cancers

Supplemental Materials: Roles of HIF and 2-Oxoglutarate-Dependent Dioxygenases in Controlling Gene Expression in Hypoxia

Julianty Frost, Mark Frost, Michael Batie, Hao Jiang and Sonia Rocha

Supplementary Table S1. 2-OGDs reported affinities for oxygen from *in vitro* assays. These Individual studies were used for calculating the median K_M for 2-OGDs with more than one reported value.

Enzyme	O_2 K_M (μM)	Calculated Median K_M
PHD2	67 ± 10 [1] 81 ± 28 [1] 229 ± 60 [1] 250 [2] Approx. > 450 [3] 1746 ± 574 [4]	240
FIH	90 ± 20 [5] 100 ± 10 [6] 0.7-110 [7] 110 ± 30 [6] 110 ± 73 [1] 150 ± 30 [1] 237 ± 28 [1]	110 ± 30
KDM4A	57 ± 10 [8] 60 ± 20 [9] 173 ± 23 [10]	60 ± 20

Supplementary Table S2. Known mutations in the hypoxia signalling system in humans.

Gene	Mutation	Phenotypes
	HIFs	
HIF-1α	c.1156C>G (L386V)	Schizophrenia [11]
	c.1744C>T (p.P582S)	Maximal oxygen consumption [12]
	c.1742(p.A588T)	Renal cell carcinoma [13]
HIF-2α	c.607A>C (p.N203H)	Congenital heart disorder [14]
	c.824G>A (p.R275H)	Autism spectrum disorder [15]
	c.1104G>A (p.M368I)	Pheochromocytoma [16]
	c.1121T>A (p.F374Y)	Pheochromocytoma and polycythaemia with paraganglioma [16,17]
	c.1234T>A (p.I412N)	Pheochromocytoma [16]
	c.1235T>A (p.I412N)	Pheochromocytoma [16]
	c.1586T>C (p.L529P)	Paraganglioma, polycythemia and somatostatinoma [18]
	c.1588G>A (p.A530T)	Erythrocytosis and polycythaemia with paraganglioma [19–21]
	c.1589C>A (p.A530E)	Pheochromocytoma [16]
	c.1589C>T (p.A530V)	Polycythaemia with paraganglioma [20]
	c.1591C>T (p.P531S)	Pheochromocytoma and polycythaemia with paraganglioma [20,22]
	c.1591C>A (p.P531T)	Pheochromocytoma and paraganglioma [22]
	c.1592C>T (p.P531L)	Pheochromocytoma and polycythaemia with paraganglioma [16,20,22]
	c.1595A>G (p.Y532C)	Paraganglioma, polycythemia and somatostatinoma [16,18]

