**Supplementary Table 1** Clinical, Biochemical, Molecular and Radiological Findings from Patients with *HIBCH* Gene Defects

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| Pt no | References | Sex | Consanguinity | Ethnicity | Mutation; Protein effect  (homozygous) | Age at onset (month) | Clinical findings | Laboratory  findings | Cranial MRI | Prognosis |
| 1 | Brown et al. 1982  Loupatty et al. 2007 | M | + | Egyptian | c.219\_220insTTGAATAG;p.K74Lfs\*13 | Birth | Physical malformations (dysmorphic facial features, multiple vertebral anomalies, tetralogy of Fallot and at postmortem examination: agenesis of the cingulate gyrus and corpus callosum),  failure to thrive and marked hypotonia | Hydroxy-C4-carnitine: NA,  20% residual activity of HIBCH activity in cultured skin fibroblasts (0% by Loupathy et al. 2007).  The urine showed abnormal levels of SCPC and SCPCM  (ninhydrin positive compound) | NA | Ex (3 months of age) |
| 2 | Loupatty et al. 2007 | M | - | European | c.365A>G;p.Y122C/c.79-3C>G;p.R27fsX50  (compound heterozygous) | 4 | Head bobbing, delay in motor milestones, ataxia, loss of skills  (developmental delay, ataxia, neurological regression) | Persistently elevated hydroxy-C4-carnitine (0.45/1.73 µM (N<0.4 µmol/L).  Complete absence of HIBCH activity (<2.6).  At metabolic decompensation:  A marked reduction of complex I and a borderline reduction of complex IV.  Excessive excretion of 3-hydroxybutyrate and acetoacetate and moderate excretion of lactate, 2-hydroxyisovalerate, 2-oxoisocaproate, dicarboxylic acids (C6, C8, C10) and methylmalonate,  Urine organic acids were normal after attack.  Normal activities of all four respiratory chain complexes after attack.  Urine samples showed ninhydrin positive compound | Signal abnormalities in the globus pallidus and the midbrain, with asymmetrical involvement of the cerebral peduncles, no structural abnormalities, Leigh disease?  (CT scan during acute encephalopathy: generalized edema of the brain, loss of grey/white differentiation in the basal ganglia) | Alive at 8 years of age |
| 3a | Ferdinandusse et al. 2013 | M | + | Pakistani | c.950G>A;p.G317E | 3 | Developmental regression with loss of smile and progressive hypotonia, Nissen fundoplication was performed at 8 months because of persistent vomiting, myoclonic jerks at 8 months and recurrent generalised seizures after 10 months, irritability, vomiting, retching, sleep disturbance, central apnea, vision impairment (optic atrophy), hearing loss, microcephaly | Hydroxy-C4-carnitine: NA  HIBCH activity: <2.6.  CSF lactate: 2.2/3.5 mmol/l (<2)  Venous blood lactate: 1.7 mmol/l (<1.8)  Low levels of complex I, II+III, IV and PDHc activities. | Altered signal and atrophy in the globi pallidi and relative sparing of the thalami. Leukoencephalopathy and some generalised atrophy | Ex (3 years of age) |
| 4a | Ferdinandusse et al. 2013 | M | + | Pakistani | c.950G>A;p.G317E | Birth | Poor sucking, feeding difficulties, nasogastric tube feeding, poor weight gain, infantile spasms, hypsarrhythmia, progressive dystonic disorder, persistent vomiting despite fundoplication, abdominal pain, extreme irritability, sleep disturbance, breath-holding episodes leading to severe oxygen desaturation, visual impairment, microcephaly | Persistent elevation of hydroxy-C4-carnitine (0.77-1.25 µmol/L, N<0.4).  HIBCH activity: <2.6.  Venous blood lactate: 4/N mmol/l (<1.8)  CSF lactate was mildly elevated on two occations at 2.1 and 2.6 mmol/l.  Muscle biopsy showed mildly increased lipid deposition within muscle fibers.  Normal PDHc and respiratory complex enzymes. | Abnormal signal within the dentate nuclei and the globi pallidi with a generalised lack of white matter | Ex (2 years 8 months of age) |
| 5b | Yamada et al. 2014 | F | - | Japanase | c.287C>A;p.A96D | 4 | Hypotonia, developmental delay | Hydroxy-C4-carnitine: 0.17 (N: 0.023±0.010 nmol/ml)  Relative HIBCH activity=22 (WT: 100%)  Muscle bx: normal | Bilateral signal abnormalities in the globi pallidi and caudate nuclei at acute attacks | Ex (4 years and 3 months of age) |
| 6b | Yamada et al. 2014 | F | - | Japanase | c.287C>A;p.A96D | 9 | Hypotonia, developmental delay, dystonia | Relative HIBCH activity=22 (WT: 100%) | Bilateral signal abnormalities in the globi pallidi | Ex (3 years and 10 months of age) |
