Supplementary Table 1: Genotype of patients with LH Receptor mutations

Exon/Intron	Variant	Type of variant	HM/CHT/HT	no of pro-bands	Region	Domain affected	Truncating or Functional receptor activity	Phenotype 46 XY: male/female/atypical 46 XX	Reference
Exon 1	P.Leu10Pro	Missense	CHT	1	Europe	Signal Peptide	p.L10P variant do not completely abolish LHCGR activity but affect receptor expression	46XY	Valeria et al (2015)[1]
	p.L10_Q17dup	Duplication	CHT	1	Europe	Extracellular binding Domain	Cell-surface expression levels were statistically lower than WT	46XY	Lulia Potorac (2019)[2]
	p.Leu11Pro	Missense	HM	1	Europe	Signal Peptide	Mutations caused abnormal LHCGR glycosylation, decreased protein level, ectopic subcellular localization, and impaired cAMP levels	46XX	Zhihua Zhang family 1 (2020)[3]
	p.Leu11_Pro19dup	Duplication	CHT	1	Asia	Extracellular binding Domain	Mutations caused abnormal LHCGR glycosylation, decreased protein level, ectopic subcellular localization, and impaired cAMP levels	46XX	Zhihua Zhang family 3 (2020)[3]
	p.Lys12_Pro20del	Deletion	CHT	1	North America	signal peptide sequence	Deletion occupies a portion of the C-flank, this could prevent signal peptide cleavage resulting in LHCGR 'trapping' within the ER resulting on receptor incapable of hormone binding	46XX	Frederic Mitri case 1 (2014)[4]
	p.K12_L15del	Deletion	CHT	1	Europe	ECD	Mutations completely abolished LHCGR activity	46XY	Lulia Potorac (2019)[2]

	p.Leu16Gln	Missense	CHT	1	Asia	ECD	Weak membrane expression	46XY	Lulia Potorac (2019)[2]
	p.Leu17_Gln18insLeuPro	Insertion	HT	1	Europe	Signal Peptide	6.7 fold less receptor activity	46XX	Yaakov Bentov (2012)[5]
	p.Gln18_Pro19ins(27)	Inframe insertion	HM	1	Asia	ECD	25% receptor activity	46XY	SK Sinha case 1(2011)[6]
	p.Gln18_Pro19ins33	Inframe insertion	CHT	1	America	ECD	-	46XY	Louisa Laue (1995)[7]
		Inframe insertion	CHT	1	Europe	ECD	No functional study done for this mutation.		Richter et al, patient 1[8]
	chr2:g.(48729228_48731226)_(48755671_?)del	Deletion (Exon1-2)	HM	1	Asia		No functional study	46XY	This Study
Intron 1	c.161 + 4A > G	Splicesite	HM	4	Asia	Extracellular binding Domain	No functional study		Aktar Karakaya Family I-1 family II-1 , family III (2022)/Amine karakaya case 1 (2020)[9,10]
Exon 3	p.Ile89Leu	Missense	CHT	1	Asia	ECD	No functional study	46XY	Junke Xia (2021)[11]
Exon 4	p.Leu104Pro	Missense	HM	1	Africa	ECD	No functional study	46XY	Heba Hassan case 2 (2020)[12]
	p.Gly117Arg	Missense	CHT	1	Asia	ECD	No functional study	46XY	Mei Yan (2019)[13]
	p.Ile114Phe	Missense	HT	1	America	ECD	*In vitro* expression studies demonstrated that this mutation results in reduced ligand binding and signal transduction of the receptor**.** (28% receptor activity)	46XY	Michael leung (2006)[14]
Intron 4	IVS4-2A>T	Splicesite	CHT	1	Asia	ECD	mutation led to three different	46XX	Zhihua Zhang family 3(2020)[3]

