	p.Lys339Arg	missense	heterozygous	0	0.1
82	nIHH	M	1	1	*HS6ST1*	c.917G>A	p.Arg306Gln	missense	heterozygous	0	0.1
83	KS	M	1	1	*HS6ST1*	c.968G>A	p.Arg323Gln	missense	heterozygous	0	0.1
84	nIHH	M	1	1	*HS6ST1*	c.1144C>T	p.Arg382Trp	missense	heterozygous	0	0.2
85	KS	M	1	1	*HS6ST1*	c.1210A>G	p.Met404Val	missense	heterozygous	0	0.1
86	KS	M	1	1	*IL17RD*	c.1403C>T	p.Ser468Leu	missense	heterozygous	0	0.1
87	KS	M	1	1	*IL17RD*	c.392A>C	p.Lys131Thr	missense	heterozygous	0.3	0.2
88	KS	M	1	1	*IL17RD*	c.392A>C	p.Lys131Thr	missense	heterozygous	0.3	0.2
89	KS	F	1	1	*IL17RD*	c.485A>G	p.Lys162Arg	missense	heterozygous	0	0.1
90	nIHH	M	1	1	*SPRY4*	c.46G>A	p.Val16Ile	missense	heterozygous	0	0.1
91	KS	M	1	1	*SPRY4*	c.299C>T	p.Thr100Met	missense	heterozygous	0	0.1
92	nIHH	M	1	1	*SPRY4*	c.313G>A	p.Asp105Asn	missense	heterozygous	0	0.1
93	KS	M	1	1	*SPRY4*	c.530A>G	p.Lys177Arg	missense	heterozygous	0	0.5
94	KS	M	1	1	*SPRY4*	c.530A>G	p.Lys177Arg	missense	heterozygous	0	0.5
95	KS	M	1	1	*SPRY4*	c.530A>G	p.Lys177Arg	missense	heterozygous	0	0.5
96	KS	M	1	1	*SPRY4*	c.530A>G	p.Lys177Arg	missense	heterozygous	0	0.5
97	KS	M	1	1	*SPRY4*	c.626G>A	p.Cys209Tyr	missense	heterozygous	0.3	0.1
98	nIHH	M	1	1	*SPRY4*	c.841G>A	p.Val281Met	missense	heterozygous	0	0.1
99	KS	F	1	1	*GNRHR*	c.317A>G	p.Gln106Arg	missense	heterozygous	0.3	1.8
100	KS	M	1	1	*GNRHR*	c.317A>G	p.Gln106Arg	missense	heterozygous	0.3	1.8

101	nIHH	F	1	1	*GNRHR*	c.317A>G	p.Gln106Arg	missense	heterozygous	0.3	1.8
102	nIHH	M	1	1	*GNRHR*	c.317A>G	p.Gln106Arg	missense	heterozygous	0.3	1.8
103	nIHH	F	1	1	*GNRHR*	c.436C>T	p.Pro146Ser	missense	heterozygous	0	0.1
104	nIHH	M	1	1	*KISS1R*	c.1079A>T	p.His360Leu	missense	heterozygous	0	0.1
105	KS	F	1	1	*PROKR2*	c.57del	p.Asp19fs	missense	heterozygous	0	0.1
106	nIHH	F	1	1	*PROKR2*	c.253C>T	p.Arg85Cys	missense	heterozygous	0	0.1
107	KS	M	1	1	*PROKR2*	c.254G>A	p.Arg85His	missense	heterozygous	0	0.1
108	KS	M	1	1	*PROKR2*	c.484A>T	p.Lys162*	missense	heterozygous	0	0.1
109	KS	M	1	1	*PROKR2*	c.491G>A	p.Arg164Gln	missense	heterozygous	0	0.1
110	KS	M	1	1	*PROKR2*	c.518T>G	p.Leu173Arg	missense	heterozygous	0	0.1
111	KS	M	1	1	*PROKR2*	c.889G>A	p.Val297Ile	missense	heterozygous	0	0.1
112	KS	M	1	1	*PROKR2*	c.1069C>T	p.Arg357Trp	missense	heterozygous	0	0.1
113	KS	M	1	1	*PROK2*	c.101G>A	p.Cys34Tyr	missense	heterozygous	0	0.1
114	KS	F	1	1	*NSMF*	c.689C>G	p.Thr203Ser	missense	heterozygous	0	0.1
115	nIHH	M	1	1	*GNRH1*	c.217C>T	p.Arg73*	missense	heterozygous	0	0.1
116	nIHH	M	1	1	*TACR3*	c.824G>A	p.Trp275*	nonsense	heterozygous	0	0.7
117	nIHH	M	1	1	*TACR3*	c.824G>A	p.Trp275*	nonsense	heterozygous	0	0.7
118	nIHH	F	1	1	*TACR3*	c.623G>A	p.Trp208*	nonsense	heterozygous	0	0.1
119	KS	M	1	1	*TACR3*	c.1264A>G	p.Arg422Gly	missense	heterozygous	0	0.1
120	nIHH	M	1	1	*TACR3*	c.857A>G	p.Lys286Arg	missense	heterozygous	0.3	0.4
121	nIHH	M	1	1	*TACR3*	c.1345G>A	p.Ala449Thr	missense	heterozygous	0.6	0.5
122	nIHH	M	1	1	*TACR3*	c.824G>A	p.Trp275*	nonsense	heterozygous	0	0.7
123	nIHH	M	1	1	*TACR3*	c.857A>G	p.Lys286Arg	missense	heterozygous	0.3	0.4
124	nIHH	M	1	1	*TACR3*	c.1345G>A	p.Ala449Thr	missense	heterozygous	0.6	0.5

