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Supplemental Data

Paralog Studies Augment Gene Discovery:

DDX and *DHX* Genes

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Supplemental Note: Individual Reports

Individual 1 was previously published in Karaca *et al.,* Neuron 2015,[6] and presented with severe DD/ID, microcephaly, dysgenesis of the corpus callosum and hypotonia. A homozygous variant in *DHX37* (NM_032656.3:c.1257C>A: p.Asn419Lys:Chr12:125453449 C>A) was proposed as the candidate causal variant at that time. This patient was born to unaffected consanguineous parents. Brain MRI revealed cortical volume loss, severe dysgenesis of the corpus callosum, colpocephaly, delayed myelination, thickened sulci, polymicrogyria, and cerebellar volume loss (Figure 2A).

Individual 2 was obtained through GeneMatcher and was seen at Federico II University Hospital in Naples and enrolled in the Telethon Undiagnosed Diseases Program (TUDP) for ES. This patient is a 19-year-old female who presented with severe DD/ID, asymmetric cerebellar hypoplasia, generalized tonic-clonic seizures, ophthalmoplegia, and severe scoliosis (Figure 2B). She was born after an uncomplicated pregnancy and she was first evaluated at 5 moths of life for developmental delay and hypotonia. At 2 years of age she was found to have strabismus, bilateral ptosis, nystagmus but no changes at the eye fundus were observed. At 6 years, she developed generalized seizures and muscle spasms that were partially controlled by anti-epileptic drugs. She never walked and she was wheelchair-bound, she was not able to manipulate objects and she did not develop any language. She had severe scoliosis and dislocation of the right hip. She had bilateral ophthalmoplegia and blindness. She underwent repeated brain MRI that showed hypoplasia of the right cerebellar hemisphere and asymmetric posterior cranial fossa. The MRI of the orbits revealed hypoplasia of extraocular muscles including superior, medial and inferior rectus. Visual evoked potentials were markedly altered.

Brainstem auditory potentials and nerve conduction study were normal. The EEG showed signs of epileptic activities in the left occipital region. Cardiac and abdominal ultrasounds were normal. Before ES, she underwent multiple metabolic and genetic testing including levels of lactate, amino acids and acylcarnitine in blood, urinary organic acids, array-CGH, and Sanger sequencing of *KIF21A*, *TUBB3*, *ROBO3* and *SLC35A3* which were all negative. Trio ES identified compound heterozygous variants in *DHX37* (NM_032656.3:c.2191G>A;p.Val731Met and NM_032656.3:c.1399C>G;p.Leu467Val) which were inherited from each unaffected parent. The two unaffected sisters were found to carry only the c.2191G>A variant.

Individual 3 was obtained through GeneMatcher and was seen at Cook Children's Hospital in Fort Worth, TX. This patient first presented at six weeks gestation when no heart beat was detected on fetal ultrasound. Ultimately, the birth was complicated by bicornuate uterus and breach presentation. The patient was delivered at 39 weeks gestation by C-section with no complications. Perimembranous VSD and secundum ASD were identified after birth and were corrected surgically at 6 months of age. Skeletal survey revealed segmentation anomalies at T3, and L5, and 13 pairs of ribs. C3 and C4 vertebral bodies were found to be flattened and dysplastic. Abdominal ultrasound showed a chronic mural thrombus. This individual also presented with plagiocephaly which was treated with a helmet. He is also mildly dysmorphic with facial asymmetry, telecanthus, and epicanthal folds, and pectus excavatum (Figure 2C). At one year old he was also found to be short for his age (30.51 in, 3rd percentile) with a head circumference in the 34th percentile (48 cm). While noted to have hypotonia, he was able to roll over.

Individual 4 is a female diagnosed with Aicardi syndrome. The pregnancy was reported to be normal; however enlarged brain ventricles were documented in the fetus in a 3D ultrasound during the second trimester. After an unremarkable vaginal birth, infantile spasms developed but were not diagnosed until 2 months of age. An MRI at 2 days of life revealed complete agenesis of the corpus callosum, and an ophthalmologic exam at 2 months revealed bilateral chorioretinal lacunae and optic nerve coloboma in the right eye. This patient also presented with ventriculomegaly, colpocephaly, cerebellar dysplasia, intracranial cysts, polymicrogyria, heterotopia, choreoathetosis, abnormal neural migration, silent aspiration requiring G-tube placement, and severe DD/ID. At baseline, she presented with flat affect, consisting of no communication methods (both verbal and physical), with poor executive functioning. She was generally flaccid in tone and her only means of movement was rolling, since she cannot sit up independently or stand. She also presented with scoliosis at 4 years and 10 months of age involving T8 to L4 with a 62 degree angle, impacting respiratory function. She was treated with a VEPTR rod placement until age 10 at which point spinal fusion was performed from T10-L5 along the thoracic and lumbar nerves. She also presented with dysmorphic features including a short philtrum, large eyes, anteverted nares, macrodontia, downturned corners of the mouth, protruding ears with abnormal pinna and a broad neck (Figure 2D). Interestingly, this patient had precocious puberty, growth attenuation and advanced bone age. At age 9 years and 5 months, her bone age was measured to be 15 years. Her height has not changed from 52 inches at 9 years old. In addition to the complete agenesis of the corpus callosum, the proband also has other abnormalities present on the most recent brain MRI which was taken at age 10.

vetriculomegaly is still present on the MRI along with colpocephaly demonstrated by disproportionate enlargement of the occipital horns of the lateral ventricles. There is also dysgenesis of the cerebellum creating an enlarged 3rd and 4th ventricle. There also appears to be some asymmetry between the right and left hemispheres, subependymal gray matter, polymicrogyria, and a small interhemispheric cyst.