							alternative splicing isoforms.		
Exon 5	p.Cys131Arg	Missense	HM/CHT /HM	3	Europe /Europe/Asia	ECD	This mutation dramatically impaired hormone binding in vitro- very weak hCG binding about 5% of the wild type.(76% receptor activity)	46XY	M. Misrahi et al(1997)/Nicolas (2011)Richard/This study[15,16]
	p.Val141Ala	Missense	CHT	1	Asia	ECD	No functional study.	46XY	Junke Xia (2021)[11]
	p.Val144Phe	Missense	HM	1	Asia	ECD	The mutant receptor is retained in the ER. Expression study confirmed that the mutant LHR-V144F receptors do not migrate to the cell surface, and the fluorescence remains intracellular. (0% receptor activity)	46XY	Richter unruh (2004)[17]
	p.Glu148Ter	Nonsense	HM	1	Africa(Egypt)	ECD	Homozygous p.Glu148Ter mutation resulted in a truncated protein of 147 amino acids instead of the wild type of 699 amino acids. No functional study.	46XY	Heba Hassan case 1a (2020)[12]
	p.Ile152Thr	Missense	CHT	1	Asia	ECD	Functional analysis of the mutant receptors indicate that the binding affinity of the mutant receptor was remarkably reduced suggesting that the missense mutation resulted in the dramatically impaired signal transduction mediated by LHCGR. (0% receptor activity)	46XY	Jie Qiao case 1(2009)[18]

Exon 6	p.Gln170Ter	Nonsense	HM	1	Africa	ECD	Truncated protein .No functional study .	46XY	Imen Hmida case 3 (2016)[19]
Intron 6	IVS6-1G>T	Splicesite	HM	1	Asia	ECD	No functional study .	46XY	Aysun Ata (2021)[20]
	IVS6-3C>A	Splicesite	CHT	1	Asia	Extracellular binding Domain	Functional Splicing Assay :This mutation c. 537-3 C>A decreased the functionality of 3' splice acceptor site, leading to skipping of exon 7 in the mature mRNA of the *LHCGR* gene *in vitro.*skipping exon 7 in our patient did not alter the reading frame of exon 8, but resulted in a deletion of 23 amino acids from the exon 6–8 boundary, which constitutes the greater part of LRR6	46XY	Jie Qiao case 1(2009)[18]
Exon 7	p.Glu188Ter	Nonsense	HM	1			nonsense variant lead to a truncated protein	46XY	Ruth baxter 2015[21]
	p.Phe194Val	Missense	HM	1	Europe	ECD	Cells with the F194V LHR mutation showed the lack of cAMP production upon hCG stimulation,indicating complete inactivation of the receptor due to impaired trafficking of the receptor to the membrane.(0% receptor activity)	46XY	Jorg Gromoll (2002)[22]
Exon 8	p.Ala221Glyfster63	Frameshift	CHT	1					
Intron 8	IVS8-1G>A	Splicesite	CHT	1	Asia		No functional study .	46XY	Yufei Xu (2018)[23]

Exon 9	p.Leu237fs	Frameshift	HM	1	Asia	ECD		46XX	Amanda Zielen Patient 1 (2018)[24]
	p.Gln246Ter	Nonsense	HM	2	Asia	ECD	No functional study.	46XY	Chen C V-1,3(2018)[25]
	p.Arg283Ter	Nonsense	HM	1	Asia	ECD	No functional study.	46XX	Chen C V-6(2018)[25]
	p.Asn312Ser	Missense	HM	1	Europe	ECD		46XY	M. Misrahi et al (1997)[15]
Exon 10	p.Asn291Ser	Missense	CHT	1	N.Amr	ECD	Ligand binding and hCG stimulation studies shows impairment in signal transduction and activity of hLHR (100% receptor activity)	46XY	Louisa L(1996)[26]
	p.Ser293Ter	Nonsense	CHT	1	Asia	ECD		46XY	Mei Yan (2019)[13]
	p.Gln303ter	Nonsense	CHT	1	Africa	ECD	No functional study. Complete termination of protein translation	46XY	Anastasia athanasoulia(2014)[27]
	p.Asn312Ser	Missense	CHT	1	Africa	ECD	No functional study.	46XY	Anastasia athanasoulia(2014)[27]
	p.Tyr317Phefster7	Frameshift	HM	1	Africa	ECD	No functional study.	46XY	Achwak Alla(2021)[28]
	Exon1 to 10 deletion	Deletion	CHT	1	Europe	ECD	Total LHCGR loss of function.	46XY	Nicolas Richard(2011)[16]
	Exon 10 deletion	Deletion	HM	1	Asia	ECD	No functional study.(Intracellular retention of receptor/reduced expression, 32.5/50% activity)	46XY	Jorg Gromo et al(2000)[29]
Intron 10	IVS10-1G>A	Splicesite	HM	1			82% receptor activity	46XY	Bruysters et al case 1 (2008)[30]
Exon 11	p.Asn312Ser	Missense	CHT	1	N.Amr	ECD	No functional study.	46XX	Frederic Mitri case 1 (2014)[4]
	p.Cys343Ser	Missense	CHT	1	Caucasian	ECD	Cells expressing hLHRC343S did not respond to hCG, indicating that the	46XY	Martens (2002)[31]

