

## **Supplementary Appendix**

*HS6ST1* insufficiency causes self-limited delayed puberty in contrast with other GnRH deficiency genes

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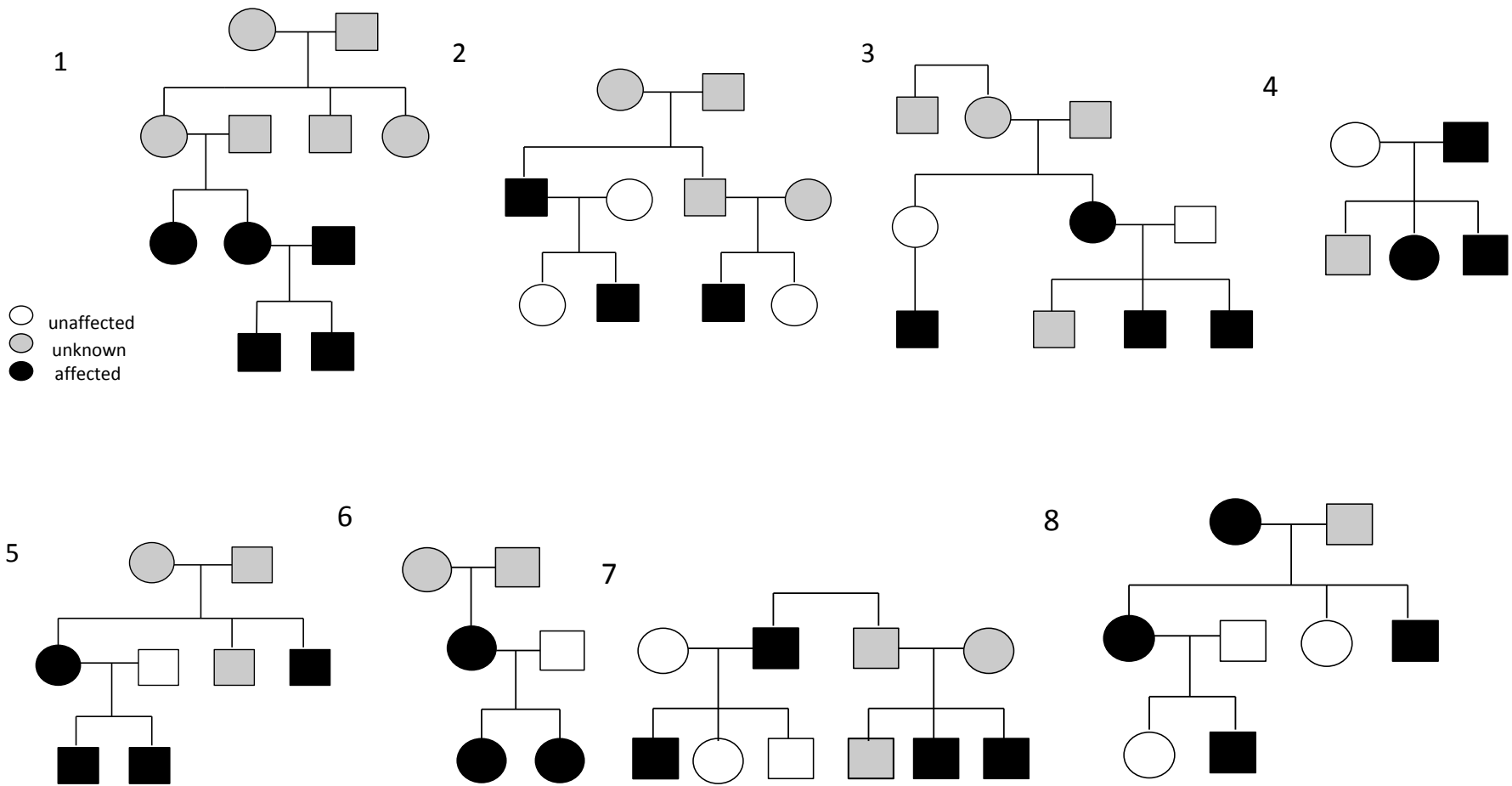
Guasti L, Ruhrberg C, Cariboni A, Dunkel L