	c.1597A>G (p.I533V)	Erythrocytosis [23]
	c.1601C>T (p.P534L)	Erythrocytosis [24]
	c.1604T>C (p.M535T)	Erythrocytosis [25]
	c.1605G>A (p.M535I)	Erythrocytosis [26]
	c.1603A>G (p.M535V)	Erythrocytosis [27]
	c.1609G>A (p.G537R)	Erythrocytosis [28], pulmonary arterial hypertension [29]
	c.1609G>T (p.G537W)	Erythrocytosis [28]
	c.1615G>T (p.D539Y)	Polycythaemia with paraganglioma [20]
	c.1617C>G (p.D539E)	Erythrocytosis [30]
	c.1620C>G (p.F540L)	Erythrocytosis [25]
	c.1625T>C (p.L542P)	Polycythaemia with paraganglioma [31]
	c.2170G>T (p.G724W)	Congenital heart disease [14]
	Dioxygenases - hydroxylases	
PHD1	rs10680577	Increased risk of hepatocellular carcinoma [32], lung cancer [33,34], gastric cancer [35], colorectal cancer [36].
	c.188T>A (p.S61R)	Pheochromocytoma/paraganglioma-polycythemia [37]
PHD2	c.12C>A(p.D4E) rs186996510	High-altitude adaptation [38]
	c.380G>C (p.S127C) rs12097901	High-altitude adaptation [38]
	c.471G>C (p.Q157H)	Erythrocytosis [39,40]
	c.599C>A (P200Q)	Erythrocytosis [39]
	c.606delG (p.M2021Ifs*71)	Erythrocytosis [41]
	c.609C>G (p.N203K)	Isolated erythrocytosis [40]
	c.610G>A (p.K204E)	Erythrocytosis [42]
	c.682G>C (p.A228S)	Pheochromocytoma/paraganglioma-polycythemia [37]
	c.760G>C (p.D254H)	Erythrocytosis [39]
	c.799G>A(p.E267K)	Pheochromocytoma [43]
	c.835del14 (p.L279Tfs43*)	Erythrocytosis [44]
	c.840_841insA (p.R281Tfs*3)	Erythrocytosis [41]
	c.853G>C (p.G285R)	Erythrocytosis [42]
	c.872A>T (p.K291I)	Familial isolated erythrocytosis [40]
	c.950C>G (p.P317R)	Familial erythrocytosis [45], cardiopulmonary [46]
	c.1000T>C (p.W334R)	Familial erythrocytosis [47]
	c.1001G>A (p.T334*)	Erythrocytosis [48]
	c.1010dup (p.V338Gfs*18)	Erythrocytosis [42]
	c.1112G>A (p.R371H)	Familial erythrocytosis [39,49]
	c.1121A>G (p.H374R)	Familial erythrocytosis and recurrent paraganglioma [50].
	c.1129C>T (p. Q377*)	Erythrocytosis [41]
	c.1192C>T (p. R398*)	Erythrocytosis [39]
	c.1267A>G (p.K423E)	Isolated erythrocytosis [51]
P4HA1	c.1323_1324insAG (p.R362Gfs*9)	Congenital-onset disorder of connective tissue [52]
	c.1553+2T>G (p.A418_A434del)	
	c.1327A>G (p.K443*)	
P4HA2	c.419A>G (p.Q140R)	High myopia [53]
	c.448A>G (p.I150V)	
	c.871G>A (p.E291K)	
	c.1327A>G (p.K443*)	
	c.1349_1350delGT (p.R451Gfs*8)	
PAHX	c.135-2A>G (p.Y46_R82del)	Refsum disease [54]
	c.164delT (p.L55fs*12)	Refsum disease [55]

	c.244C>G (p.R82G)	Nonsyndromic cleft lip and palate [56]
	c.247A>T (p.N83Y)	Refsum disease [57]
	c.258_265del (p.E86fs*26)	Refsum disease [57]
	c.375_376delGG (p.E126fs*1)	Refsum disease [57]
	c.412_675del (p.E138_W225del)	Refsum disease [58]
	c.457delG (p.A152fs*5)	Refsum disease [57]
	c.497-2A>G (p.A166fs*3)	Refsum disease [57]
	c.517C>T (p.P173S)	Refsum disease [54]
	c.524A>G (p.H175R)	Refsum disease [57]
	c.526C>A (p.Q176K)	Refsum disease [54]
	c.530A>G (p.N177G)	Refsum disease [54]
	c.576_577insGCC (p.192_193insA)	Refsum disease [54]
	c.577T>C (p.W193R)	Refsum disease [54]
	c.589G>C (p.E197Q)	Refsum disease [54]
	c.595A>T (p.I199F)	Refsum disease [54]
	c.610G>A (p.G204S)	Refsum disease [59]
	c.658C>T (p.H220Y)	Refsum disease [54]
	c.678+2T4G (p.A166fs*3)	Refsum disease [57]
	c.678+5G4T (p.A166fs*3)	Refsum disease [57]
	c.679–1G4T (p.A166fs*3)	Refsum disease [57]
	c.683_684insG (p.G228fs*2)	Refsum disease [57]
	c.703G>A (p.G235R)	Refsum disease [60]
	c.734G>A (p.R245Q)	Refsum disease [54], nonsyndromic cleft lip and palate [56]
	c.770T>C (p.F257S)	Refsum disease [54]
	c.805A>C (N269H)	Refsum disease [55]
	c.824G>A (p.R275Q)	Refsum disease [54]
	c.823C>T (p.R275W)	Refsum disease [61]
	c.829C>A (p.A277Q)	Refsum disease [62]
	c.1014_1015insATC (p.N337_L338insH)	Nonsyndromic cleft lip and palate [56]
FIH	c.121C>G (p.P41A)	Colorectal cancer [63]
TET1	NR	
TET2	c.1037T>C (p.L346P)	Myelodysplastic/myeloproliferative disease [64]
	c.1652A>C (p.D551A)	Prostate cancer [65]
	c.4115A>T (p.T1372I)	Myeloproliferative neoplasms [66]
	c.3853_3855del (p.S1285del)	
	p.Q891	
	c.3629T>C(p.L1210P)	
	p.Arg544*	
	splice donor c.3980 + 2G→T	
	p.D1858fs	
	c.3524G>A(p.G1275E)	
TET3	c.1215delA (p.W406Gfs*135)	Intellectual disability, developmental delay, autistic traits, hypotonia, growth abnormalities, facial dysmorphism and movement disorders [67]
	c.2254C>T (p.R752C)	
	c.2552C>T (p.T851M)	
	c.2722G>T (p.V908L)	
	c.3215T>G (p.F1072C)	
	c.3226G>A (p.A1076T)	