| 7 | Reuter et al. 2014 | M | + | Tunisia | c.1128\_1129insT;p.K377\* | 7 | Severe developmental delay, seizures, convergent strabismus, bilateral cryptorchidism, gastrostomy tube feeding, blindness | Hydroxy-C4-carnitine: 0.66/0.81 (N <0.4 µM)  HIBCH activity: undetectable.  Elevated blood lactate.  Complexes I-IV and PDH activties: N  Complex I, I+III, cytochrome c oxidase deficiencies in skeletal muscle bx,  borderline depletion of mtDNA (30%) in muscle tissue, | Hyperintensities of the basal ganglia, progressive brain atrophy, optic nerve atrophy | Last seen at 5 years of age with severe developmental delay and seizures |
| 8 | Soler-Alfanso et al. 2015 | F | - | Caucasian | c.517+1G>A splicing/c.410C>T;p.A137V  (compound heterozygous) | 3 | Global hypotonia, developmental delay, feeding difficulty, nystagmus, failure to thrive, necessating gastrostomy tube, developmental regression, URTI, mildly dysmorphic (low set ears, downslanting palpebral fissures, mild bilateral ptosis, significiant joint laxity), unable to speak | Acylcarnitine profile showed mild elevations of iso-butyryl carnitine of 1.37 µmol/L (0.06-1.05), hexanoyl carnitine of 0.04 µmol/L (0.01-0.22), and 3-OH oleyl carnitine of 0.04 µmol/L (0.00-0.03).  A-follow up acylcarnitine profile at 2 years and 10 months showed elevated acetyl carnitine of 23.86 µmol/L (0.31-14.96) and normal iso-butyryl, hexanoyl and 3-OH-oleyl carnitine.  Muscle biopsy at 29 months of age: moderate type 2 fiber atrophy with normal electron microscopy and normal electron transport chain analyses. | Brain MRI at 13 months of age: restricted diffusion in the bilateral globi pallidi, increased T2 signal in the caudate nucleus, globus pallidus and putamen without apparent lesions in the pons.  Brain MRI at 16 months: progression of the previously observed lesions with increased T2 signal in the caudate nuclei, lentiform nuclei, globi pallidi, the dorsum of the pons and adjacent cerebellar white matter.  Brain MRS demonstrated abnormal lactate peaks in the basal ganglia.  Brain MRI at 4 years 11 months of age (after valine restricted theraphy): Decrease in the size of basal ganglia lesions, normal pons | Mild clinical improvement after a valine restricted diet.  Alive at 5 years of age |
| 9 | Peters et al. 2015 | F | - | Anglo-Celtic family | c.129dupA;  p.G44RfsX20/c.1033G>A;p.G345S  (compound heterozygous) | 2 | Intrauterine growth retardation, hypotonia, developmental delay | Hydroxy-C4-carnitine:1.2/0.8/3.6 (<1.3 µmol/L).  HIBCH activity in cultured skin fibroblasts was below the limit of detection, <2.6 nmol/min/mg protein (N: 5.3-10.5).  Decreased pyruvate dehydrogenase activity in cultured skin fibroblasts. Respiratory chain complexes activities were normal in liver and muscle. | Cerebral atrophy with markedly delayed myelination, thinning of the corpus callosum and markedly increased signals in the brain stem, upper pons, basal ganglia and thalami at 10 months. Progression of these findings at 17 months | Severe developmental delay at age 7 years.  Exitus at age 8 years old |
| 10 | Zhu et al. 2015 | F | - | Chinese | c.1027C>G;p.H343D/c.79-1G>T splicing  (compound heterozygous) | NA | Developmental delay, acute encephalopathy and severe extrapyramidal symptoms preceded by fever (Leigh-like syndrome) | ?  (Literature was in Chinese) | Bilateral symmetrical lesions in basal ganglia.  Aggravated lesions in bilateral basal ganglia, new lesions in the midbrain cerebral peduncle and pons and cerebellar atrophy at 5 years 5 months old during acute encephalopathy attack | Severe developmental delay at 5 years-5 months old at the time of report |
| 11c | Stiles et al. 2015 | F | + | Lebanese | c.196C>T;p.R66W | 4-6 | Developmental delay, dystonia, spastic quadriplegia, optic atrophy, failure to thrive, gastrostomy tube feeding | Hydroxy-C4-carnitine: 0.88 µM (<0.3),  HIBCH activity: 1.1 [N: 5.3-10.5 nmol/(min.mg.protein)] | High signal lesions in the globus pallidus, head of the caudate nucleus, with patchy high signal in the periventricular white matter and a focal lesion in the left cerebral peduncle at 2 years. Progression of the lesions at 6.3 years. Residual cystic changes in the globus pallidus, basal ganglia atrophy, persistent generalized brain atrophy and white matter changes at age of 12 | Severe developmental delay, gastric tube feeding, severe scoliosis, mild joint contractures, a dislocated hip at age 13 years at the time of report |