Trio ES identified a mosaic variant in *DXH37* at position NM_032656.3:c.1145A>G:p.Asp382Gly (Chr12:125455894T>C). Deep sequencing using MiSeq yielded 1 million reads at this locus (247388 called a C and 745504 called a T), giving an approximate C to T ratio of confirmed 20:80 vR:tR.

Individual 5 was originally seen at Cook Children's Hospital in Fort Worth, Texas at 15 months old. He presented with hypotonia and developmental delay. At that time, he babbled but had no words, and did not yet pull up to standing. A physical exam found him to be small for his age in both height (78.1 cm, 10th centile) and weight (4.6 kg, 9th centile), with an FOC of 45.9 cm (14.5th centile) but proportional. The head showed mild plagiocephaly and flattening of the right occipital region. He had undergone testing for Prader-Willi and Angelman syndromes, fragile X, and myotonic dystrophy which were all normal. The initial ES report indicated a *de novo* heterozygous variant of unknown significance in *SETBP1* (c.2621A>G; p.Asn874Gly). The patient was eventually enrolled in the BHCMG program at Baylor College of Medicine due to the non-diagnostic ES result. Examination at the age of 10 years revealed developmental delay, speech delay, dysmorphic features including hypertelorism, a pointed chin and midface hypoplasia, hypotonia, tooth agenesis, hypoplastic nails and Wolff-Parkinson White syndrome.

ES data identified a variant in *DHX37* NM_032656.3:c.3281C>T:p.Thr1094Met (Chr12:125434541G>A).

Individual 6 is a female who presented with infantile spasms at 10 weeks of age following an uneventful birth. A brain MRI performed at 2 months of age revealed agenesis of the corpus callosum and subependymal heterotopia. At five months of age the head circumference was 15 ¾ cm (10-25th percentile). At this time, she showed poor head control, hypotonia, poor visual tracking, and slow social smile. Ophthalmologic exam showed chorioretinal lacunae, and areas of depigmentation around the optic nerve. Given the presence of the cardinal features, she was given a clinical diagnosis of Aicardi syndrome. She was enrolled in the BHCMG and received Trio ES on a research basis. Trio ES identified a variant in *DHX16* NM_003587.4:c.1744T>A:p.Phe582Ile (Chr6:30627820 A>T).

Individual 7 was a female infant born by emergency C-section at 32 weeks gestation due to non-reassuring fetal heart tones. The birth measurements showed the proband to be below the fifth percentile for length (37 cm) and limbs appeared short in comparison to the body. The proband also presented with bilateral epicanthal folds and posteriorly rotated, simple auricles. A prenatal SNP array indicated no AOH, and postnatal brain ultrasound was normal. An abdominal ultrasound showed a normal liver but enlarged kidneys with poor corticomedullary differentiation and multiple cysts. This patient passed away at DOL 16 and no autopsy was performed. Trio ES identified a variant in *DHX16* at Chr 6:30624786 C>A position NM_003587.4:c.2091G>T:p.Gln697His.

Individual 8 is a now deceased 4 month old male infant. He presented with a severe congenital hypotonia, bilateral talipes equinovarus, and flexion contractures of the hands and knees with diminished limb movements, along with poor postnatal growth and feeding, requiring nasogastric gavage. Recurrent respiratory distress persisted including choking on his oro-pharyngeal secretions and aspiration. Electrophysiological studies (diminished nerve conduction velocities, and absent sensory nerve action potentials) and audiology, identified both an axonal sensory and denervating motor neuropathy, and sensorineural deafness. High-frequency, low-amplitude horizontal nystagmus was also noted on ophthalmologic review. An MRI of the brain in life was normal. At four months of age, he was admitted with acute chronic respiratory failure in the setting of a coronavirus pneumonitis and despite intensive care support passed away. Post mortem examination showed normal central cerebral myelination, and in the sural nerve, a paucity of large myelinated axons rimmed only by thin myelin sheaths or completely lacking myelin with atrophic myofibers consistent with denervation in the quadriceps musculature. ES performed at the Northwest Clinical Genomics Laboratory at the University of Washington identified a *de novo* variant in *DHX16* NM_003587.4:c.1280G>A:p.Gly427Glu (Chr6:30632615).