	c.3265G>A (p.V1089M)	
	c.4977_4983del (p.H1660Pfs*52)	
	c.5030C>T (p.P1677L)	
	c.5083C>T (p.Q1695*)	
FTO	c.812A>C (p.H271P)	Developmental delay and dysmorphic facial features [68].
	c.947G>A (p.R316Q)	Growth retardation and multiple malformations [68].
	c.956C>T (p.S319F)	Developmental delay and growth retardation [69].
	c.965G>A (p.R322Q)	Growth retardation and multiple malformations [70].
	rs9939609 and rs8050136	Obesity [71].
	rs9939609	Type II diabetes [72]
	rs7202116	Obesity [73].
	rs9939609	Metabolic syndrome including obesity, hypertension, dyslipidemia, and defective glucose tolerance [74].
	rs8050136	
	rs1558902	
	rs1421085	
Dioxygenases – lysine demethylases		
KDM3A	c.1934C>A (p.P645Q)	Male infertility [75]
	c.3956delA (p.G1211fs)	Male infertility [75]
KDM3B	c.4216C>T (p.R1406W)	Schizophrenia [76]
	c.2624del (p.L875Rfs*8)	Intellectual disability [77]
	c.3422A>G (p.N1141S)	Wilms tumour and hyperpigmentation [78]
	c.916_917delAG	Hepatoblastoma, autism, intellectual disability, and abnormal pigmentation [78]
	c.277G>T (p.E93*)	Acute myeloid leukemia, mild intellectual disability, congenital hypothyroidism and congenital hip dysplasia [78]
	c.3095A>T (p.D1032V)	Hodgkin lymphoma, feeding difficulties, intellectual disability, umbilical and inguinal hernia [79]
	c.133C>T (p.R45*)	Intellectual disability, facial dysmorphism and short stature [79]
	c.277G>T (p.E93*)	
	c.349T>C (p.W117R)	
	c.1007A>G (p.D336G)	
	c.2479C>T (p.Q827*)	
	c.2827C>T (p.R943W)	
	c.2828G>A (p.R943Q)	
	c.3083G>A (p.R1028Q)	
	c.3095A>T (p.D132V)	
	c.4526T>C (p.L1509P)	
	c.4549C>T (p.R1517*)	
	c.4631A>G (p.Y1544C)	
	c.1519G>A (p.E1731K)	
	c.5191G>A (p.E1731K)	
JMJD1C	c.748_749delTT (p.L250fs	Congenital heart disease in patients with 22q11.2 deletion syndrome [80]
	c.488C>T (p.P163L)	Rett syndrome [81]
	c.511G>A (p.V171I)	Intracranial germ cell tumour [82]
	c.268A>G (p.N190D)	Congenital heart disease in patients with 22q11.2 deletion syndrome [80]
	c.860C>G (p.P287R)	Congenital heart disease in patients with 22q11.2 deletion syndrome [80]