| 12c | Stiles et al. 2015 | M | + | Lebanese | c.196C>T;p.R66W | 6 | Failure to thrive, developmental delay, gastrostomy tube feeding, optic nerve atrophy, strabismus | Hydroxy-C4-carnitine: 1.23 µM (<0.3),  HIBCH activity: 1.7 [N: 5.3-10.5 nmol/(min.mg.protein)] | Swelling of the globus pallidus, bilaterally with diffuse abnormal high signal and generalized atrophy throughout the deep white matter at 1.6 years of age. Progression of the lesions with time | Clinical findings were same with his sister at 12 years old at the time of report.  Scoliosis surgery at 11 years. History of femur fractures secondary to osteopenia |
| 13D | Schottmann et al. 2016 | M | + | Turkish | c.913A>G;p.T305A | 48 | Unsteady gait, impaired motor coordination, nonprogressive ataxia, dysarthria, muscular hypotonia, mild intellectual disability | Hydroxy-C4-carnitine: normal,  HIBCH activity: NA | Abnormalities in the pallidum suggestive of Leigh syndrome | Last assesment 43 years of age |
| 14d | Schottmann et al. 2016 | F | + | Turkish | c.913A>G;p.T305A | 12 | Congenital diaphragmatic hernia, atrioventricular canal, severely impaired mental and motor development, without ability to speak and walk | Hydroxy-C4-carnitine: normal,  HIBCH activity: NA | Abnormalities in the pallidum suggestive of Leigh syndrome | Last assesment 18 years of age |
| 15d | Schottmann et al. 2016 | M | + | Turkish | c.913A>G;p.T305A | 12 | Unsteady gait, impaired motor coordination, nonprogressive ataxia, dysarthria, muscular hypotonia, mild intellectual disability | Hydroxy-C4-carnitine: mildly elevated,  HIBCH enzyme activity in cultured skin fibroblasts was markedly reduced | Abnormalities in the pallidum suggestive of Leigh syndrome | Last assesment 12 years of age |
| 16e | Schottmann et al. 2016 | M | + | Turkish | c.913A>G;p.T305A | 36 | Transient deterioration of motor skills following febrile infections. Spastic-dystonic tetraparesis and dysarthria | Hydroxy-C4-carnitine: 4.24 µmol/l (N <2.8),  HIBCH activity: NA | MRI at 5 years of age revealed lesions suggestive of Leigh syndrome | At 26 years of age he can only walk short distances and depends on comprehensive care in his daily life |
| 17e | Schottmann et al. 2016 | M | + | Turkish | c.913A>G;p.T305A | 48 | Progressive painful dystonic movement disorder predominantly of the left side | Hydroxy-C4-carnitine: 3.26 µmol/l (N<2.8),  HIBCH activity: Below the limit of quantification | Signs of Leigh syndrome  progressive necrosis of the basal ganglia | Last assesment 14 years of age |
| 18# | Charng et al. 2016 | NA | NA | Arab family (Saudi Arabia) | NA | NA | NA (Neurodevelopmental disorder) | NA | NA | NA |
| 19 | Tan et al. 2018 | M | - | Chinese | c.304+3A>G;p.K74X /c.1010\_1011+3delTGGTA; p.V298RfsX50 (compound heterozygous) | 3 | Atypical bilateral syndactyly, right indirect inguinal hernia, neurodegenerative symptoms | Hydroxy-C4-carnitine: 0.79 µmol/l (N<0.6),  HIBCH activity: NA,  Absence of HIBCH protein was shown by western blotting | Widened cerebral sulci and thinning of corpus callosum at age of 5 months | At 16 months old: Severe developmental delay with cocktail therapy, dietary valine restriction and symptomatic treatment at the time of writing |
| 20 | Yang et al. 2018 | M | NA | Chinese | c.439-2A>G/c.958A>G;p.K320E  (compound heterozygous) | 18? | Developmental regression and paroxysmal dystonia after pyrexia and diarrhea | ?  (Literature was in Chinese) | Symmetrical lesions in the bilateral basal ganglia | Improvements in dystonia and motor and intellectual development after cocktail therapy and valine restriction |
| 21 | Karimzadeh et al. 2019 | M | - | Iranian | c.641C>T;p.T214I/c.913A>G;p.T305A  (compound heterozygous) | 15 | Recurrent attacks following febrile disease with symptoms including weakness, myoclonus, nystagmus | Tandem mass: N (Hydroxy-C4-carnitine was not reported),  Urine organic acid analyses showed elevated 3-hydroxy-isovaleric acid: 110 mmol/mol creatinine (N<44)  HIBCH activity: NA | Bilateral high signal abnormalities of the basal ganglia (globus pallidus) at 2 years old | At age of 3.5 years, the patient neither could walk indepently, nor talk naturally |