Individual 9 is a male proband, the first child of German parents. Both parents and the younger sister have no relevant medical complaints. The pregnancy and delivery, postnatal adaptation and development were normal until the 10th month of life. At that time, he presented with a febrile seizure, which re-occurred at the 15th and 17th month of life and led to initiation of anti-epileptic treatment with desoxyphenobarbital. At the age of four years he had a generalized

tonic-clonic seizure, at that time the EEG showed multifocal hypersynchronic activity. He could stand without support at 11 months and started to walk with support at 13 months. By the age of 20 months an unsteady gait and hypertrophic calf muscles were noted, and he stopped walking. The CK was unremarkable (177 U/l, Ref. < 270). Based on a muscle biopsy showing myopathy with atrophy of type I fibers and mild signs of inflammation, the diagnosis of a myositis was made and treated with cortisol. This led to prompt improvement with regaining of muscle strength and unsupported walking. At the age of five years the gait was noted to be broad based and atactic, he could not jump, had bilateral pointed feet and no deep tendon reflexes. Follow-up muscle biopsy one and three years later showed a degenerative myopathy with isolated necrotic fibers without signs of inflammation.

The CK reached a maximum at age seven years (689 U/l, Ref <270). Electron microscopy showed glycogen storage and fatty vacuoles. At the age of seven years ophthalmological investigation revealed pale pupils, shrunken vessel and pigmentary alterations. Neurophysiological investigations at the same time showed extensive myopathic changes in the EMG, pathological visual evoked potentials (VEP), auditory evoked potentials (AEP), and a pathological EEG with severe signs of generalized and multifocally diminished seizure threshold. The SSEP of the N. tibialis was pathological indicating a conductance deficit. At the age of nearly nine years sensorineural deafness was diagnosed. IQ-testing at that time was unremarkable. The vision decreased over the years with corresponding changes at the fundus starting at age 4 years showing “salt-and-pepper-fundus”, at age six years “Fundus flavimaculatus”, and the electroretinogram showed no activity on either side. Later a tapetoretinal degeneration was described. He suffered an absence epileptic state at age 14 years. Since then progredient

unsteadiness, distal muscle atrophy, multiple contractures and tunnel vision were seen. In summary, this patient has a multisystem involvement with developmental delays and normal intellectual capacity; epilepsy, retinopathy, sensorineural deafness, myopathy and neuropathy. He is currently 34 years old, wheelchair-bound, blind and seizure-free. Trio ES revealed the following *de novo* variant in *DHX16* (NM_003587.4:c.2021C>T:p.Thr674Met).

Individual 10 is one of a set of female twins born full term with a vaginal delivery. The sister is unaffected but it is unknown whether the twins are monozygotic. The proband was noted to have developmental delay in the first year of life. She first sat unsupported at eight months old, stood at two years old, and walked unsupported at three years old. At three years old, she was diagnosed with epilepsy which resolved with age. She was noted to have right sided dystonia and hand tremors at five years old. Her metabolic workup was normal including prolactin, AFP levels, plasma amino acids, carnitine, and hexosaminidase enzyme levels, as was her karyotype and fragile X screen, echocardiogram and eye exam. An initial brain MRI was reportedly normal, however a repeat MRI six years later showed abnormal signal changes in bilateral cerebral peduncles, thalami and in the peritrigonal preiventricular white matter. This signal remained unchanged in a followup MRI eight years later. Trio ES identified two variants in *DDX54* NM_001111322.1:c.647A>G:p.Asn216Ser (Chr 12:113614866 T>C), which was confirmed by Sanger to be inherited from the father (Figure 2), and NM_001111322.1:c.892C>T:p.Leu298Phe (Chr12:113612724 G>A), which was confirmed to be *de novo*.

Individual 11 is a second child of healthy parents of Caucasian and African descent. The girl was born after uncomplicated pregnancy at term with normal measurements. The first month of life were complicated by unexplained recurrent vomiting but normal weight gain. The gross motor development was mildly delayed; she started walking with 17 months. At the age of two years a delay in speech development was diagnosed, followed by the diagnosis of mild global development delay at the age of three years. In addition, she showed a deficit in fine motor skills and behavioral problems. Hearing tests were normal as well as an eye examination. At the age of 6 years she was affected by severe speech impairment, moderate intellectual disability, poor fine motor skills, and repetitive movements and behavior. Mild facial dysmorphisms were noted including broad forehead, broad eyebrows, up-slanting palpebral fissures, high nasal bridge and broad nasal tip, and small teeth. Further, she had a 3x3 cm hypopigmentation at back and right thigh. All measurements were within the normal range. An extended metabolic work up gave normal results except for a slight elevation of glutamine in plasma. Eye examination and ultrasound of heart, abdominal organs and kidney were normal. MRI of the brain revealed multiple pineal cysts without other malformations. Spectroscopy of brain was normal.

Karyotyping and SNP-array were both normal. Trio-ES identified compound heterozygous variants in *DDX54*, a paternally inherited NM_001111322.1:c.58T>A;p.Trp20Arg and a maternally inherited NM_001111322.1:c.1832G>A;p.Arg611Gln. The latter was confirmed by Sanger sequencing.