							mutant receptors are completely deficient in signaling (0% receptor activity)		
	p.Glu354Lys	Missense	HM	1	America	TM7	The mutagenesis-transfection analysis showed that this mutation caused complete loss of receptor function (failure of CAMP production after hCG stimulation) and causes receptor signal deficiency.(0% receptor activity)	46XY	Staros Stavrou(1998)[32]
	p.Ile374Thr	Missense	CHT	1	Asia	TM1	Cells transfected with mutant receptor did not respond to hCG and are completely deficient in signaling.The mutanat receptors are retained intracellularly and completely lack ligand binding.(47% receptor activity)	46XY	Robin pals(2005)[33]
	p.Thr392Ile	Missense	CHT	1	Asia	IC	Cells transfected with mutant receptor did not respond to hCG and are completely deficient in signaling.The mutanat receptors are retained intracellularly and completely lack ligand binding.(0% receptor activity)	46XY	Robin pals(2005)[33]
	p.Asn400Ser	Missense	HM	1	Asia		**No functional study.**	46XX	Kemal Yaris et al case 1(2011)[34]
	p.Ile415Thr	Missense	CHT	1	Europe		Cell surface expression of mutant receptor reduced and the receptor protein is intracellularly retained. CAMP production upon stimulation hCG stimulation is completely	46XY	Nina kossack et al(2013)[35]

							abolished .		
	p.Ala449Thr	Missense	HM	1	Asia			46XX	Ping Yuan(2017)[36]
	p.Thr461Ile	Missense	CHT	1	Europe				Nina Kossack Case3(2008)[37]
	p.Trp465Ter	Nonsense	HM	1		TM3			Philibert er al patient 8(2010)[38]
	p.Arg479Ter	Nonsense	HM	1	Asia	TM7	No functional study.	46XY	Fatma Comlek (2021)[39]
		Nonsense	HM	1	Africa		No functional study.	46XY	Imen Hmida case 2(2016)[19]
	p.Ala483Asp	Missense	HM	1	Asia	TM4	No functional study.	46XY	Aktar karakaya Family IV-1 (20221[10])
		Missense	HM	1	Asia	TM4	No functional study.	46XY	Aysun Ata(2021)[20]
		Missense	HM	1	Asia	TM4	No functional study.	46XY	Özen S, et al Horm Res Paediatr. 2017;87(2):81-87. doi: 10.1159/000452995. Epub 2016 Nov 30. PMID: 27898418
	p.Trp491ter	Nonsense	CHT	1	Europe	TM4	No functional study done for this mutation.	46XY	Richter-Unruh A, et al Clin Endocrinol (Oxf). 2002 Jan;56(1):103-12. doi: 10.1046/j.0300-0664.2001.01437.x. PMID: 11849253
	p.Leu502Pro	Missense	HM	1	Americ	TM4	Expression study of the mutated hLHR	46XY	Leung MY, et al Am

