LETTER TO THE EDITOR

Iron deficiency responses and integrated compensations in patients according to hereditary hemorrhagic telangiectasia *ACVRL1, ENG* and *SMAD4* genotypes

Lakshya Sharma,[1,2] Fatma Almaghlouth,[1] Heidi Mckernan,[3] James Springett,[3] Hannah C. Tighe,[3] Genomics England Research Consortium[4] and Claire L. Shovlin[1,2,3]

[1]National Heart and Lung Institute, Imperial College London; [2]NIHR Imperial Biomedical Research Center; [3]Specialist Medicine, Imperial College Healthcare NHS Trust and [4]Genomics England, London, UK

Correspondence:
C.L. SHOVLIN - c.shovlin@imperial.ac.uk

https://doi.org/10.3324/haematol.2022.282038

Iron deficiency responses and integrated compensations in patients according to hereditary haemorrhagic telangiectasia *ACVRL1¸ ENG* and *SMAD4* genotypes

Lakshya Sharma,[1,2] Fatma Almaghlouth,[1] Heidi Mckernan,[3] James Springett,[3] Hannah C. Tighe,[3] Genomics England Research Consortium, [4] Claire L. Shovlin[1,2,3]

1 National Heart and Lung Institute, Imperial College London, UK

2 NIHR Imperial Biomedical Research Centre, London, UK

3 Specialist Medicine, Imperial College Healthcare NHS Trust, London, UK

4 Genomics England, London, UK.

Running Head: HHT genotypes and iron

SUPPLEMENTARY DATA

Table S1 Population demographic data for all measurements by HHT genotype.....2
Figure S1 First-visit measurement analyses 3
Table S2: The Genomics England Research Consortium Members 8th May 2022 4

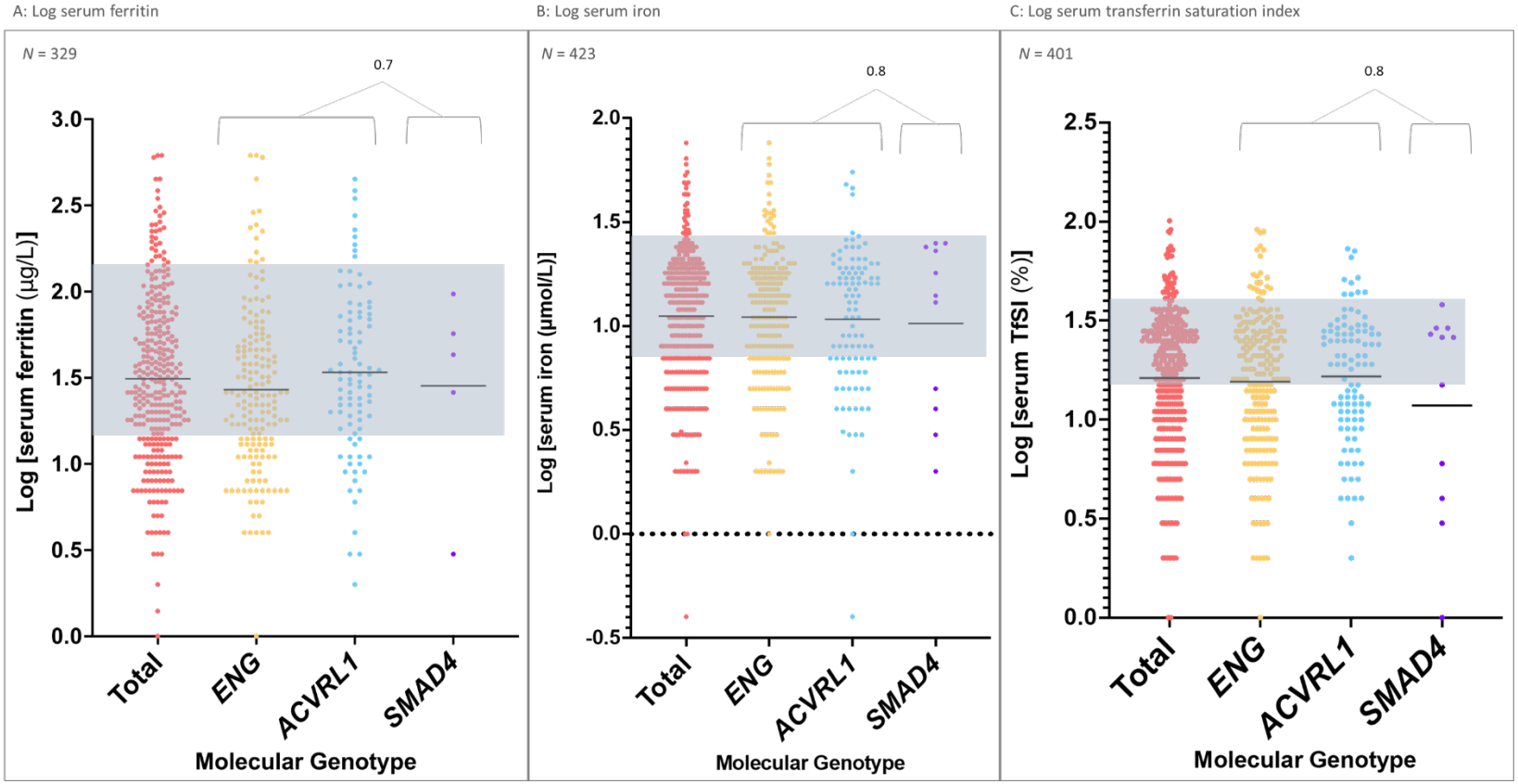
Table S1 Population demographic data for all measurements by HHT genotype