Individual 12 was born in a consanguineous family of Arabic decent. Renal ultrasound showed poor corticomedullary differentiation, multiple cysts and both kidneys were small for age. ES analysis identified a homozygous variant in *DDX54* NM_001111322.1:c.856G>A:p.Val286Met (chr12:113612859) (Figure 2L). Parental samples were unavailable for segregation analysis.

Individual 13 is a 12 year old female born to consanguineous Turkish parents after an uneventful birth. She presented with short stature (120cm, <3%ile), microcephaly (OFC 46.5cm, <3%ile), hyperextensibility, hip dislocations and a solitary kidney. She also was found to have dysmorphic features including a prominent forehead, high frontal hairline and a narrow palate. ES identified a homozygous variant in *DHX34* at position NM_014681.5:c.1322A>G:p.Asn441Ser (19:47863274A>G). Sanger sequencing confirmed her parents are heterozygous carriers of this variant allele. Additionally, analysis of her exome for evidence of absence of heterozygosity (AOH) showed these variants occur in an AOH stretch of 2656788 bp (342673086 bp total). This patient was previously reported [6] to have another homozygous variant contained within an AOH block in *CEP97* NM_024548.2:c.1148A>G:p.His383Arg (Chr3:101476598A>G), which was proposed as a novel candidate gene for the neurodevelopmental phenotype.

Individual 14 is the first child of multiple to consanguineous parents. At the 23rd week of pregnancy bilateral polycystic kidneys were discovered by ultrasound, followed by the diagnosis of oligohydramnion in the week 26. The boy was born at 37 weeks of pregnancy with a birth weight of 3030 g (-0.3 z), birth length of 48 cm (-1.1 z) and OFC of 32 cm (-1.8 z). At birth postaxial polydactyly of his right hand and both feet were observed. The postnatal period was

complicated by respiratory failure requiring assisted ventilation, pneumothorax, pulmonary hypertension, and renal failure requiring peritoneal dialysis. Further analysis revealed hypothyroidism and a suspicion of deafness. Over the course of disease the renal function recovered to a compensated renal failure. Nevertheless, the pulmonary function did not show a substantial improvement and lead to recurrent hypercapnia and ventilation dependence. Lung biopsy showed emphysema without interstitial fibrosis. The psychomotor development was poor and he displayed a failure to thrive. At age of three months he had a weight of 4350 g (-1.9 z), a length of 54 cm (-2.0z z) and an OFC of 35 cm (-4.5 z). Kidney ultrasound revealed hyperechoic kidneys without cortex / medulla differentiation, with mild hydronerphosis of left kidney. Ultrasound of the liver showed diffuse hyperechoic structure, probably due to an arterial perfusions deficiency. Echocardiography showed a small persistent foramen ovale. Electroencephalography was normal. His karyotype was normal. Trio-ES revealed a homozygous nonsense mutation NM_000547.5:c.1618C>T:p.Arg540* in *TPO* as the probable cause of the hypothyroidism. In addition, we identified a homozygous nonsense mutation NM_014681.5:c.466C>T, p.Gln156* in *DXH34* within an AOH block of 12931821 bp.

Individual 15 is an eight year-old female, the oldest of three siblings, born from non-consanguineous parents, with Ashkenazi and Sephardim ancestry. Family history is unremarkable.

She was born at term by caesarean section due to breech presentation, after an uneventful pregnancy. Her anthropometric measurements at birth were a weight of 2720g, length of 48 cm and head circumference of 34.5 cm. There were no complications during the neonatal period

and she was released from the hospital 72 hours after birth. Hypotonia was noticed within a few months of life and her neuropsychomotor development was subsequently delayed. She walked without support at 19 months and spoke only a few words by the third year of age. She presently has intellectual deficiency, with significant compromise in expressive language, and displays good social interaction and a friendly disposition. She had no history of epilepsy but recently presented an isolated seizure episode and Valproic acid was initiated after an electroencephalogram (EEG) revealing frequently occurring epileptic activity multifocal with generalized projection.

Laboratory studies previously performed included a normal peripheral blood G-banded female karyotype (46,XX), a normal CGH-array and a brain MRI disclosing no abnormalities.

Physical examination at seven years and 11 months revealed height of 119 cm (-1.5 S.D), weight of 19kg (-2 S.D.), head circumference of 51 cm (-0.49 S.D.), and no significant dysmorphisms.

Potential candidate gene *DDX47* identified in a single family. The proband is a 5.5 year old old female born to consanguineous Turkish parents after three sequential infant losses before the age of one year. All children shared a phenotype of hypotonia and epilepsy. At 5.5 years of age, she weighed 21kg, has seizures about once a week, and is severely hypotonic (unable to lift her head). A cranial MRI revealed a T2 signal abnormality in the bilateral periventricular deep white matter and a lacunar infarct with gliosis measuring 4mm on the right occipital lobe (Figure 2). Previous *GLUT1* sequencing and array-CGH (60k, Agilent Inc.) were normal. ES analysis identified compound heterozygous variants in *DDX47* at position