Dx= diagnosis, M= male, F= female, MAF= minor allele frequency.

Table S4. Variants in Unaffected Control Subjects

#	Sex	# of genes with variants	# of alleles with variants	Gene	Nucleotide change	Amino acid change	Variant type	Genotype	Prediction Programs					Annotated SNP	MAF in controls (%)	MAF in individuals (%)	Seen in individuals
									Polyphen	SIFT	pMut	Mutation Taster	NNSplice				
1	F	1	2	*NSMF*	c.1438A>G	p.Thr480Ala	missense	heterozygous	benign	--	pathological	polymorphism	--	rs121918340	0.3	0	no
				NSMF	c.1447A>G	p.Thr483Ala	missense	heterozygous	benign	--	pathological	polymorphism	--	--	0.3	0	no
2	M	1	1	*NSMF*	c.763G>A	p.Ala255Thr	missense	heterozygous	probably damaging	--	neutral	disease causing	--	rs142726563	0.3	0	no
3	F	1	1	*NSMF*	c.1492C>T	p.Gln498*	missense	heterozygous	--	--	--	disease causing	--	--	0.3	0	no
4	M	1	1*	*KAL1*	c.1759G>T	p.Val587Leu	missense	hemizygous	probably damaging	tolerated	pathological	disease causing	--	--	0.4	0.2	this study
5	F	1	1	*KAL1*	c.94G>A	p.Ala32Thr	missense	heterozygous	benign	not tolerated	neutral	polymorphism	--	--	0.3	0	no
6	M	1	1	*FGFR1*	c.1368G>T	p.Met456Ile	missense	heterozygous	benign	tolerated	neutral	disease causing	--	--	0.3	0	no
7	F	1	1	*FGFR1*	c.1609A>G	p.Met537Val	missense	heterozygous	benign	tolerated	neutral	disease causing	--	--	0.3	0	no
8	F	1	1	*FGF8*	c.1-5G>A	-	missense	heterozygous	--	--	--	disease causing	--	--	0.3	0	no
9	F	1	1	*FGF8*	c.77C>T	p.Pro26Leu	missense	heterozygous	probably damaging	not tolerated	neutral	polymorphism	--	rs137852660	0.3	0.1	this study
10	M	1	1	*FGF8*	c.451G>A	p.Gly151Ser	missense	heterozygous	possibly damaging	tolerated	pathological	disease causing	--	--	0.3	0	no
11	F	1	1	*IL17RD*	c.311G>C	p.Gly104Ala	missense	heterozygous	probably damaging	not tolerated	neutral	disease causing	--	--	0.3	0	no
12	M	1	1	*IL17RD*	c.392A>C	p.Lys131Thr	missense	heterozygous	possibly damaging	not tolerated	pathological	disease causing	--	rs184758350	0.3	0.2	this study
13	M	1	1	*IL17RD*	c.1058G>A	p.Arg353Gln	missense	heterozygous	benign	tolerated	pathological	disease causing	--	--	0.3	0	no
14	M	1	1	*IL17RD*	c.2009C>T	p.Pro670Leu	missense	heterozygous	probably damaging	not tolerated	pathological	disease causing	--	rs143119752	0.3	0	no
15	M	1	1	*SPRY4*	c.722C>A	p.Ser241Tyr	missense	heterozygous	probably damaging	not tolerated	neutral	disease causing	--	rs139512218	0.6	0.5	this study
16	M	1	1	*SPRY4*	c.722C>A	p.Ser241Tyr	missense	heterozygous	probably damaging	not tolerated	neutral	disease causing	--	rs139512218	0.6	0.5	this study
17	M	1	1	*HS6ST1*	c.1168G>A	p.Glu390Lys	missense	heterozygous	benign	tolerated	neutral	disease causing	--	--	0.3	0	no
18	F	1	1	*HS6ST1*	c.1235A>G	p.*412Trp	missense	heterozygous	--	--	--	polymorphism	--	--	0.6	0	no
19	M	1	1	*HS6ST1*	c.1235A>G	p.*412Trp	missense	heterozygous	--	--	--	polymorphism	--	--	0.6	0	no
20	M	1	1	*HS6ST1*	c.1236G>C	p.*412Tyr	missense	heterozygous	--	--	--	polymorphism	--	--	0.3	0	no
21	M	1	1	*GNRHR*	c.317A>G	p.Gln106Arg	missense	heterozygous	probably damaging	tolerated	neutral	polymorphism	--	rs104893836	0.3	1.8	this study
22	M	1	1	*PROKR2*	c.868C>T	p.Pro290Ser	missense	heterozygous	probably damaging	not tolerated	neutral	polymorphism	--	rs149992595	0.3	0	litterature
23	M	1	1	TACR3	c.107C>A	p.Ala36Glu	missense	heterozygous	benign	tolerated	pathological	polymorphism	--	--	0.3	0	no
24	F	1	1	TACR3	c.857A>G	p.Lys286Arg	missense	heterozygous	benign	tolerated	neutral	disease causing	--	rs2276973	0.3	0.4	this study
25	M	1	1	TACR3	c.1345G>A	p.Ala449Thr	missense	heterozygous	benign	tolerated	neutral	polymorphism	--	rs17033889	0.6	0.5	this study
26	M	1	1	TACR3	c.1345G>A	p.Ala449Thr	missense	heterozygous	benign	tolerated	neutral	polymorphism	--	rs17033889	0.6	0.5	this study

