**Supplementary Table 1 |** **Known mutations in the hypoxia signalling system in humans.**

|  |  |  |
| --- | --- | --- |
| Gene | Mutation | Phenotypes |
| HIFs |
| *HIF‑1α* | c.1156C>G (L386V) | Schizophrenia [1] |
|  | c.1744C>T (p.P582S) | Maximal oxygen consumption [2] |
|  | c.1742(p.A588T) | Renal cell carcinoma [3] |
| *HIF‑2α* | c.607A>C (p.N203H) | Congenital heart disorder [4] |
|  | c.824G>A (p.R275H) | Autism spectrum disorder [5] |
|  | c.1104G>A (p.M368I) | Pheochromocytoma [6] |
|  | c.1121T>A (p.F374Y) | Pheochromocytoma and polycythaemia with paraganglioma [6,7] |
|  | c.1234T>A (p.I412N) | Pheochromocytoma [6] |
|  | c.1235T>A (p.I412N) | Pheochromocytoma [6] |
|  | c.1586T>C (p.L529P) | Paraganglioma, polycythemia and somatostatinoma [8] |
|  | c.1588G>A (p.A530T) | Erythrocytosis and polycythaemia with paraganglioma [9-11] |
|  | c.1589C>A (p.A530E) | Pheochromocytoma [6] |
|  | c.1589C>T (p.A530V) | Polycythaemia with paraganglioma [10] |
|  | c.1591C>T (p.P531S) | Pheochromocytoma and polycythaemia with paraganglioma [10,12] |
|  | c.1591C>A (p.P531T) | Pheochromocytoma and paraganglioma [12] |
|  | c.1592C>T (p.P531L) | Pheochromocytoma and polycythaemia with paraganglioma [6,10,12] |
|  | c.1595A>G (p.Y532C) | Paraganglioma, polycythemia and somatostatinoma [6,8] |
|  | c.1597A>G (p.I533V) | Erythrocytosis [13] |
|  | c.1601C>T (p.P534L) | Erythrocytosis [14] |
|  | c.1604T>C (p.M535T) | Erythrocytosis [15] |
|  | c.1605G>A (p.M535I) | Erythrocytosis [16] |
|  | c.1603A>G (p.M535V) | Erythrocytosis [17] |
|  | c.1609G>A (p.G537R) | Erythrocytosis [18], pulmonary arterial hypertension [19] |
|  | c.1609G>T (p.G537W) | Erythrocytosis [18] |
|  | c.1615G>T (p.D539Y) | Polycythaemia with paraganglioma [10] |
|  | c.1617C>G (p.D539E) | Erythrocytosis [20] |
|  | c.1620C>G (p.F540L) | Erythrocytosis [15] |
|  | c.1625T>C (p.L542P) | Polycythaemia with paraganglioma [21] |
|  | c.2170G>T (p.G724W) | Congenital heart disease [4] |
| Dioxygenases - hydroxylases |
| *PHD1* | rs10680577 | Increased risk of hepatocellular carcinoma [22], lung cancer [23,24], gastric cancer [25], colorectal cancer [26]. |
|  | c.188T>A (p.S61R) | Pheochromocytoma/paraganglioma-polycythemia [27] |
| *PHD2* | c.12C>A(p.D4E) rs186996510 | High-altitude adaptation [28] |
|  | c.380G>C (p.S127C) rs12097901 | High-altitude adaptation [28] |
|  | c.471G>C (p.Q157H) | Erythrocytosis [29,30] |
|  | c.599C>A (P200Q) | Erythrocytosis [29] |
|  | c.606delG (p.M2021Ifs\*71) | Erythrocytosis [31] |
|  | c.609C>G (p.N203K) | Isolated erythrocytosis [30] |
|  | c.610G>A (p.K204E) | Erythrocytosis [32] |
|  | c.682G>C (p.A228S) | Pheochromocytoma/paraganglioma-polycythemia [27] |
|  | c.760G>C (p.D254H) | Erythrocytosis [29] |
|  | c.799G>A(p.E267K) | Pheochromocytoma [33] |
|  | c.835del14 (p.L279Tfs43\*) | Erythrocytosis [34] |
|  | c.840\_841insA (p.R281Tfs\*3) | Erythrocytosis [31] |