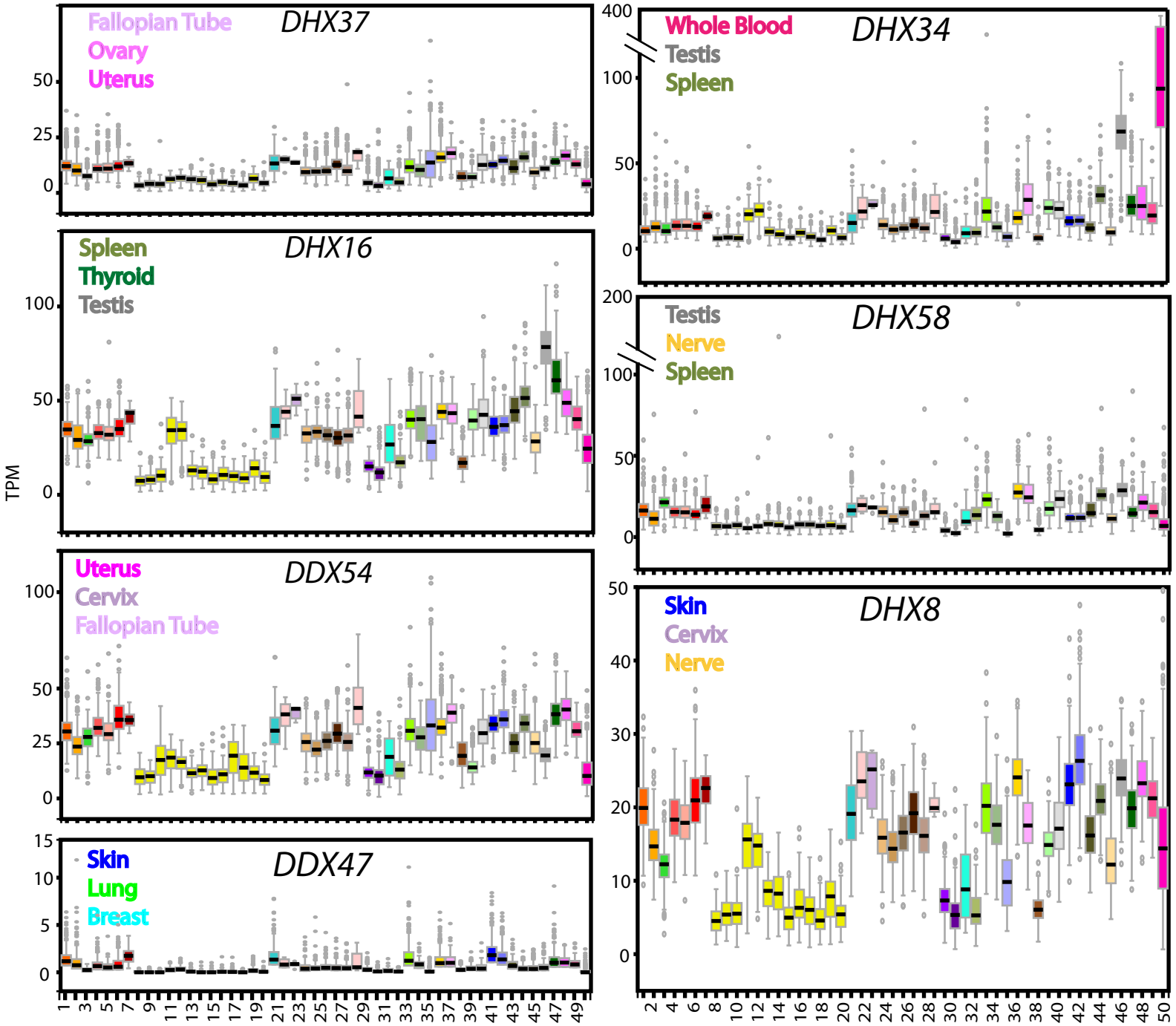
NM_016355.3:c.22G>T;p.Asp8Tyr (12:12966323G>T) which was confirmed by Sanger sequencing to be inherited from the father, and NM_016355.3:c.319C>G;p.Gln107Glu (12:12974279C>G) which was confirmed to be inherited from the mother. DNA from deceased siblings was not available for sequencing. We also identified a homozygous variant in *SLC13A5* XM_005256612.1:c.15331A>G;p.Thr511Ala (17:6589651T>C) which occurs in an AOH block measuring 504308 bp (491 Mb genome-wide total AOH).

Potential candidate gene *DHX58* identified in a single family. The proband was a seven year old female born to consanguineous parents. She was found prenatally to have a thin corpus callosum and midmuscular VSD. At birth she weighed 2.8kg, was 45 cm long and her OFC was 32.5cm. She had recurrent infections since birth including adenovirus, rhinovirus, Staphylococcus and CMV infections. She was reported to have intermittent neutropenia but sequencing of ELA-2, GCP-3, GCSF-R and HAX-1 were all normal. She presented with severe developmental delay with limited motor development, no independent sitting or standing and no speech. She has physically normal eyes with delayed visual maturation. She presented with febrile seizure at 5 months of age which progressed into tonic-clonic seizures. At three years of age her weight, height, and OFC were all below the 3rd percentile (10.3 kg, 83.5cm, and 45.5 cm). She passed away from status epilepticus at seven years old. An older brother had previously died from a similar disease with an additional kidney involvement.