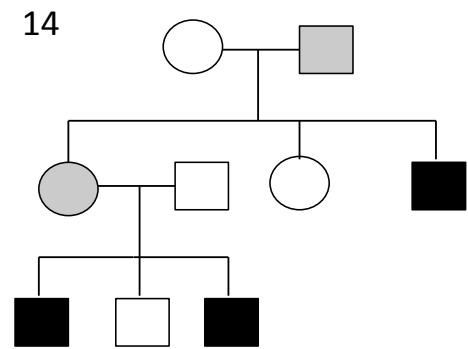
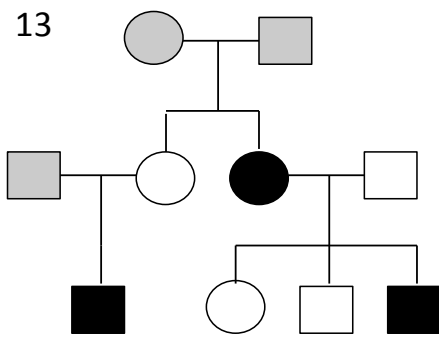
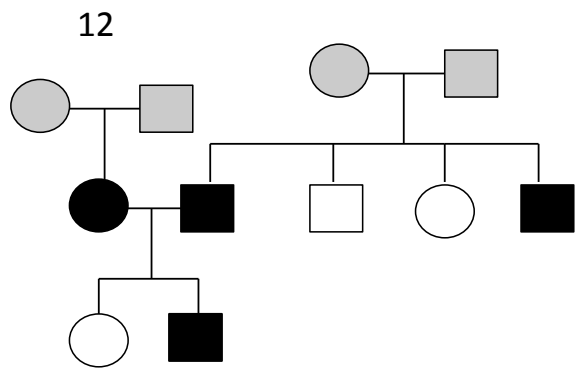
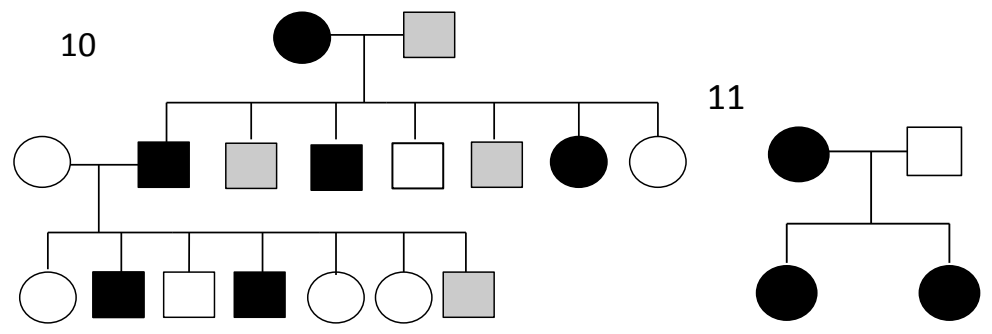
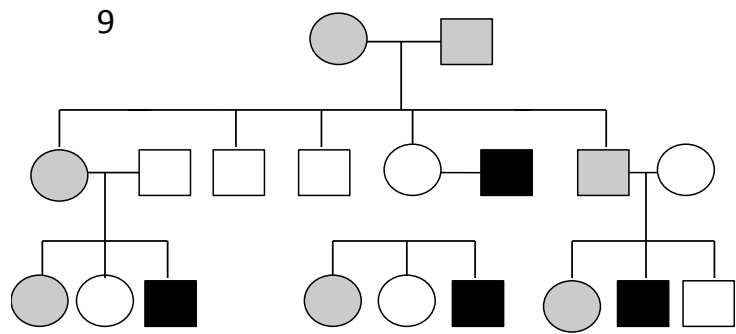
AA Change	dbSNP137	PhyloP <sup>1</sup> Pred	SIFT <sup>2</sup> Pred	Polyphen2 <sup>3</sup> Pred	LRT <sup>4</sup> Pred	MutationTaster <sup>5</sup> Pred	FATHMM <sup>6</sup> Pred	CADD <sup>7</sup> Pred	GERP <sup>8++</sup>
p.Arg375His	rs182882999	C	T	B	D	D	D	D	4.3