	c.1636C>T (p.H546Y)	Congenital heart disease in patients with 22q11.2 deletion syndrome [80]
	c.1957C>T (p.P653S)	Congenital heart disease in patients with 22q11.2 deletion syndrome [80]
	c.2636_2637insTT (p.S880P)	Intracranial germ cell tumour [82]
	c.2822A>G (p.H941R)	Congenital heart disease in patients with 22q11.2 deletion syndrome [80]
	c.2830C>T (p.P944S)	Autism spectrum disorder [81]
	c.3268A>G (p.K1060E)	Intracranial germ cell tumour [82]
	c.3308A>G (p.N1103S)	Intellectual disability [81]
	c.3349A>C (p.I1117L)	Congenital heart disease in patients with 22q11.2 deletion syndrome [80]
	c.3487A>G (p.I1163V)	Autism spectrum disorder [83]
	c.3559A>G (p.T1187A)	Intellectual disability [81]
	c.3743A>G (p.Q1248R)	Intellectual disability [81]
	c.3982C>G (p.R1328G)	Autism spectrum disorder [81]
	c.4286C>T (p.S1429L)	Congenital heart disease in patients with 22q11.2 deletion syndrome [80]
	c.2924G>C (p.K1462N)	Intracranial germ cell tumour [82]
	c.4420T>C (p.S1474P)	Congenital heart disease in patients with 22q11.2 deletion syndrome [80]
	c.4781T>C (p.I1594T)	Intracranial germ cell tumour [82]
	c.6432A>G (p.I2144M)	Intracranial germ cell tumour [82]
	c.6997A>G (p.T2333A)	Autism spectrum disorder [81]
	c.7396C>T (H2466Y)	Congenital heart disease in patients with 22q11.2 deletion syndrome [80]
KDM4C	c.1186G>A (p.D396N)	Upper aerodigestive tract cancer [84]
	c.3115G>A (p.V1039I)	Age at menarche [85]
KDM5A	c.2155C?G (p.R719G)	Intellectual disability [86].
	c.4522C>T (p.R1508W)	Congenital heart disease [87].
KDM5B	c.4109T>G (p.L1370*)	Intellectual disability, dyslexia, global developmental delay, facial dysmorphism [88]
	c.2475-2A>G	Global developmental delay, intellectual disability, aggressive behaviour, facial dysmorphism [88]
	c.895C>T (p.R299*)	
	c.3906delC (p.N1302Kfs*45)	Global developmental delay, hypospadias, facial dysmorphism [88]
	c.622dupT (p.Y208Lfs*5)	
KDM5C	c.2T>C (p.M1T)	X-linked intellectual disability [89]
	c.229G>A (p.A77T)	X-linked mental retardation [90]
	c.260A>G 9p.D87G)	X-linked mental retardation [91]
	c.994C>T (p.R332*)	X-linked mental retardation [91]
	c.1162G>C (p.A388P)	X-linked mental retardation [92]
	c.1204G>T (p.D402Y)	X-linked mental retardation [92]
	c.1270G>T (p.E424*)	Intellectual disability [93]
	c.1353C>G (p.S451R)	X-linked mental retardation [94]
	c.1439C>T (p.P480L)	X-linked intellectual disability [95]
	c.1510G>A (p.V504M)	X-linked mental retardation [90]
	c.1660C>A (p.P554T)	X-linked mental retardation [96]
	c.1919G>A (p.C640Y)	X-linked mental retardation [97]
	c.1924T>C (p.F642L)	X-linked mental retardation [91]