	Total (Patients, N=426)	***ENG*$^{+/-}$** (Patients, N=246)	***ACVRL1*$^{+/-}$** (Patients, N=102)	***SMAD4*$^{+/-}$** (Patients, N=11)
Female	*N*=264 [62.0%]	*N*=154 [62.6%]	*N*=57 [55.9%]	*N*=4 [36.4%]
Pulmonary arteriovenous malformation(s)	*N*=297 [69.7%]	*N*=189 [76.8%]	*N*=48 [47.1%]	*N*=3 [27.3%]
Age	50.0 [39.0,62.0]	49.0 [37.0,60.0]	55.0 [43.0,65.0]	40.0 [32.0,46.8]
Body mass index (kg/m2)	26.7 [22.6,30.4]	27.1 [22.6,30.5]	26.1 [23.0,28.9]	22.6 [17.7,26.7]
Red cell count *(million/mm^3)*	4.7 [4.4,5.1]	4.8 [4.3,5.1]	4.7 [4.2,5.0]	5.4 [4.9,6.0]
Haemoglobin *(g/dL)*	13.7 [11.8,15.1]	13.6 [11.6,15.2]	13.3 [11.6,15.0]	13.2 [11.6,14.5]
Haematocrit (%)	0.42 [0.38,0.45]	0.42 [0.37,0.46]	0.41 [0.36,0.44]	0.43 [0.38,0.44]
Mean corpuscular volume, MCV *(fl)*	89.0 [84.1, 92.7]	89.0 [84.0, 92.9]	89.7 [86.0, 93.0]	75.1 [69.8, 87.4]
Mean corpuscular haemoglobin, MCH *(g/dL)*	29.3 [26.8,30.9]	29.0 [26.7,30.9]	29.7 [27.9,30.8]	22.6 [20.9,27.8]
Mean corpuscular haemoglobin concentration *(g/dL)*	32.6 [31.1,33.8]	32.5 [31.0,33.7]	32.8 [31.7,33.7]	30.8 [29.6,32.0]
Red cell distribution width *(%)*	14.3 [13.2,16.8]	14.4 [13.3,17.1]	14.2 [13.1,15.9]	17.2 [13.4,20.0]
Serum ferritin *(µg/L)*	28.0 [14.0,67.0]	25.0 [13.0,50.5]	31.0 [17.5,75.0]	26.0 [5.00,39.5]
Serum iron *(µmol/L)*	11.0 [6.0,18.0]	11.0 [6.0,18.0]	12.0 [7.0,18.0]	5.00 [3.0,16.5]
Serum transferrin saturation index, T*f*SI *(%)*	18.0 [9.00,28.0]	16.0 [8.00,28.0]	19.0 [11.0,28.0]	7.00 [4.00,26.0]
C reactive protein *(mg/L)*	2.0 [0.8,4.2]	2.0 [0.70,4.0]	2.0 [1.0,4.5]	2.0 [1.0,3.7]
Erect SaO_2 *(%)*	95.0 [91.5,96.8]	95.0 [91.0,96.8]	96.0 [95.0,97.0]	95.0 [88.3,97.0]
Supine SaO_2 *(%)*	95.0 [92.5,96.5]	94.8 [92.0,96.5]	96.0 [95.0,96.6]	94.3 [91.1,96.6]
Erect pulse/minute	86.5 [76.3,98.3]	87.9 [77.8,98.8]	87.4 [78.3,91.9]	108 [98.2,123]
Supine pulse/minute	71.9 [63.5,80.4]	73.0 [64.1,81.5]	72.0 [63.3,81.5]	81.5 [74.0,91.2]
Arterial oxygen content *(mls/dL)*	17.9 [15.0,18.9]	17.1 [14.6,19.0]	17.2 [15.0,19.0]	16.0 [14.4,17.4]

Measurements available for all patients in the database including patients with variants in *ENG, ACVRL1, SMAD4, GDF2* and those who tested negative for variants in known HHT causal genes. Binary variables (sex and female and presence of pulmonary AVMs) are reported as number of patients (N) and percentage (%). Continuous variables reported as median and interquartile range. Data on 'gene negative' patients not presented separately. Trends were still apparent in the smaller dataset of first measurements only per patient (**S2**).
***Study Cohort and Assessment**: For the purposes of the current manuscript, all patients who had been genotyped through clinical or research programmes were included. As described[1,2], full blood count, serum iron and transferrin saturation index (TfSI) have been measured in all patients since 1999, and serum ferritin in all patients since 2005. Additionally, since 1986, at each assessment, postural oxygen saturation (SaO_2) and pulse is measured by pulse oximetry (Ohmeda Biox 3900, Boulder, Colorado) for 10 minutes in supine and erect postures, recorded at one minute intervals, with the mean values from minutes 7-10 reported, and arterial oxygen content (CaO2, mls/dL) calculated by 1.34 x haemoglobin x SaO2, as discussed elsewhere.[3-10]

