UKGTN Testing Criteria

Test name: **Iron Regulatory 16 Gene Panel**	
Approved name and symbol of disorder/condition(s): See Appendix 1	**OMIM number(s):**
Approved name and symbol of gene(s): See Appendix 1	**OMIM number(s):**

Patient name:	**Date of birth:**
Patient postcode:	**NHS number:**
Name of referrer:	
Title/Position:	**Lab ID:**

Referrals will only be accepted from one of the following:	
Referrer	**Tick if this refers to you.**
Consultant Haematologist	
Consultant Gastroenterologist	
Consultant Hepatologist	
Consultant Clinical Geneticist	
Consultant Endocrinologist	
Consultant Rheumatologist	

Minimum criteria required for testing to be appropriate as stated in the Gene Dossier:	
Criteria	**Tick if this patient meets criteria**
Juvenile Haemochromatosis <30 years with severe iron overload in liver **AND/OR** heart. Raised serum ferritin >1000ug/L and transferrin saturation >90%	
OR Juvenile Haemochromatosis >30 years with unexplained severe haemochromatosis and HFE negative	
OR Ferroportin disease: raised serum ferritin with normal transferrin saturation and evidence of reticulo-endothelial iron staining on liver biopsy or splenic iron overload on MRI and HFE mutations negative.	
OR Haemochromatosis: raised serum ferritin and transferrin saturation C282Y negative	
OR Hereditary Hyperferritinemia cataract syndrome: High and constant levels of serum ferritin unresponsive to iron depletion and no signs of iron overload and no relevant clinical symptoms apart from visual impairment by cataract	

continued/…

OR Biochemical evidence of unexplained iron overload and lack of homozygous/compound homozygous HFE mutations	
OR Iron Refractory Iron Deficiency Anaemia (IRIDA): Very low mean corpuscular volume (MCV) and low serum iron and low transferrin saturation, normal ferritin or ferritin levels in the lower limits of normal, no response to oral iron treatment.	

Additional Information:

For panel tests:

At risk family members where familial mutation is known do not require a full panel test but should be offered analysis of the known mutation.

If the sample does not fulfil the clinical criteria or you are not one of the specified types of referrer and you still feel that testing should be performed please contact the laboratory to discuss testing of the sample.

Appendix 1

Genes in panel test and associated conditions

Rows that are highlighted in blue show where the gene is currently being fully analysed in the context of a single separate UKGTN test

HGNC standard name and symbol of the gene	HGNC number	OMIM number	OMIM standard name of condition and symbol	Mode of inheritance	OMIM number	Evidence of association between gene(s) and condition	% of horizontal coverage of gene	MLPA	Comments
solute carrier family 40 (iron-regulated transporter), member 1; SLC40A1	10909	604653	Ferroportin disease, classical, type 4A and an iron overload, type 4B	AD	606069	FERROPORTIN DISEASES: FUNCTIONAL STUDIES, A LINK BETWEEN GENETIC AND CLINICAL PHENOTYPE LENAICK DETIVAUD ET AL HUMAN MUTATION VOL34, ISSUE 11 PG 1529-1536 NOV 2013	100	YES	
Hemojuvelin; HFE2	4887	608374	Juvenile Haemochromatosis (Type 2A)	AR	602390	NON-HFE HEPATIC IRON OVERLOAD PIETRANGELO A ET AL SEMIN LIVER DIS 2011 AUG:31(3):302-18	100	YES	
HEPCIDIN ANTIMICROBIAL PEPTIDE; HAMP	15598	606464	Juvenile Haemochromatosis (Type 2B)	AR	613313	NON-HFE HEPATIC IRON OVERLOAD PIETRANGELO A ET AL SEMIN LIVER DIS 2011 AUG:31(3):302-18	96	YES	
Transferrin Receptor 2;TFR2	11762	604720	Haemochromatosis, (type 3)	AR	604250	NON-HFE HEPATIC IRON OVERLOAD PIETRANGELO A ET AL SEMIN LIVER DIS 2011 AUG:31(3):302-18	99	YES	
Haemochromatosis; HFE	4886	613609	Haemochromatosis (Type 1)	AR	235200	NON-HFE HEPATIC IRON OVERLOAD PIETRANGELO A ET AL SEMIN LIVER DIS 2011 AUG:31(3):302-18	97	YES	
Ceruloplasmin; CP	2295	117700	Aceruloplasminemia	AR	604290	Aceruloplasminemia: an update. Kono S.	100		