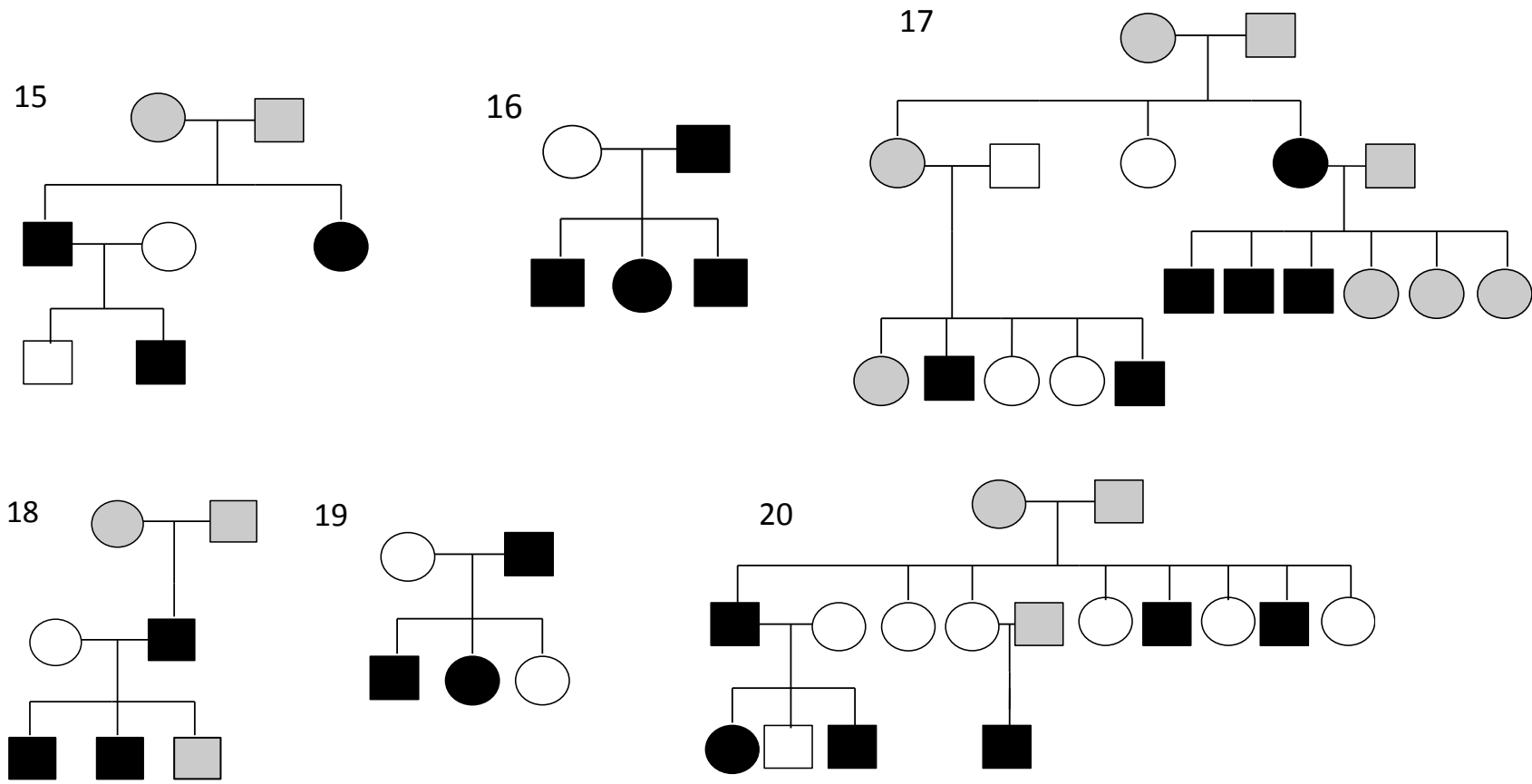
**Supplementary Table 1 – Prediction of variants according to web-based prediction software programs and conservation across species.** C – conserved, D – deleterious, disease causing or damaging, B – benign, T - tolerated

Nucleotide change	Amino acid change	Exon	MAF from DP probands (%) (n=109)	MAF from cohort controls (%) (n=145)	MAF from Exac database (%) Finnish/European/All
c.1124G>A	p.Arg375His	2	0.92	0	0.03/0.003/0.03

**Supplementary Table 2 – Minor allele frequency in study population and control cohorts.** Minor allele frequency data for the control population was retrieved from the ExAC Browser (Exome Aggregation Consortium (ExAC), Cambridge, MA: <http://exac.broadinstitute.org>, accessed May 2017).







Supplementary Figure 1 – 20 example cohort pedigrees from which probands were sent for initial whole exome sequencing

species	match	gene	aa alignment
Human			375 Q L E R R E Q R L R S R E E R L L H R A K E A L
mutated	not conserved		375 Q L E R R E Q R L R S H E E R L L H R A K E A
Ptroglydytes	all identical	<a href="#">ENSPTRG00000012440</a>	375 Q L E R R E Q R L R S R E E R L L H R A K E A
Mmulatta	all identical	<a href="#">ENSMUG00000030614</a>	359 Q L E R R E Q R L R S R E E
Fcatus	all identical	<a href="#">ENSFCAG00000012548</a>	375 Q L E R R E Q R L K S R E E R L L H R A K E A
Mmusculus	all identical	<a href="#">ENSMUSG00000045216</a>	375 Q L E R R E Q R L R N R E E R L L H R S K E A
Ggallus	all identical	<a href="#">ENSGALG00000002155</a>	346 Q L E R M E Q R I K N R E E R L L H R S N E A
Trubripes	not conserved	<a href="#">ENSTRUG00000015423</a>	383 Q Q E R R Q R I K N H I R Q S L T S K L E D
Drerio	no alignment	<a href="#">ENSDARG00000054754</a>	n/a
Dmelanogaster	no alignment	<a href="#">FBgn0038755</a>	n/a
Celegans	no alignment	<a href="#">Y34B4A.3</a>	n/a
Xtropicalis	all identical	<a href="#">ENSXETG00000016769</a>	370 M E Q R K K N R E E R L L H R S N E A

**Supplementary Figure 2 Multiple sequence alignment (m.s.a.) for the p.Arg375 (R375) residue.**

M.s.a. was generated using MutationTaster<sup>5</sup>. The p.Arg375 residue is highly conserved amongst different species, GERP score 4.3.

## References

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