					a		in human embryonic kidney (HEK)293 cells showed reduced cAMP production and ligand binding.Expression study of the mutated hLHR in human embryonic kidney (HEK)293 cells showed reduced cAMP production and ligand binding.(8% receptor activity)		J Med Genet A. 2004 Oct 1;130A(2):146-53. doi: 10.1002/ajmg.a.20681. PMID: 15372531
	p.Gln525Ter	Nonsense	HM	1	Africa	TM5	No functional study.	46XY	Imen Hmida case 1(2016)[19]
	p.Ile528Ter	Nonsense	CHT	1	Asia	TM5	No functional study.	46XY	Yufei Xu (2018)[23]
	p.Cys543Arg	Missense	CHT	1	Caucasian	TM5	Cells expressing hLHRC543receptor did not respond to hCG, indicating that the mutant receptors are completely deficient in signaling.	46XY	Martens (2002)[31]
	p.Cys545Ter	Nonsense	CHT	1	America	TM5	This mutation causes loss of function of the receptor by introducing a stop codon at residue 545.Surface expression of the truncated hLHR (hLHR-t545) in HEKcells was diminished compared to the wild-type hLHR and hCG-induced cAMP accumulation was impaired.(0% receptor activity)	46XY	Louisa Laue(1995)[7]
	p.Arg554Ter	Nonsense	HM	1	S.Amr	Intracellular loop	No functional study done for this mutation.Truncation of receptor(Premature interruption of translation process)	46XY	Latronico AC, et al. N Engl J Med. 1996 Feb 22;334(8):507-12. doi: 10.1056/NEJM199602223340805. PMID: 8559204

	p.Ala589Cysfster17	Frameshift	HM	1	Asia	TM6	No functional study.	46XY	Richter unruh(2005)[8]
	p.Ala593Pro	Missense	HM	1	S.Amr	TM6	In-Vitro studies indicate that this missense mutation completely abolishes signal transduction and the ligand binding does not result in increased CAMP production.(0% receptor activity)	46XY	Kremer H et al Nat Genet. 1995 Feb;9(2):160-4. doi: 10.1038/ng0295-160. PMID: 7719343.
	p.Thr600Ile	Missense	HM	1	Asia		No functional study.		This Study
	p.Tyr612ter	Nonsense	HM	1	Asia	TM7	In vitro studies have shown that Y612* mutantdevoid of cAMP signaling.In vitro studies demonstrate that there is no appreciable ligand binding in whole lysates or on the surface of the cells expressing the Y612* mutant receptor, and there is absence of cAMP production after hCG stimulation.(0% receptor activity)	46XY	Salameh W, et al Mol Cell Endocrinol. 2005 Jan 14;229(1-2):57-64. doi: 10.1016/j.mce.2004.09.005. PMID: 15607529
	p.Ser616Tyr	Missense	CHT	1		TM7	No specific LH binding was found in the cells transfected with mutant (Tyr616) LH-receptor cDNA. Mutation impaired the function of the LH receptor and prevented it from transmitting the hormonal signal in the testes and ovaries of the affected patients. (14.90% receptor activity)	46XY	Latronico AC, et al. N Engl J Med. 1996 Feb 22;334(8):507-12. doi: 10.1056/NEJM199602223340805. PMID: 8559204
		Missense	CHT	1	N.Amr	TM7	Transfectants expressing p.Ser616Tyr mutants demonstrated greatly reduced ligand binding and ligand induced cAMP accumulation in comparison to those expressing wild	46XY	Louisa L(1996)[26]

							type hLHR.		
		Missense	CHT	1	Europe	TM7	No functional study done for this mutation.	46XY	Valeria et al (2015)[1]
	p.Ile625Lys	Missense	HM	1	Europe	TM7	In *vitro* analysis of this mutant LHR, LHR(I625K), in HEK293 cells indicated that the signaling efficiency was significantly impaired, which explains the partial phenotype.LHR(I625K) is poorly expressed and impaired in responding to hCG.(60% receptor activity)	46XY	Case 1a Martens JW, et al. Mol Endocrinol. 1998 Jun;12(6):775-84. doi: 10.1210/mend.12.6.0124. PMID: 9626653
		Missense		1	S.Amr	TM7	This mutation causes severe impairment of hormone dependent receptor signaling.		Richter-Unruh A, et al Clin Endocrinol (Oxf). 2002 Jan;56(1):103-12. doi: 10.1046/j.0300-0664.2001.01437.x. PMID: 11849253