|  | c.853G>C (p.G285R) | Erythrocytosis [32] |
|  | c.872A>T (p.K291I) | Familial isolated erythrocytosis [30] |
|  | c.950C>G (p.P317R) | Familial erythrocytosis [35], cardiopulmonary [36] |
|  | c.1000T>C (p.W334R) | Familial erythrocytosis [37] |
|  | c.1001G>A (p.T334\*) | Erythrocytosis [38] |
|  | c.1010dup (p.V338Gfs\*18) | Erythrocytosis [32] |
|  | c.1112G>A (p.R371H) | Familial erythrocytosis [29,39] |
|  | c.1121A>G (p.H374R) | Familial erythrocytosis and recurrent paraganglioma [40]. |
|  | c.1129C>T (p. Q377\*) | Erythrocytosis [31] |
|  | c.1192C>T (p. R398\*) | Erythrocytosis [29] |
|  | c.1267A>G (p.K423E) | Isolated erythrocytosis [41] |
| *P4HA1* | c.1323\_1324insAG (p.R362Gfs\*9) | Congenital-onset disorder of connective tissue [42] |
|  | c.1553+2T>G (p.A418\_A434del) |
|  | c.1327A>G (p.K443\*) |
| *P4HA2* | c.419A>G (p.Q140R) | High myopia [43] |
|  | 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 [44] |
|  | c.164delT (p.L55fs\*12 ) | Refsum disease [45] |
|  | c.244C>G (p.R82G) | Nonsyndromic cleft lip and palate [46] |
|  | c.247A>T (p.N83Y) | Refsum disease [47] |
|  | c.258\_265del (p.E86fs\*26) | Refsum disease [47] |
|  | c.375\_376delGG (p.E126fs\*1) | Refsum disease [47] |
|  | c.412\_675del (p.E138\_W225del) | Refsum disease [48] |
|  | c.457delG (p.A152fs\*5) | Refsum disease [47] |
|  | c.497-2A>G (p.A166fs\*3) | Refsum disease [47] |
|  | c.517C>T (p.P173S) | Refsum disease [44] |
|  | c.524A>G (p.H175R) | Refsum disease [47] |
|  | c.526C>A (p.Q176K) | Refsum disease [44] |
|  | c.530A>G (p.N177G) | Refsum disease [44] |
|  | c.576\_577insGCC (p.192\_193insA) | Refsum disease [44] |
|  | c.577T>C (p.W193R) | Refsum disease [44] |
|  | c.589G>C (p.E197Q) | Refsum disease [44] |
|  | c.595A>T (p.I199F) | Refsum disease [44] |
|  | c.610G>A (p.G204S) | Refsum disease [49] |
|  | c.658C>T (p.H220Y) | Refsum disease [44] |
|  | c.678+2T4G (p.A166fs\*3) | Refsum disease [47] |
|  | c.678+5G4T (p.A166fs\*3) | Refsum disease [47] |
|  | c.679–1G4T (p.A166fs\*3) | Refsum disease [47] |
|  | c.683\_684insG (p.G228fs\*2) | Refsum disease [47] |
|  | c.703G>A (p.G235R) | Refsum disease [50] |
|  | c.734G>A (p.R245Q) | Refsum disease [44], nonsyndromic cleft lip and palate [46] |
|  | c.770T>C (p.F257S) | Refsum disease [44] |
|  | c.805A>C (N269H) | Refsum disease [45] |
|  | c.824G>A (p.R275Q) | Refsum disease [44] |
|  | c.823C>T (p.R275W) | Refsum disease [51] |
|  | c.829C>A (p.A277Q) | Refsum disease [52] |
|  | c.1014\_1015insATC (p.N337\_L338insH) | Nonsyndromic cleft lip and palate [46] |
| *FIH* | c.121C>G (p.P41A) | Colorectal cancer [53] |
| *TET1* | NR |  |
| *TET2* | c.1037T>C (p.L346P) | Myelodysplastic/myeloproliferative disease [54] |
|  | c.1652A>C (p.D551A) | Prostate cancer [55] |
|  | c.4115A>T (p.T1372I) | Myeloproliferative neoplasms [56] |
|  | 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 [57] |