M= male, F= female, SNP= single-nucleotide polymorphism, MAF= minor allele frequency

Table S5. IBAS Rank

Rank in Proteome	Significance of IBAS score	Candidate HUGO	IBAS Score	Candidate ENSG	Kallmann interactor HUGO	Interaction Data Source (Database PMID OrganismID:SWISSProtID::Database PMID OrganismID:SWISSProtID)
1 of 12507	P<0.007	**IL17RD**	0.489135803	ENSG00000144730	FGFR1	hprd 12604616 9606:P11362-Q8NFM7 15 vv::hprd 12604616 9606:P11362-Q8NFM7 hprd_0 vv
2 of 12507	P<0.007	**FGF17**	0.408032946	ENSG00000162344	FGFR1	hprd 10751172 9606:P11362-O60258 32 vt
3 of 12507	P<0.007	FGF19	0.408032946	ENSG00000158815	FGFR1	KEGG_PPrel 0 9606:ENSG00000162344-ENSG00000077782
4 of 12507	P<0.007	FGF18	0.408032946	ENSG00000156427	FGFR1	hprd 10751172 9606:P11362-O76093 33 vt
5 of 12507	P<0.007	FGF13	0.408032946	ENSG00000129682	FGFR1	KEGG_PPrel 0 9606:ENSG00000077782-ENSG00000129682
6 of 12507	P<0.007	FGF6	0.408032946	ENSG00000111241	FGFR1	hprd 8663044 9606:P10767-P11362 2 vt
7 of 12507	P<0.007	FGF8	0.408032946	ENSG00000107831	FGFR1	hprd 10574949 9606:P55075-P11362 25 vt::hprd 10574949 9606:P55075-P11362 25 vv
8 of 12507	P<0.007	FGF9	0.408032946	ENSG00000102678	FGFR1	hprd 10574949 9606:P31371-P11362 26 vt::hprd 10574949 9606:P31371-P11362 26 vv
9 of 12507	P<0.007	FGF22	0.408032946	ENSG00000070388	FGFR1	KEGG_PPrel 0 9606:ENSG00000070388-ENSG00000077782
10 of 12507	P<0.007	KL	0.408032946	ENSG00000133116	FGFR1	reactome_indirec 0 9606:ENSG00000133116-ENSG00000077782
11 of 12507	P<0.007	FGF12	0.408032946	ENSG00000114279	FGFR1	KEGG_PPrel 0 9606:ENSG00000114279-ENSG00000077782
12 of 12507	P<0.007	BNIP2	0.408032946	ENSG00000140299	FGFR1	GRID_xml 10551883 9606:P11362-NP_004321 6301 Invivo::hprd 10551883 9606:P11362-Q12982 12 vt::hprd 10551883 9606:P11362-Q12982 12 vv
13 of 12507	P<0.007	SNAI1	0.408032946	ENSG00000124216	FGFR1	KEGG_PPrel 0 9606:ENSG00000124216-ENSG00000077782
14 of 12507	P<0.007	FGF11	0.408032946	ENSG00000161958	FGFR1	KEGG_PPrel 0 9606:ENSG00000077782-ENSG00000161958
15 of 12507	P<0.007	REN	0.408032946	ENSG00000143839	PCSK1	hprd 1597471 9606:P00797-P29120 2 vt::hprd 1597471 9606:P00797-P29120 2 vv
16 of 12507	P<0.007	FGF21	0.408032946	ENSG00000105550	FGFR1	KEGG_PPrel 0 9606:ENSG00000077782-ENSG00000105550