Potential candidate gene *DHX8* identified in a single family. The proband is a nearly eight year old male of Indian descent. He originally presented with a febrile urinary tract infection at two

months of age, at which time a renal ultrasound found a 6.1 cm kidney, moderate hydronephrosis, and distal ureteral dilation. A repeat ultrasound at five years old showed a 9 cm single kidney.

Figure S1: Expression Profiles of each Candidate DExD/H-Box Helicase Genes. Expression profiles of each candidate were queried in the GTEx database and are presented here.



1. Adipose-subcutaneous
2. Adipose- Visceral
3. Adrenal Gland
4. Artery - Aorta
5. Artery - Coronary
6. Artery - Tibial
7. Bladder
8. Brain - Amygdala
9. Brain - Anterior cingulate cortex
10. Brain - Caudate
11. Brain - Cerebellar Hemisphere
12. Brain - Cerebellum
13. Brain - Cortex
14. Brain - Frontal Cortex
15. Brain - Hippocampus
16. Brain - Hypothalamus
17. Brain - Nucleus accumbens
18. Brain - Putamen
19. Brain - Spinal cord
20. Brain - Substantia nigra
21. Breast
22. Cervix - Ectocervix
23. Cervix - Endocervix
24. Colon - Sigmoid
25. Colon - -Transverse
26. Esophagus - Gastroesophageal Junction
27. Esophagus - Musculans
28. Fallopian Tube
29. Heart - Atrial Appendage
30. Heart - Left Ventricle
31. Kidney - Cortex
32. Liver
33. Lung
34. Minor Salivary Gland
35. Muscle - Skeletal
36. Nerve - Tibial
37. Ovary
38. Pancreas
39. Pituitary
40. Prostate
41. Skin - Not Sun Exposed
42. Skin - Sun Exposed
43. Small Intestine - Terminal Ileum
44. Spleen
45. Stomach
46. Testis
47. Thyroid
48. Uterus
49. Vagina
50. Whole Blood

Figure S2: Unsupervised Clustering of DDX and DHX Genes. Unsupervised hierarchical clustering of *DHX8*, *DHX16*, *DHX34*, *DHX37*, *DDX47*, *DDX54*, and *DHX58* based on mRNA levels in the brain tissue.

