In format provided by Ranke & Wit (doi:10.1038/nrendo.2018.22)

Supplementary Table S1. Genes associated with disorders of the GH-IGF axis

GENES	INHER	CLINICAL FEATURES	REFS
Growth hormone deficiency and potential for combined pituitary hormone deficiency (Secondary IGF-deficiency)			
FGF8	AR	Holoprosencephaly, septo-optic dysplasia, hypogonadism	1
FGFR1	AD	Hypoplasia pituitary, corpus callosum, ocular defects, hypogonadism.	2
GLI2	AD	Holoprosencephaly, single central incisor, partial agenesis corpus callosum	3
GLI3	AD	Pallister-Hall S., hypothalamic hamartoma, central polydactyly	4
GRP161	AR	Pituitary stalk interruption, intellectual disability, facial + hand dysmorphy	5
HESX1	AR, AD	Optic nerve hypoplasia, pituitary hypoplasia, midline abnormalities, absent corpus callosum	6
HMGA2	AD	Ectopic posterior pituitary	7
IGSF1	XLR	Macro-orchidism, disharmonious pubertal development	8
LX3	AR	Sensorineural hearing loss, cervical abnormalities, short stiff neck	9
LX4	AD, AR	Pituitary and cerebellar defects, abnormalities of sella turcica	10
OTX2	AD	Ocular anomalies	11,12
PITX2	AD	Axenfeld-Rieger S., coloboma, glaucoma, dental and brain abnormalities	13
POU1F1	AR, AD		14
PROKR2	AD	Variable hypopituitarism	2
PROP1	AR	Pituitary can be enlarged	15
ROBO1	AD	Pituitary stalk interruption syndrome	16
SOX2	AD	Hypogonadism, anophthalmia, developmental delay	17
SOX3dup	XLR	Mental retardation	18
SPR	AR	Fluctuating movement disorder, cognitive delay, neurologic dysfunction	19
WDR11	?	PSIS (digenic inheritance, *PROKR2* and *WDR11*)	20
Isolated growth hormone deficiency or bioinactivity (secondary IGF-deficiency)			
ALMS1	AR	Almstrom S.	21
BTK	XLR	Agammaglobulinemia	22
GH1	AR	Type IA, complete GHD, growth-attenuating Abs to hGH treatment	23-25
GH1	AR	Type IB, less complete GHD	
GH1	AD	Type II variable height deficit or pituitary size; other pit. Def. develop	
GH1	?	Bioinactive but immunoactive GH	
GHRHR	AR	Low but measurable GH peak	26
GHSR	AR,AD	Variable serum GH and IGF-I	27
IFT172	AR	Functional GHD, retinopathy, metaphyseal dysplasia, hypertension	28
RNPC3	AR	Severe GHD, hypoplasia anterior pituitary	29
Primary IGF-I deficiency (GH normal/high; IGF-I low)			
GHR	AR, AD	Variable height deficit and GHBP, midfacial hypoplasia	30
IGF1	AR, AD	SGA, microcephaly, deafness; ↑GH and IGFBP-3; IGF-I dependent on assay	31,32
IGFALS	AR	Mild height deficit; IGFBP-3 SDS<IGF-I SDS	33
IKBKB	AR, AD	Immunodeficiency;	34
IL2RG	XLR	Non-response to GH injections	35
STAT3	AD(act)	Associated with early-onset multi-organ autoimmune disease	36
STAT5B	AR	Midfacial hypoplasia, immunodeficiency; ↑GH and PRL	37
(Apparent) IGF-I insensitivity (IGF-I usually >mean for age)			
IGF1R	AD,AR	SGA, microcephaly; GH ↑; IGF-I and IGFBP-3 normal	38
PAPPA2	AR	Microcephaly, skeletal abnormalities, ↑GH, IGF-I, IGFBP-3 and ALS	39
IGF2	impr	Phenotype resembles SRS	40
	Impr	SRS, severe IUGR, triangular shaped face, broad forehead, asymmetry, minor malformations	41,42

Abbreviations: Abs, antibodies; act, activating; AR, autosomal recessive; AD, autosomal dominant; ALS, acid labile; subunit; IGF, Insulin-like growth factor; IGFBP, IGF binding protein; GH, growth hormone; GHD, growth hormone deficiency; Impr, imprinted; IUGR, intrauterine growth retardation; PRL,

© 2018 Macmillan Publishers Limited. All rights reserved

prolactin; PSIS, pituitary stalk interruption syndrome; S, syndrome; SDS, standard deviation score; SRS, Silver-Russell syndrome

1 Raivio, T. *et al.* Genetic overlap in Kallmann syndrome, combined pituitary hormone deficiency, and septo-optic dysplasia. *J Clin Endocrinol Metab* **97**, E694-699, doi:10.1210/jc.2011-2938 (2012).

2 Correa, F. A. *et al.* FGFR1 and PROKR2 rare variants found in patients with combined pituitary hormone deficiencies. *Endocr. Connect* **4**, 100-107, doi:EC-15-0015 [pii];10.1530/EC-15-0015 [doi] (2015).