17 of 12507	P<0.007	FGF14	0.408032946	ENSG00000102466	FGFR1	KEGG_PPrel 0 9606:ENSG00000102466-ENSG00000077782
18 of 12507	P<0.007	IAPP	0.408032946	ENSG00000121351	PCSK1	hprd 3053705 9606:P10997-P29120 0 vt::hprd 3053705 9606:P10997-P29120 1 vv::hprd 3053705 9606:P10997-P29120 hprd_0 vv
19 of 12507	P<0.007	FRS2	0.407679349	ENSG00000166225	FGF8	reactome_indirec 0 9606:ENSG00000107831-ENSG00000166225
19 of 12507	P<0.007	FRS2	0.407679349	ENSG00000166225	FGFR1	BIND 11729184 10090:NP_034336-NP_808466 130922 elisa::BIND 11729184 10090:NP_034336-NP_808466 130922 immunoprecipitation::BIND 10629055 10090:NP_034336-NP_808466 197402 affinity-chromatography::BIND 10629055 10090:NP_034336-NP_808466 197402 immunoprecipitation::GRID_xml 11877385 9606:P11362-NP_001036020 287448 Reconstituted Complex::GRID_xml 10629055 9606:P11362-NP_001036020 287738 Affinity Capture-Western::GRID_xml 9660748 9606:P11362-NP_001036020 288016 Two-hybrid::GRID_xml 11090629 9606:P11362-NP_001036020 6304 Invivo::hprd 11877385 9606:P11362-Q8WU20 13 vt::hprd 11877385 9606:P11362-Q8WU20 13 vv
20 of 12507	P<0.007	FRS3	0.407679349	ENSG00000137218	FGFR1	GRID_xml 9660748 9606:NP_006644-P11362 6310 Two-hybrid::hprd 9660748 9606:O43559-P11362 14 2H::hprd 9660748 9606:O43559-P11362 14 vt
20 of 12507	P<0.007	FRS3	0.407679349	ENSG00000137218	FGF8	reactome_indirec 0 9606:ENSG00000107831-ENSG00000137218
21 of 12507	P<0.007	TAC3	0.407679349	ENSG00000166863	TACR3	GRID_xml 8990205 9606:NP_001050-Q9UHF0 10328 Invivo::hprd 8990205 9606:P29371-Q9UHF0 1 vt::hprd 8990205 9606:P29371-Q9UHF0 1 vv
21 of 12507	P<0.007	TAC1	0.407679349	ENSG00000006128	TACR3	GRID_xml 8702757 9606:P20366-NP_001050 287509 Reconstituted Complex::hprd 9272936 9606:P20366-P29371 3 vv::hprd 9272936 9606:P20366-P29371 hprd_0 vv
22 of 12507	P<0.007	RGS10	0.407679349	ENSG00000148908	GNRHR	hprd 12062898 9606:O43665-P30968 1 vv
23 of 12507	P<0.007	TAC4	0.407679349	ENSG00000176358	TACR3	hprd 11786503 9606:P29371-255061 2 vt::hprd 11786503 9606:P29371-255061 2 vv
24 of 12507	P<0.007	MMP16	0.407679349	ENSG00000156103	KISS1	hprd 12879005 9606:Q15726-P51512 1 vt::hprd 12879005 9606:Q15726-P51512 1 vv
25 of 12507	P<0.007	GNRH	0.407679349	ENSG00000147437	GNRHR	hprd 9414473 9606:P01148-P30968 2 vv::hprd 9414473 9606:P01148-P30968 hprd_0 vv