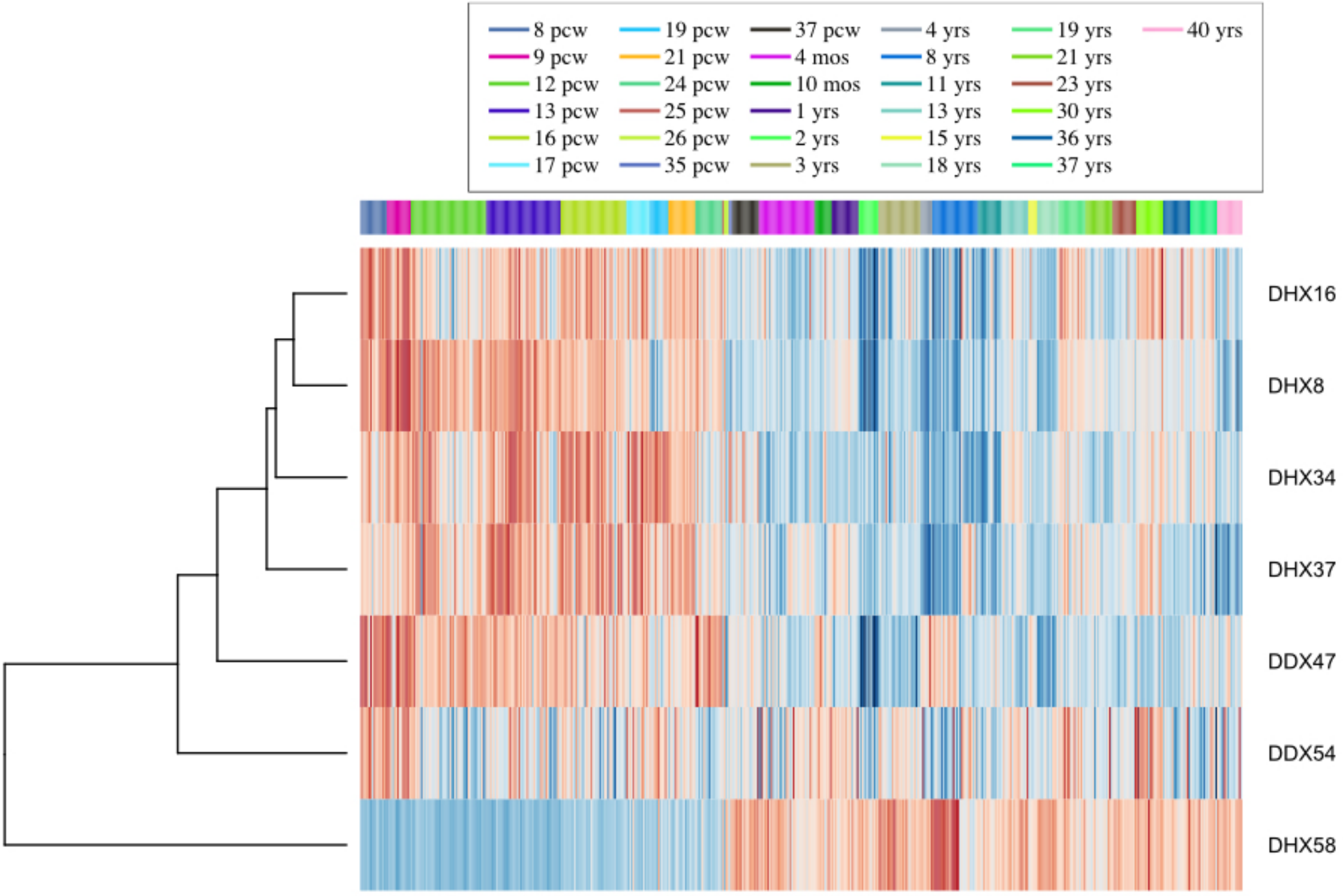
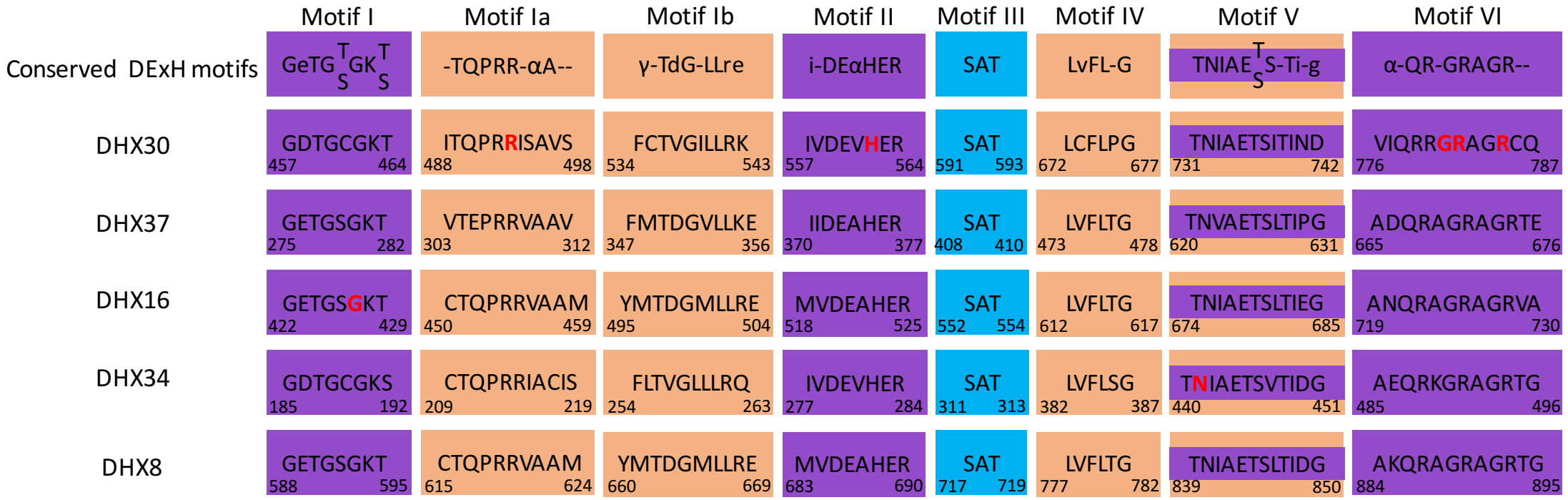

8 pcw
9 pcw
12 pcw
13 pcw
16 pcw
17 pcw
19 pcw
21 pcw
24 pcw
25 pcw
26 pcw
35 pcw
37 pcw
4 mos
10 mos
1 yrs
2 yrs
3 yrs
4 yrs
8 yrs
11 yrs
13 yrs
15 yrs
18 yrs
19 yrs
21 yrs
23 yrs
30 yrs
36 yrs
37 yrs
40 yrs
DHX16
DHX8
DHX34
DHX37
DDX47
DDX54
DHX58

Figure S3: Conserved Motif Schematic. Schematic protein structure of DExD/H-box RNA helicases showing conserved motifs of the helicase core region. Nucleotide-interacting motifs (I, II and VI) are shown in purple, nucleic acid-binding motifs (Ia, Ib and IV) in orange, motif V, which binds nucleic acid and interacts with nucleotides, in purple and orange, and motif III, which couples ATP hydrolysis to RNA unwinding, in blue. The position of the first and last amino acid within each motif is denoted below left and right, respectively. The patient-mutated residues are marked in red.