[1]Shovlin et al PLoS One 2014;9(2):e88812; [2]Thielemans et al Haematologica 2019;104(4):e127-e130. [3]Santhirapala et al PLoS One 2014;9(3):e90777; [4]Santhirapala et al. Thorax 2014;69(11):1046-7; [5] Yasuda et al. Thorax 2015;70(6):601-3. [6]Rizvi et al. Ann Am Thorac Soc 2017;14(6):903-911; [7]Boother et al Clin Infect Dis 2017;65(4):595-603; [8]Shovlin et al BMJ Open Respir Res 2017;4(1):e000198; [9]Gawecki et al BMJ Open Respir Res 2019;6(1):e000351.[10]Gawecki et al QJM 2019;112(5):335-342.

Figure S1 First-visit measurement analyses



Distributions and means of first measurements only per patient, reference ranges shaded for A) Ferritin 15-150 mg/L (log transformed: 1.18-2.18); B Serum iron 7-27 µmol/L (log transformed: 0.85-1.43); C) . Transferrin saturation index (T*f*SI, 15-40% (log transformed: 1.18-1.60). P values calculated by Mann Whitney between *SMAD4* and non *SMAD4* genotypes as indicated. We considered it preferable to include all datapoints to promote further research and advance clinical care, rather than excluding the smaller number of *SMAD4* cases as is usually the case in 'HHT genotype phenotype' studies.[11-21]

[11]Berg et al J Med Genet. 2003 Aug;40:585-90; [12]Wehner et al Clin Genet. 2006;69:239-45; [13]Bayrak-Toydemir et al Am J Med Genet A 2006;140:463-70; [14]Letteboer et al J Med Genet 2006;43:371-7; [15]Bossler et al Hum Mutat 2006;27:667-75; [16]Lesca et al Genet Med 2007;9:14-22;[17]Sabbà et al J Thromb Haemost 2007;5:1149-57;[18]Letteboer et al Am J Med Genet A 2008;146A:2733-9;[19]Sadick et al BMC Med Genet 2009;10:53;[20]Chen et al. Eur J Clin Invest 2013;43:1016-24;[21]Massa et al Int J Hematol 2015;101:23-31;[22]Krings et al. AJNR Am J Neuroradiol 2015;36:863-70;[23]Mu et al Genet Med 2018;20:639-644;[24]Sánchez-Martínez et al Orphanet J Rare Dis 2020;15:138;[25]Beckman et al Orphanet J Rare Dis 2020;15:185;[26]Kilian et al J Clin Med 2020;9:2714;[27]Joyce et al Blood Ad. 2022;6:3956-3969;

Table S2: The Genomics England Research Consortium Members 8th May 2022

Ambrose, J. C. 1 ; Arumugam, P.1 ; Bevers, R.1 ; Bleda, M. 1 ; Boardman-Pretty, F. 1,2 ; Boustred, C. R. 1 ; Brittain, H.1 ; Brown, M.A.; Caulfield, M. J.1,2 ; Chan, G. C. 1 ; Giess A. 1; Griffin, J. N. ; Hamblin, A.1; Henderson, S.1,2; Hubbard, T. J. P. 1 ; Jackson, R. 1 ; Jones, L. J. 1,2; Kasperaviciute, D. 1,2 ; Kayikci, M. 1 ; Kousathanas, A. 1; Lahnstein, L. 1 ; Lakey, A.; Leigh, S. E. A. 1 ; Leong, I. U. S. 1 ; Lopez, F. J. 1 ; Maleady-Crowe, F. 1 ; McEntagart, M.1; Minneci F. 1 ; Mitchell, J. 1 ; Moutsianas, L. 1,2 ; Mueller, M. 1,2 ; Murugaesu, N. 1; Need, A. C. 1,2 ; O'Donovan P. 1; Odhams, C. A. 1 ; Patch, C. 1,2 ; Perez-Gil, D. 1 ; Pereira, M. B.1 ; Pullinger, J. 1 ; Rahim, T. 1 ; Rendon, A. 1 ; Rogers, T. 1 ; Savage, K. 1 ; Sawant, K. 1; Scott, R. H. 1 ; Siddiq, A. 1 ; Sieghart, A. 1 ; Smith, S. C. 1; Sosinsky, A. 1,2 ; Stuckey, A. 1 ; Tanguy M. 1 ; Taylor Tavares, A. L.1; Thomas, E. R. A. 1,2 ; Thompson, S. R. 1 ; Tucci, A. 1,2 ; Welland, M. J. 1 ; Williams, E. 1 ; Witkowska, K. 1,2 ; Wood, S. M. 1,2; Zarowiecki, M. 1 .

1. Genomics England, London, UK
2. William Harvey Research Institute, Queen Mary University of London, London, EC1M 6BQ, UK.