As: Asia, La: Latin America, Af: Africa, E: Europe, Am North America, ***A cryptic exon 6A (resides in intron 6) with mutations (A557C or G558C).**
HM homozygous, CHT compound heterozygous, Ht heterozygous

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Supplementary table 2: Genotypic-Phenotypic characteristics of 46 XY patients with LHCGR pathogenic defects between different domains affected

		Genital Phenotype		
Domain affected	**Serum Testosterone, ng/ml, Median (range)**	**Male-like (Sinnecker score 1)**	**Atypical genitalia (Sinnecker score 2&3)**	**Female-like (Sinnecker score 4&5)**
Extracellular (n=24)	0.10 (0-0.72), n=20	5/23	2/23	16/23
Transmembrane (n=15)	0.17 (0.025-4.3), n=9	2/14	0/14	12/14
Cytoplasmic Tail (n=1)	0.27 (n=1)	0/1	0/1	1/1
Signal Peptide (n=3)	0.06 (0.025-0.17), n=3	0/3	0/3	3/3
Non-Extracellular domains (Transmembrane, Cytoplasmic tail, Signal Peptide)	0.15 (0.025-4.3), n=13	2/18	0/18	16/18

P value 0.502 in testosterone between Extracellular vs others (Transmembrane, Cytoplasmic, Signal Peptide)

P value 0.437 in Male-Like between Extracellular vs others (Transmembrane, Cytoplasmic, Signal Peptide)

P value 0.495 in Atypical Genitalia between Extracellular vs others (Transmembrane, Cytoplasmic, Signal Peptide)

P value 0.254 in Female-Like between Extracellular vs others (Transmembrane, Cytoplasmic, Signal Peptide)

Supplementary table 3: Genotypic-Phenotypic characteristics of 46 XY patients with LHCGR between

		Genital Phenotype		
Type of pathogenic variant	**Serum Testosterone, ng/ml, Median (range)**	**Male-like (Sinnecker score 1)**	**Atypical genitalia (Sinnecker score 2&3)**	**Female-like (Sinnecker score 4&5)**
Homozygous (n=38)	0.13 (0-4.3), n=28	7/36	1/36	28/36
Compound heterozygous (n=13)	0.10 (0-0.31), n=11	0/13	4/13	9/13

Homozygous and Compound Heterozygous pathogenic defects

P value 0.218 in testosterone between Homozygous and Compound heterozygous variant

P value 0.166 in male-like genitalia between Homozygous and Compound heterozygous variant

P value 0.166 in atypical and female like genitalia between Homozygous and Compound Heterozygous variant.

Supplementary Table 4: Joanna Briggs Institute (JBI) critical appraisal for case series

Study name	Year	1. Were there clear criteria for inclusion in the case series?	2. Was the condition measured in a standard, reliable way for all participants included in the case series?	3. Were valid methods used for identification of the condition for all participants included in the case series?	4. Did the case series have consecutive inclusion of participants?	5. Did the case series have complete inclusion of participants?	6. Was there clear reporting of the demographics of the participants in the study?	7. Was there clear reporting of clinical information of the participants?	8. Were the outcomes or follow up results of cases clearly reported?	9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	10. Was statistical analysis appropriate?	Overall score
Kremer H et al	1995	1	1	1	2	2	1	1	1	1	3	7/9
Laue L et al	1995	1	1	1	1	2	1	1	1	1	3	8/9
Latronico AC et al	1996	1	1	1	1	2	1	1	1	1	3	8/9
Martens JW et al	1998	1	1	1	1	2	1	1	1	1	3	8/9
Stavrou SS et al	1998	1	1	1	1	2	1	1	1	1	3	8/9
Richter-Unruh A et al	2002	1	1	1	1	2	1	1	1	1	3	8/9
Bruysters M et al	2008	1	1	1	2	2	1	1	1	1	3	7/9
Kossack N et al	2008	1	1	1	1	2	1	1	1	1	3	8/9
Qiao J et al	2009	1	1	1	1	2	1	1	2	1	3	7/9
Philibert P et al	2010	1	1	1	1	2	1	1	1	1	3	8/9
Yariz KO et al	2011	1	1	1	1	2	1	1	1	1	3	8/9
Rivero-Muller A et al	2015	1	1	1	1	2	1	1	1	1	3	8/9
Baxter RM et al	2015	1	1	1	1	1	2	2	2	2	3	5/9
Ben Hadj Hmida I et al	2016	1	1	1	1	2	1	1	1	1	3	8/9
Ozen S et al	2016	1	1	1	1	2	1	1	1	1	3	8/9
Zielen AC et al	2018	1	1	1	2	2	1	1	1	1	3	7/9
Chen C et al	2018	1	1	1	2	2	1	1	1	1	3	7/9
Zhang Z et al	2020	1	1	1	2	2	1	1	1	1	3	7/9
Aktar Karakaya A et al	2020	1	1	1	1	2	1	1	1	1	3	8/9
Hassan HA et al	2020	1	1	1	1	2	1	1	1	1	3	8/9
Alla A et al	2021	1	1	1	1	2	1	1	1	1	3	8/9