Motif I
Motif Ia
Motif Ib
Motif II
Motif III
Motif IV
Motif V
Motif VI
Conserved DExH motifs
GeTG T/S GK T/S
-TQPRR-αA--
γ-TdG-LLre
i-DEαHER
SAT
LvFL-G
TNIAE T/S S-Ti-g
α-QR-GRAGR--
DHX30
GDTGCGKT 457 464
ITQPRRISAVS 488 498
FCTVGILLRK 534 543
IVDEVHER 557 564
SAT 591 593
LCFLPG 672 677
TNIAETSITIND 731 742
VIQRRGRAGRCQ 776 787
DHX37
GETGSGKT 275 282
VTEPRRVAAV 303 312
FMTDGVLLKE 347 356
IIDEAHER 370 377
SAT 408 410
LVFLTG 473 478
TNVAETSLTIPG 620 631
ADQRAGRAGRTE 665 676
DHX16
GETGSGKT 422 429
CTQPRRVAAM 450 459
YMTDGMLLRE 495 504
MVDEAHER 518 525
SAT 552 554
LVFLTG 612 617
TNIAETSLTIEG 674 685
ANQRAGRAGRVA 719 730
DHX34
GDTGCGKS 185 192
CTQPRRIACIS 209 219
FLTVGLLLRQ 254 263
IVDEVHER 277 284
SAT 311 313
LVFLSG 382 387
TNIAETSVTIDG 440 451
AEQRKGRAGRTG 485 496
DHX8
GETGSGKT 588 595
CTQPRRVAAM 615 624
YMTDGMLLRE 660 669
MVDEAHER 683 690
SAT 717 719
LVFLTG 777 782
TNIAETSLTIDG 839 850
AKQRAGRAGRTG 884 895

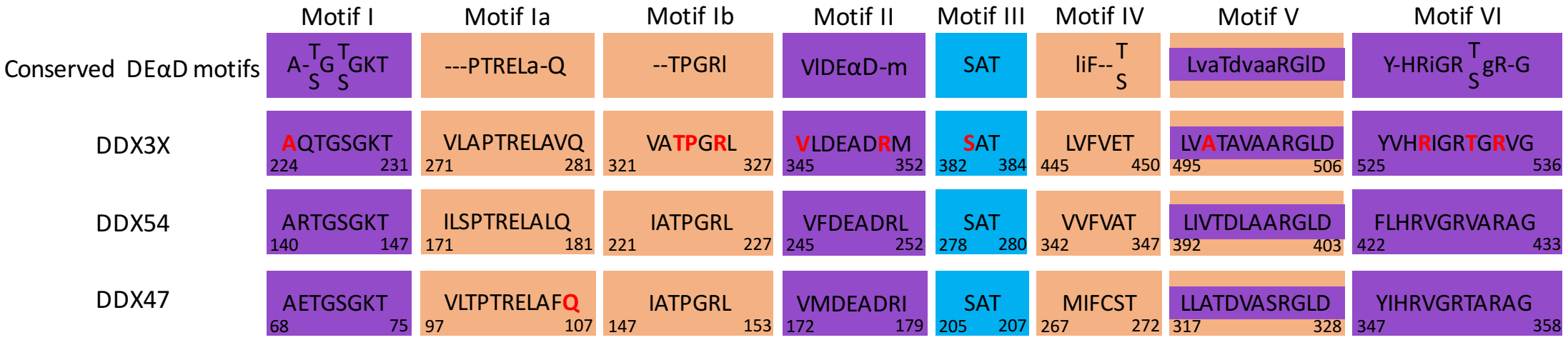

Motif I
Motif Ia
Motif Ib
Motif II
Motif III
Motif IV
Motif V
Motif VI
Conserved DEαD motifs
A-T/S G T/S GKT
---PTRELa-Q
--TPGRl
VIDEαD-m
SAT
liF-- T/S
LvaTdvaaRGlD
Y-HRiGR T/S gR-G
DDX3X
AQTGSGKT 224 231
VLAPTRELAVQ 271 281
VATPGRL 321 327
VLDEADRM 345 352
SAT 382 384
LVFVET 445 450
LVATAVAARGLD 495 506
YVHRIGRTGRVG 525 536
DDX54
ARTGSGKT 140 147
ILSPTRELALQ 171 181
IATPGRL 221 227
VFDEADRL 245 252
SAT 278 280
VVFVAT 342 347
LIVTDLAARGLD 392 403
FLHRVGRVARAG 422 433
DDX47
AETGSGKT 68 75
VLTPTRELAFQ 97 107
IATPGRL 147 153
VMDEADRI 172 179
SAT 205 207
MIFCST 267 272
LLATDVASRGLD 317 328
YIHRVGRTARAG 347 358

Table S1. Genotype Table. All variants for which a minor allele frequency > 0 was identified in ExAC or gnomAD had no stances of homozygous inheritance. *DHX37* was observed to have a probability of loss-of-function intolerance (pLI) of 0.99. While *DHX16*, *DDX54*, and *DHX34* each have a pLI score of 0 in gnomAD, they each display somewhat lower observed:expected ratios of LOF variants (*DHX16* 31:63.7; *DDX54* 22:46.3; *DHX34* 28:48.8). ND denotes no data; NA denotes not applicable.

Supplemental References

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