|  | 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 [58]. |
|  | c.947G>A (p.R316Q) | Growth retardation and multiple malformations {Boissel, 2009. |
|  | c.956C>T (p.S319F) | Developmental delay and growth retardation [59]. |
|  | c.965G>A (p.R322Q) | Growth retardation and multiple malformations [60]. |
|  | rs9939609 and rs8050136 | Obesity [61]. |
|  | rs9939609 | Type II diabetes [62] |
|  | rs7202116 | Obesity [63]. |
|  | rs9939609 | Metabolic syndrome including obesity, hypertension, dyslipidemia, and defective glucose tolerance [64]. |
|  | rs8050136 |
|  | rs1558902 |
|  | rs1421085 |
| Dioxygenases – lysine demethylases |
| *KDM3A* | c.1934C>A (p.P645Q) | Male infertility [65] |
|  | c.3956delA (p.G1211fs) | Male infertility [65] |
| *KDM3B* | c.4216C>T (p.R1406W) | Schizophrenia [66] |
|  | c.2624del (p.L875Rfs\*8) | Intellectual disability [67] |
|  | c.3422A>G (p.N1141S) | Wilms tumour and hyperpigmentation [68] |
|  | c.916\_917delAG | Hepatoblastoma, autism, intellectual disability, and abnormal pigmentation [68] |
|  | c.277G>T (p.E93\*) | Acute myeloid leukemia, mild intellectual disability, congenital hypothyroidism and congenital hip dysplasia [68] |
|  | c.3095A>T (p.D1032V) | Hodgkin lymphoma, feeding difficulties, intellectual disability, umbilical and inguinal hernia [69] |
|  | c.133C>T (p.R45\*) | Intellectual disability, facial dysmorphism and short stature [69] |
|  | 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 [70] |
|  | c.488C>T (p.P163L) | Rett syndrome [71] |
|  | c.511G>A (p.V171I) | Intracranial germ cell tumour [72] |
|  | c.268A>G (p.N190D) | Congenital heart disease in patients with 22q11.2 deletion syndrome [70] |
|  | c.860C>G (p.P287R) | Congenital heart disease in patients with 22q11.2 deletion syndrome [70] |
|  | c.1636C>T (p.H546Y) | Congenital heart disease in patients with 22q11.2 deletion syndrome [70] |
|  | c.1957C>T (p.P653S) | Congenital heart disease in patients with 22q11.2 deletion syndrome [70] |
|  | c.2636\_2637insTT (p.S880P) | Intracranial germ cell tumour [72] |
|  | c.2822A>G (p.H941R) | Congenital heart disease in patients with 22q11.2 deletion syndrome [70] |
|  | c.2830C>T (p.P944S) | Autism spectrum disorder [71] |
|  | c.3268A>G (p.K1060E) | Intracranial germ cell tumour [72] |
|  | c.3308A>G (p.N1103S) | Intellectual disability [71] |
|  | c.3349A>C (p.I1117L) | Congenital heart disease in patients with 22q11.2 deletion syndrome [70] |
|  | c.3487A>G (p.I1163V) | Autism spectrum disorder [73] |
|  | c.3559A>G (p.T1187A) | Intellectual disability [71] |
|  | c.3743A>G (p.Q1248R) | Intellectual disability [71] |
|  | c.3982C>G (p.R1328G) | Autism spectrum disorder [71] |
|  | c.4286C>T (p.S1429L) | Congenital heart disease in patients with 22q11.2 deletion syndrome [70] |
|  | c.2924G>C (p.K1462N) | Intracranial germ cell tumour [72] |