						Int Rev Neurobiol. 2013;110:125-51			
Hephaestin; HEPH	4866	300167	Iron Deficiency anaemia.	X			100		
Transmembrane Protease Serine 6;TMPRSS6	16517	609862	Iron Refractory iron deficiency anaemia, IRIDA	AR	206200	IRON REFRACTORY IRON DEFICIENCY ANAEMIA LUIGIA DE FALCO ET AL HAEMATOLOGICA 2013; 98(3)	100		
Solute carrier family 11 (proton-coupled divalent metal ion transporter), member 2; SLC11A2	10908	600523	Iron deficiency anaemia.	AR	206100	THE MOLECULAR BASIS OF IRON OVERLOAD DISORDERS AND IRON LINKED ANAEMIAS J KAPLAN ET AL INT J HEMATOL (2011) 93: 14-20	100		
Ferritin Light Chain; FTL	3999	134790	1.Hyperferritinemia–cataract syndrome 2. Hyperferritinemia 3. Neuroferritinopathy	AD AD	600886 606159	ABNORMAL IRON HOMEOSTASIS AND NEUROGENERATION BARRY B MUHOBERAC ET AL FRONTIERS IN AGING NEUROSCIENCE JULY 2013 VOL 5 ARTICLE 32 Hyperferritinemia–cataract syndrome: Worldwide mutations and phenotype of an increasingly diagnosed genetic disorder Gunda Millonig,1* Martina U. Muckenthaler2 and Sebastian Mueller1 HUMAN GENOMICS. VOL 4. NO. 4. 250–262 APRIL 2010 A new missense mutation in the L ferritin coding sequence associated with elevated levels of glycosylated ferritin in serum and absence of iron overload Caroline Kannengiesser et al haematologica | 2009; 94(3)	100		
Ferritin Heavy Chain 1; FTH1	3976	134770	Bilateral cataracts and affects iron storage	AD	615517	J Exp Med. 2013 Aug 26;210(9):1779-91 Human L-ferritin deficiency is characterized by idiopathic generalized seizures and atypical restless leg syndrome. Cozzi A, Santambrogio P, Privitera D, Broccoli V, Rotundo LI, Garavaglia B, Benz R,	100		

						Altamura S, Goede JS, Muckenthaler MU, Levi S.			
aminolevulinate, delta-, synthase 2; ALAS2	**397**	**301300**	**X-linked Sideroblastic anaemia**	**X**	**300751**	**Systematic Molecular Genetic Analysis of Congenital Sideroblastic Anaemia: Evidence for Genetic Heterogeneity and Identification of Novel Mutations Anke K. Bergmann ET AL Pediatr Blood Cancer. 2010 February ; 54(2): 273–278**	**79**		
Transferrin; TF	**11740**	**190000**	**Atransferrinemia** **Dysfunctional transferrinaemia** **Hypotransferrinaemia**	**AR**	**209300**	**British Journal of Haematology, 2013, 163, 404–420 Two novel missense mutations in iron transport protein transferrin causing hypochromic microcytic anaemia and haemosiderosis: molecular characterization and structural implications. Athiyarath R, Arora N, Fuster F, Schwarzenbacher R, Ahmed R, George B, Chandy M, Srivastava A, Rojas AM, Sanchez M, Edison ES.**	**100**		
Bone morphogenetic protein 4; BMP4	**1071**	**112262**	**Most iron-related disorders are attributed to a deregulation of liver hepcidin expression. These disorders include the various forms of hereditary haemochromatosis, which is associated with low hepcidin expression or functionality, genetic iron-refractory iron deficiency anaemia, which is associated with high hepcidin levels and iron restriction. BMP-HJV-SMAD signaling pathway is the core axis of hepcidin control**			Down-regulation of Bmp/Smad signaling by Tmprss6 is required for maintenance of systemic iron homeostasis. Finberg KE, Whittlesey RL, Fleming MD, Andrews NC. Blood. 2010 May 6;115(18):3817-26	**100**		

Bone morphogenetic protein 6; BMP6	**1073**	**112266**	**Most iron-related disorders are attributed to a deregulation of liver hepcidin expression. These disorders include the various forms of hereditary haemochromatosis, which is associated with low hepcidin expression or functionality, genetic iron-refractory iron deficiency anaemia, which is associated with high hepcidin levels and iron restriction. BMP-HJV-SMAD signaling pathway is the core axis of hepcidin control**	**AR/AD**		Down-regulation of Bmp/Smad signaling by Tmprss6 is required for maintenance of systemic iron homeostasis. Finberg KE, Whittlesey RL, Fleming MD, Andrews NC. Blood. 2010 May 6;115(18):3817-26	**100**		
SMAD family member 4; SMAD4	**6770**	**600993**	**Most iron-related disorders are attributed to a deregulation of liver hepcidin expression. These disorders include the various forms of hereditary haemochromatosis, which is associated with low hepcidin expression or functionality, genetic iron-refractory iron deficiency anaemia, which is associated with high hepcidin levels and iron restriction. BMP-HJV-SMAD signaling pathway is the core axis of hepcidin control**	**AR/AD**		Down-regulation of Bmp/Smad signaling by Tmprss6 is required for maintenance of systemic iron homeostasis. Finberg KE, Whittlesey RL, Fleming MD, Andrews NC. Blood. 2010 May 6;115(18):3817-26	**100**		