3 Roessler, E. *et al.* A previously unidentified amino-terminal domain regulates transcriptional activity of wild-type and disease-associated human GLI2. *Hum Mol Genet* **14**, 2181-2188, doi:10.1093/hmg/ddi222 (2005).

4 Kang, S., Graham, J. M., Jr., Olney, A. H. & Biesecker, L. G. GLI3 frameshift mutations cause autosomal dominant Pallister-Hall syndrome. *Nat Genet* **15**, 266-268, doi:10.1038/ng0397-266 (1997).

5 Karaca, E. *et al.* Whole-exome sequencing identifies homozygous GPR161 mutation in a family with pituitary stalk interruption syndrome. *J Clin Endocrinol Metab* **100**, E140-E147, doi:10.1210/jc.2014-1984 [doi] (2015).

6 Dattani, M. T. *et al.* Mutations in the homeobox gene HESX1/Hesx1 associated with septo-optic dysplasia in human and mouse. *Nat Genet* **19**, 125-133, doi:10.1038/477 (1998).

7 Gorbenko del, B. D., de Graaff, L. C., Posthouwer, D., Visser, T. J. & Hokken-Koelega, A. C. Isolated GH deficiency: mutation screening and copy number analysis of HMGA2 and CDK6 genes. *Eur. J Endocrinol* **165**, 537-544, doi:EJE-11-0478 [pii];10.1530/EJE-11-0478 [doi] (2011).

8 Sun, Y. *et al.* Loss-of-function mutations in IGSF1 cause an X-linked syndrome of central hypothyroidism and testicular enlargement. *Nat. Genet* **44**, 1375-1381, doi:ng.2453 [pii];10.1038/ng.2453 [doi] (2012).

9 Netchine, I. *et al.* Mutations in LHX3 result in a new syndrome revealed by combined pituitary hormone deficiency. *Nat Genet* **25**, 182-186, doi:10.1038/76041 (2000).

10 Machinis, K. *et al.* Syndromic short stature in patients with a germline mutation in the LIM homeobox LHX4. *Am J Hum Genet* **69**, 961-968 (2001).

11 Dateki, S. *et al.* OTX2 mutation in a patient with anophthalmia, short stature, and partial growth hormone deficiency: functional studies using the IRBP, HESX1, and POU1F1 promoters. *J Clin Endocrinol Metab* **93**, 3697-3702, doi:10.1210/jc.2008-0720 (2008).

12 Diaczok, D., Romero, C., Zunich, J., Marshall, I. & Radovick, S. A novel dominant negative mutation of OTX2 associated with combined pituitary hormone deficiency. *J Clin Endocrinol Metab* **93**, 4351-4359, doi:10.1210/jc.2008-1189 (2008).

13 Semina, E. V. *et al.* Cloning and characterization of a novel bicoid-related homeobox transcription factor gene, RIEG, involved in Rieger syndrome. *Nat Genet* **14**, 392-399, doi:10.1038/ng1296-392 (1996).

14 Pfaffle, R. W. *et al.* Mutation of the POU-specific domain of Pit-1 and hypopituitarism without pituitary hypoplasia. *Science* **257**, 1118-1121 (1992).

15 Wu, W. *et al.* Mutations in PROP1 cause familial combined pituitary hormone deficiency. *Nat. Genet* **18**, 147-149 (1998).

16 Bashamboo, A., Bignon-Topalovic, J., Moussi, N., McElreavey, K. & Brauner, R. Mutations in the Human ROBO1 Gene in Pituitary Stalk Interruption Syndrome. *J Clin Endocrinol Metab* **102**, 2401-2406, doi:10.1210/jc.2016-1095 (2017).

17 Kelberman, D. *et al.* Mutations within Sox2/SOX2 are associated with abnormalities in the hypothalamo-pituitary-gonadal axis in mice and humans. *J Clin Invest* **116**, 2442-2455, doi:10.1172/JCI28658 (2006).

© 2018 Macmillan Publishers Limited. All rights reserved

18 Laumonnier, F. *et al.* Transcription factor SOX3 is involved in X-linked mental retardation with growth hormone deficiency. *Am J Hum Genet* **71**, 1450-1455, doi:10.1086/344661 (2002).

19 Zielonka, M. *et al.* Dopamine-Responsive Growth-Hormone Deficiency and Central Hypothyroidism in Sepiapterin Reductase Deficiency. *JIMD Rep* **24**, 109-113, doi:10.1007/8904_2015_450 (2015).

20 McCormack, S. E. *et al.* Digenic Inheritance of PROKR2 and WDR11 Mutations in Pituitary Stalk Interruption Syndrome. *J Clin Endocrinol Metab* **102**, 2501-2507, doi:10.1210/jc.2017-00332 (2017).

21 Romano, S. *et al.* Alstrom syndrome is associated with short stature and reduced GH reserve. *Clin Endocrinol (Oxf)* **79**, 529-536, doi:10.1111/cen.12180 [doi] (2013).

22 Vorechovsky, I. *et al.* Mutation pattern in the Bruton's tyrosine kinase gene in 26 unrelated patients with X-linked agammaglobulinemia. *Hum Mutat* **9**, 418-425, doi:10.1002/(SICI)1098-1004(1997)9:5<418::AID-HUMU7>3.0.CO;2-# (1997).