|  | c.4420T>C (p.S1474P) | Congenital heart disease in patients with 22q11.2 deletion syndrome [70] |
|  | c.4781T>C (p.I1594T) | Intracranial germ cell tumour [72] |
|  | c.6432A>G (p.I2144M) | Intracranial germ cell tumour [72] |
|  | c.6997A>G (p.T2333A) | Autism spectrum disorder [71] |
|  | c.7396C>T (H2466Y) | Congenital heart disease in patients with 22q11.2 deletion syndrome [70] |
| *KDM4C* | c.1186G>A (p.D396N) | Upper aerodigestive tract cancer [74] |
|  | c.3115G>A (p.V1039I) | Age at menarche [75] |
| *KDM5A* | c.2155C?G (p.R719G) | Intellectual disability [76]. |
|  | c.4522C>T (p.R1508W) | Congenital heart disease [77]. |
| *KDM5B* | c.4109T>G (p.L1370\*) | Intellectual disability, dyslexia, global developmental delay, facial dysmorphism [78] |
|  | c.2475-2A>G | Global developmental delay, intellectual disability, aggressive behaviour, facial dysmorphism [78] |
|  | c.895C>T (p.R299\*) |
|  | c.3906delC (p.N1302Kfs\*45) | Global developmental delay, hypospadias, facial dysmorphism [78] |
|  | c.622dupT (p.Y208Lfs\*5) |
| *KDM5C* | c.2T>C (p.M1T) | X-linked intellectual disability [79] |
|  | c.229G>A (p.A77T) | X-linked mental retardation [80] |
|  | c.260A>G 9p.D87G) | X-linked mental retardation [81] |
|  | c.994C>T (p.R332\*) | X-linked mental retardation [81] |
|  | c.1162G>C (p.A388P) | X-linked mental retardation [82] |
|  | c.1204G>T (p.D402Y) | X-linked mental retardation [82] |
|  | c.1270G>T (p.E424\*) | Intellectual disability [83] |
|  | c.1353C>G (p.S451R) | X-linked mental retardation [84] |
|  | c.1439C>T (p.P480L) | X-linked intellectual disability [85] |
|  | c.1510G>A (p.V504M) | X-linked mental retardation [80] |
|  | c.1660C>A (p.P554T) | X-linked mental retardation [86] |
|  | c.1919G>A (p.C640Y) | X-linked mental retardation [87] |
|  | c.1924T>C (p.F642L) | X-linked mental retardation [81] |
|  | c.2080C>T (p.R694\*) | X-linked mental retardation [82] |
|  | c.2092G>A (p.E698K) | X-linked mental retardation [82] |
|  | c.2152G>C (p.A718P) | Intellectual disability [88] |
|  | c.2172C>A (p.C724\*) | X-linked intellectual disability [89] |
|  | c.2191C>T (p.L731F) | X-linked mental retardation [82] |
|  | c.2248C>T (p.R750W) | X-linked mental retardation [81] |
|  | c.2252A>G (p.Y751C) | X-linked mental retardation [81] |
|  | c.2296C>T (p.R766W) | Autism spectrum disorder [90] |
|  | c.2908C>T (p.Q970\*) | Intellectual disability [91] |
|  | c.3285C>A (p.C1095\*) | Intellectual disability [81] |
|  | c.3864G>A (p.W1288\*) | X-linked mental retardation [82] |
|  | IVS11ds+5G>A | X-linked mental retardation [80] |
|  | IVS5ds+2T>C | Intellectual disability [91] |
|  | c.1600delT(p.W534Gfs\*15) | Intellectual disability [91] |
|  | c.2047delG (p.A683Pfs\*81) | Intellectual disability [81] |
|  | c.3223delG (p.V1075Yfs\*2) | X-linked intellectual disability [92] |
|  | c.4441\_4442delAG (p.R1481Gfs\*9) | X-linked mental retardation [80] |