26 of 12507	P<0.007	GNRHR	0.407679349	ENSG00000109163	GNRH	hprd 9414473 9606:P01148-P30968 2 vv::hprd 9414473 9606:P01148-P30968 hprd_0 vv
27 of 12507	P<0.007	MMP24	0.407679349	ENSG00000125966	KISS1	hprd 12879005 9606:Q9Y5R2-Q15726 3 vt::hprd 12879005 9606:Q9Y5R2-Q15726 3 vv::hprd 12879005 9606:Q9Y5R2-Q15726 hprd_0 vv
28 of 12507	P<0.007	GPR54	0.407679349	ENSG00000116014	KISS1	GRID_xml 11457843 9606:NP_115940-NP_002247 26232 Invivo::hprd 11457843 9606:Q969F8-Q15726 4 vt::hprd 11457843 9606:Q969F8-Q15726 4 vv::hprd 11457843 9606:Q969F8-Q15726 hprd_0 vv
29 of 12507	P<0.007	MMP2	0.407679349	ENSG00000087245	FGFR1	hprd 8692946 9606:P11362-P08253 6 vt::hprd 8692946 9606:P11362-P08253 6 vv
30 of 12507	P<0.007	MMP2	0.407679349	ENSG00000087245	KISS1	hprd 12879005 9606:Q15726-P08253 23 vt::hprd 12879005 9606:Q15726-P08253 23 vv::hprd 12879005 9606:Q15726-P08253 hprd_0 vv
31 of 12507	P<0.007	GPRASP1	0.407325753	ENSG00000198932	TAC3	GRID_xml 16169070 9606:Q9UHF0-NP_001092881 270830 Two-hybrid::hprd 16169070 9606:Q9UHF0-Q5JY77 15 2H::MINT 16169070 9606:Q9UHF0-Q5JY77 15513 two hybrid
31 of 12507	P<0.007	GPRASP1	0.407325753	ENSG00000198932	TACR3	hprd 15452121 9606:P29371-Q5JY77 3 vt
32 of 12507	P<0.007	TACR1	0.326576492	ENSG00000115353	TAC3	hprd 12727971 9606:Q9UHF0-P25103 2 vt
33 of 12507	P<0.007	TACR3	0.326576492	ENSG00000169836	TAC3	GRID_xml 8990205 9606:NP_001050-Q9UHF0 10328 Invivo::hprd 8990205 9606:P29371-Q9UHF0 1 vt::hprd 8990205 9606:P29371-Q9UHF0 1 vv
34 of 12507	P<0.007	TACR2	0.326576492	ENSG00000075073	TAC3	GRID_xml 7961636 9606:NP_001048-Q9UHF0 10317 Invivo::hprd 7961636 9606:P21452-Q9UHF0 1 vv::hprd 7961636 9606:P21452-Q9UHF0 hprd_0 vv
35 of 12507	P<0.007	KISS1	0.326576492	ENSG00000170498	GPR54	GRID_xml 11457843 9606:NP_115940-NP_002247 26232 Invivo::hprd 11457843 9606:Q969F8-Q15726 4 vt::hprd 11457843 9606:Q969F8-Q15726 4 vv::hprd 11457843 9606:Q969F8-Q15726 hprd_0 vv

All proteins with a significant IBAS score and the CHH-associated protein with which they interact. The last column indicates the source of evidence for the interaction. Genes reported in this study (*IL17RD, FGF17*) are noted in bold. The proteins highlighted in yellow are among the ones the IBAS model was trained on.

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