Ata A et al	2021	1	1	1	1	1	2	2	2	2	1	6/10
Xia J et al	2021	1	1	1	1	1	1	1	2	1	3	8/9
Aktar Karakaya A et al	2022	1	1	1	1	1	1	1	1	1	3	9/9
Coding for answers to the questions: 0 No, 1 Yes, 2 unclear, 3 Not Applicable												

Supplementary Table 5: Joanna Briggs Institute (JBI) critical appraisal for case reports

Study name	Year	1.Were patient's demographic characteristics clearly described?	2. Was the patient's history clearly described and presented as a timeline?	3.Was the current clinical condition of the patient on presentation clearly described?	4. Were diagnostic tests or assessment methods and the results clearly described?	5. Was the intervention(s) or treatment procedure(s) clearly described?	6.Was the post-intervention clinical condition clearly described?	7. Were adverse events (harms) or unanticipated events identified and described?	8. Does the case report provide takeaway lessons?	Overall score
Laue L et al	1996	1	1	1	1	1	1	2	1	7/8
Mishrahi M et al	1997	1	1	1	1	1	1	2	1	7/8
Gromoll J et al	2000	1	1	1	1	1	1	2	1	7/8
Gromoll J et al	2002	1	1	1	1	1	1	2	1	7/8
Martens JW et al	2002	1	1	1	1	1	1	2	1	7/8
Leung M et al	2004	1	1	1	1	1	1	2	1	7/8
Richter-Unruh A et al	2004	1	1	1	1	1	1	2	1	7/8
Richter-Unruh A et al	2005	1	1	1	1	1	1	2	1	7/8
Pals-Rylaarsdam R et al	2005	1	1	1	1	1	1	2	1	7/8
Salameh W et al	2005	1	1	1	1	1	1	2	1	7/8
Leung M et al	2006	1	1	1	1	1	1	2	1	7/8
Richard N et al	2011	1	1	1	1	1	1	2	1	7/8
Sinha SK et ak	2011	1	1	1	1	1	1	2	1	7/8
Bentov Y et al	2012	1	1	1	1	1	1	2	1	7/8
Kossack N et al	2013	1	1	1	1	1	1	2	1	7/8
Mitri F et al	2014	1	1	1	1	1	1	2	1	7/8
Athanasoulia AP et al	2014	1	1	1	1	1	2	2	1	6/8
Bakircioglu ME et al	2014	1	1	1	1	1	1	2	1	7/8
Vezzoli V et al	2015	1	1	1	1	1	1	2	1	7/8
Yuan P et al	2017	1	1	1	1	1	1	2	1	7/8
Xu Y et al	2018	1	1	1	1	1	1	2	1	7/8

Potorac I et al	2019	1	1	1	1	1	1	2	1	7/8
Yan M et al	2019	1	1	1	1	1	2	2	1	6/8
Comlek FO et al	2021	1	1	1	1	1	1	2	1	7/8
Coding for the questions: 0 No, 1 Yes, 2 unclear, 3 Not Applicable										