|  | c.202\_203insC (p.68fs\*7) | X-linked mental retardation [82] |
|  | c.1296dup (p.E433\*) | Intellectual disability [88] |
|  | c.3258\_3259insC (p.K1087fs\*43) | X-linked mental retardation [86] |
|  | 0.4 Mb microdeletion at Xp11.22 | Intellectual disability [93] |
| *KDM6A* | c.171dupT (p.G58Wfs\*7) | Kabuki syndrome [94] |
|  | c.190G>T (p.E64\*) | Kabuki syndrome [94] |
|  | c.335−1G>T | Kabuki syndrome [95] |
|  | c.342C>T (p.R172\*) | Kabuki syndrome [96,97] |
|  | c.443+5G>C | Kabuki syndrome [94] |
|  | c.563A>G (p.K188R) | Kabuki syndrome [96] |
|  | c.619+6T>C | Kabuki syndrome [94] |
|  | c.620−2A>G | Kabuki syndrome [94] |
|  | c.752G>A (p.W251\*) | Kabuki syndrome [98] |
|  | c.1555C>T (p.R519\*) | Kabuki syndrome [99] |
|  | c.1834C>T (p.R612\*) | Renal cancer [100] |
|  | c.1846\_1849delACTC (p.T616Yfs\*8) | Kabuki syndrome [97] |
|  | c.1909\_1912delTCTA (p.S637Tfs\*53) | Kabuki syndrome [101] |
|  | c.2226\_2227dupCA (p.S743Tfs\*13) | Kabuki syndrome [94] |
|  | c.2515\_2518del (p.N839Vfs\*27) | Kabuki syndrome [102] |
|  | c.2729A>G (p.N910S) | Kabuki syndrome [94] |
|  | c.2832+1G>A | Kabuki syndrome [94] |
|  | c.2839A>T (p.D980V) | Kabuki syndrome [97] |
|  | c.3073A>G (p.S1025G) | Kabuki syndrome [94] |
|  | c.3109C>T (p.Q1037\*) | Kabuki syndrome [94] |
|  | c.3284+3\_3284+6delAAGT (p.N1070\_K1094del) | Kabuki syndrome [97] |
|  | c.3354\_3356delTCT (p.L1119del) | Kabuki syndrome [101] |
|  | c.3717G>A (p.W1239\*) | Kabuki syndrome [101] |
|  | c.3763C>T (p.R1255W) | Kabuki syndrome [94] |
|  | c.3835C>T (p.R1279\*) | Kabuki syndrome [103] |
|  | c.4051C>T (p.R1351\*) | Kabuki syndrome [99] |
|  | c.3284+1G>T | Kabuki syndrome [96] |
|  | c.3548+2T>C | Kabuki syndrome [96] |
|  | Exon 6 deletion | Kabuki syndrome [96] |
|  | sitec.3878+3\_3878+6delAAGT (c.3878+3\_3878+6delAAGT | Kabuki syndrome [96] |
|  | c.3501delT (p.F1167Lfs\*11) | Kabuki syndrome [96] |
|  | c.3736+2T>C | Kabuki syndrome [98] |
|  | c. 3835C>T (p.R1279\*) | Biliary atresia with Kabuki syndrome-like features [104] |
|  | c.3876\_3878delTAA+1delG | Kabuki syndrome [105] |
| *KDM6B* | c.2661C>T (p.P888S) | Intellectual disability [76] |
|  | IVS9ds+5G>T | Intellectual disability, brachydactyly and dysmorphism [106] |
| *KDM7B* | c.529A>T (p.K177\*) | X-linked mental retardation with cleft lip/palate [107] |
|  | c.631C>T (p.R211\*) | X-linked mental retardation with cleft lip/palate [108] |
|  | c.836T>C (p.F279S) | X-linked mental retardation with cleft lip/palate [109] |
|  | p.S969del | Autism and Asperger syndrome [110] |
|  | c.943\_954del | X-linked mental retardation with cleft lip/palate [108] |
|  | g.218-254 kb covering KDM7B | Autism spectrum disorder, intellectual disability, cleft palate and Aarskog syndrome [111] |
|  | g.236,505 bp | Intellectual disability [91] |

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