	c.2080C>T (p.R694*)	X-linked mental retardation [92]
	c.2092G>A (p.E698K)	X-linked mental retardation [92]
	c.2152G>C (p.A718P)	Intellectual disability [98]
	c.2172C>A (p.C724*)	X-linked intellectual disability [99]
	c.2191C>T (p.L731F)	X-linked mental retardation [92]
	c.2248C>T (p.R750W)	X-linked mental retardation [91]
	c.2252A>G (p.Y751C)	X-linked mental retardation [91]
	c.2296C>T (p.R766W)	Autism spectrum disorder [100]
	c.2908C>T (p.Q970*)	Intellectual disability [101]
	c.3285C>A (p.C1095*)	Intellectual disability [91]
	c.3864G>A (p.W1288*)	X-linked mental retardation [92]
	IVS11ds+5G>A	X-linked mental retardation [90]
	IVS5ds+2T>C	Intellectual disability [101]
	c.1600delT(p.W534Gfs*15)	Intellectual disability [101]
	c.2047delG (p.A683Pfs*81)	Intellectual disability [91]
	c.3223delG (p.V1075Yfs*2)	X-linked intellectual disability [102]
	c.4441_4442delAG (p.R1481Gfs*9)	X-linked mental retardation [90]
	c.202_203insC (p.68fs*7)	X-linked mental retardation [92]
	c.1296dup (p.E433*)	Intellectual disability [98]
	c.3258_3259insC (p.K1087fs*43)	X-linked mental retardation [96]
	0.4 Mb microdeletion at Xp11.22	Intellectual disability [103]
KDM6A	c.171dupT (p.G58Wfs*7)	Kabuki syndrome [104]
	c.190G>T (p.E64*)	Kabuki syndrome [104]
	c.335−1G>T	Kabuki syndrome [105]
	c.342C>T (p.R172*)	Kabuki syndrome [106,107]
	c.443+5G>C	Kabuki syndrome [104]
	c.563A>G (p.K188R)	Kabuki syndrome [106]
	c.619+6T>C	Kabuki syndrome [104]
	c.620−2A>G	Kabuki syndrome [104]
	c.752G>A (p.W251*)	Kabuki syndrome [108]
	c.1555C>T (p.R519*)	Kabuki syndrome [109]
	c.1834C>T (p.R612*)	Renal cancer [110]
	c.1846_1849delACTC (p.T616Yfs*8)	Kabuki syndrome [107]
	c.1909_1912delTCTA (p.S637Tfs*53)	Kabuki syndrome [111]
	c.2226_2227dupCA (p.S743Tfs*13)	Kabuki syndrome [104]
	c.2515_2518del (p.N839Vfs*27)	Kabuki syndrome [112]
	c.2729A>G (p.N910S)	Kabuki syndrome [104]
	c.2832+1G>A	Kabuki syndrome [104]
	c.2839A>T (p.D980V)	Kabuki syndrome [107]
	c.3073A>G (p.S1025G)	Kabuki syndrome [104]
	c.3109C>T (p.Q1037*)	Kabuki syndrome [104]
	c.3284+3_3284+6delAAGT (p.N1070_K1094del)	Kabuki syndrome [107]
	c.3354_3356delTCT (p.L1119del)	Kabuki syndrome [111]
	c.3717G>A (p.W1239*)	Kabuki syndrome [111]

	c.3763C>T (p.R1255W)	Kabuki syndrome [104]
	c.3835C>T (p.R1279*)	Kabuki syndrome [113]
	c.4051C>T (p.R1351*)	Kabuki syndrome [109]
	c.3284+1G>T	Kabuki syndrome [106]
	c.3548+2T>C	Kabuki syndrome [106]
	Exon 6 deletion	Kabuki syndrome [106]
	site c.3878+3_3878+6delAAGT c.3878+3_3878+6delAAGT	Kabuki syndrome [106]
	c.3501delT (p.F1167Lfs*11)	Kabuki syndrome [106]
	c.3736+2T>C	Kabuki syndrome [108]
	c. 3835C>T (p.R1279*)	Biliary atresia with Kabuki syndrome-like features [114]
	c.3876_3878delTAA+1delG	Kabuki syndrome [115]
KDM6B	c.2661C>T (p.P888S)	Intellectual disability [86]
	IVS9ds+5G>T	Intellectual disability, brachydactyly and dysmorphism [116]
KDM7B	c.529A>T (p.K177*)	X-linked mental retardation with cleft lip/palate [117]
	c.631C>T (p.R211*)	X-linked mental retardation with cleft lip/palate [118]
	c.836T>C (p.F279S)	X-linked mental retardation with cleft lip/palate [119]
	p.S969del	Autism and Asperger syndrome [120]
	c.943_954del	X-linked mental retardation with cleft lip/palate [118]
	g.218-254 kb covering KDM7B	Autism spectrum disorder, intellectual disability, cleft palate and Aarskog syndrome [121]
	g.236,505 bp	Intellectual disability [101]

NR, not reported.

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