23 Braga, S., Phillips, J. A., III, Joss, E., Schwarz, H. & Zuppinger, K. Familial growth hormone deficiency resulting from a 7.6 kb deletion within the growth hormone gene cluster. *Am. J Med. Genet* **25**, 443-452, doi:10.1002/ajmg.1320250306 [doi] (1986).

24 Phillips, J. A., III & Cogan, J. D. Genetic basis of endocrine disease. 6. Molecular basis of familial human growth hormone deficiency. *J Clin Endocrinol Metab* **78**, 11-16, doi:10.1210/jcem.78.1.8288694 [doi] (1994).

25 Takahashi, Y. *et al.* Brief report: short stature caused by a mutant growth hormone [see comments]. *N. Engl. J. Med* **334**, 432-436 (1996).

26 Wajnrajch, M. P., Gertner, J. M., Harbison, M. D., Chua, S. C., Jr. & Leibel, R. L. Nonsense mutation in the human growth hormone-releasing hormone receptor causes growth failure analogous to the little (lit) mouse. *Nat. Genet* **12**, 88-90, doi:10.1038/ng0196-88 [doi] (1996).

27 Pantel, J. *et al.* Loss of constitutive activity of the growth hormone secretagogue receptor in familial short stature. *J Clin Invest* **116**, 760-768 (2006).

28 Lucas-Herald, A. K. *et al.* A case of functional growth hormone deficiency and early growth retardation in a child with IFT172 mutations. *J Clin Endocrinol Metab* **100**, 1221-1224, doi:10.1210/jc.2014-3852 [doi] (2015).

29 Argente, J. *et al.* Defective minor spliceosome mRNA processing results in isolated familial growth hormone deficiency. *EMBO Mol. Med* **6**, 299-306, doi:emmm.201303573 [pii];10.1002/emmm.201303573 [doi] (2014).

30 Amselem, S. *et al.* Laron dwarfism and mutations of the growth hormone-receptor gene. *N. Engl. J Med* **321**, 989-995, doi:10.1056/NEJM198910123211501 [doi] (1989).

31 Woods, K. A., Camacho-Hubner, C., Savage, M. O. & Clark, A. J. Intrauterine growth retardation and postnatal growth failure associated with deletion of the insulin-like growth factor I gene. *N. Engl. J Med* **335**, 1363-1367 (1996).

32 Walenkamp, M. J. *et al.* Homozygous and heterozygous expression of a novel insulin-like growth factor-I mutation. *J Clin Endocrinol Metab* **90**, 2855-2864 (2005).

33 Domene, H. M. *et al.* Deficiency of the circulating insulin-like growth factor system associated with inactivation of the acid-labile subunit gene. *New Engeland Journal of Medicine* **350**, 570-577 (2004).

34 Wu, S. *et al.* Growth hormone and insulin-like growth factor I insensitivity of fibroblasts isolated from a patient with an I{kappa}B{alpha} mutation. *J Clin Endocrinol Metab* **95**, 1220-1228 (2010).

35 Ursini, M. V. *et al.* Atypical X-linked SCID phenotype associated with growth hormone hyporesponsiveness. *Clin Exp. Immunol* **129**, 502-509, doi:1823 [pii] (2002).

36 Flanagan, S. E. *et al.* Activating germline mutations in STAT3 cause early-onset multi-organ autoimmune disease. *Nat. Genet* **46**, 812-814, doi:ng.3040 [pii];10.1038/ng.3040 [doi] (2014).

37 Kofoed, E. M. *et al.* Growth hormone insensitivity associated with a STAT5b mutation. *N. Engl. J Med* **349**, 1139-1147 (2003).

© 2018 Macmillan Publishers Limited. All rights reserved

In format provided by Ranke & Wit (doi:10.1038/nrendo.2018.22)

38 Abuzzahab, M. J. *et al.* IGF-I receptor mutations resulting in intrauterine and postnatal growth retardation. *N. Engl. J Med* **349**, 2211-2222 (2003).
39 Dauber, A. *et al.* Mutations in pregnancy-associated plasma protein A2 cause short stature due to low IGF-I availability. *EMBO Mol Med* **8**, 363-374, doi:10.15252/emmm.201506106 (2016).
40 Begemann, M. *et al.* Paternally Inherited IGF2 Mutation and Growth Restriction. *N. Engl. J Med*, doi:10.1056/NEJMoa1415227 [doi] (2015).
41 Binder, G. *et al.* The endocrine phenotype in silver-russell syndrome is defined by the underlying epigenetic alteration. *J Clin Endocrinol Metab* **93**, 1402-1407, doi:jc.2007-1897 [pii];10.1210/jc.2007-1897 [doi] (2008).
42 Netchine, I. *et al.* 11p15 imprinting center region 1 loss of methylation is a common and specific cause of typical Russell-Silver syndrome: clinical scoring system and epigenetic-phenotypic correlations. *J Clin Endocrinol Metab* **92**, 3148-3154 (2007).

© 2018 Macmillan Publishers Limited. All rights reserved