| 22# | Candelo et al. 2019 | F | + | Colombian | c.808A>G;p.S270G | 2 | Frequently hospitalised for persistent vomiting, anorexia, irritability, swallowing difficulties, poor feeding, psychomotor developmental delay, no language skills and developmental regression since she was 2- months old. Gastrostomy tube was placed and Nissen fundoplication was performed at 3 months old. At 9 months old, multiple episodes of seizures and myoclonus developed. Facial dysmorphia, microcephaly, hypotonia, hepatomegaly, spastic legs.  Cardiac septal ventricular hypertrabeculation | Tandem mass: N (Hydroxy-C4-carnitine was not reported)  HIBCH activity: NA  PDHc: NA | Bilateral damage of the basal ganglia and general cerebral volume loss in white and grey matter.  Brain MRS showed lactate peak | Severe developmental delay, feeding diffuculty requiring gastrostomy tube. Valine free diet allows changes in her behaviour but it does not contribute to control of seizure episodes and developmental delay |
| 23# | Candelo et al. 2019 | M | - | Colombian | c.808A>G;p.S270G/c.173A>G;p.N58S  (compound heterozygous) | 3 | Generalised axial hypotonia, spactic hypertonia predominantly in the lower limbs, increased deep tendon reflexes and poor weight increase, severe developmental delay, rotatory nystagmus, convergent strabismus | Tandem mass: N (Hydroxy-C4-carnitine was not included)  HIBCH activity: NA  PDHc: NA | Cerebral atrophy and bilateral basal ganglia involvement. Lactate peak in brain MRS | NA |
| 24 | Xu et al. 2019 | F | - | Chinese | c.1027C>G;p.H343D/c.383T>A;p.V128D  (compound heterozygous) | 36 | Complaint of frequent cramps in the right leg after prolonged and intense exercise.  Dystonic posturing in both lower extremities and the waist triggered by mild physical activity, which resolves after 1 hour rest | Tandem mass: N  HIBCH activity: NA Mild elevated levels of ammonia, lactate and creatine kinase.  A reduction in the activity of complex V in peripheral leukocytes.  Muscle bx: normal  PDHc: NA | Bilateral symmetrical signal abnormalities in the globus pallidus. Brain MRS was normal | Alive at six years old at the time of report.  Clinical improvement after a valine restricted diet |
| 25# | D’Gama et al. 2020 | F | - | NA | c.852delA;p.L284FfsX10/c.488G>T;p.C163F | Birth | Poor feding, hypotonia, nystagmus, severe apneic episodes requiring intubation, multifocal seizures  Metabolic autopsy demonstrated generalized CNS atrophy, hepatic steatosis, left ventricular hypertrophy with aortic myxoid proliferation | Metabolic screening: Normal  (C4-OH: normal)  HIBCH activity: markedly reduced (0.8 ± 0.1 nmol/(min.mg) (N: 5.3-10.5) | Progressive abnormal T2 prolongation and reduced diffusivity in cerebral hemispheres, reduced diffusivity in the basal ganglia, thalami, cerebellar hemispheres, superior cerebellar peduncles, and midbrain in brain MRI. Lactate peak in the right basal ganglia on brain MRS. | Ex (within the first month of life) |
| 26 | This report | F | + | Turkish | c.556C>G;p.R186G | 9 | Hypotonia, bilaterally increased deep tendon reflexes and positive babinsky sign, she could not sit without support. At 18 months, recurrent generalized seizures were observed. Because of feeding problems, nasogastric tube feeding was started. | Hydroxy-C4-carnitine: 3.84/3.6 µmol/l (N<0.6)  HIBCH activity: NA | Cerebral atrophy and symmetric signal hyperintensity and swelling in basal ganglia and increased periventricular signal intensities. Brain MRS showed lactate peak | Six years old.  Severe developmental delay, failure to thrive, nasogastric tube feeding, traechostomy |

The same superscribed lower case letters are siblings. Parents are denoted with superscribed capital letters. N: normal, NA: not available, Pt: patient, PDHc: pyruvate dehydrogenase complex, URTI: upper respiratory tract infection, HIBCH fibroblast enzyme activity: N: 7.9±1.3 nmol/(min.mg), WT: Wild type, # : whole exome sequencing analyses, MRI: magnetic resonance imaging, MRS: magnetic resonance spectroscopy,

SCPC: S-(2-carboxypropyl) cysteine, SCPCM: S-(2-carboxypropyl) cysteamine.