Supplemental Data

Supplemental Note: Case Reports individuals with *PHIP* mutation:

Individual 1

This 15-year-old boy was born at 37+4 weeks as one of dizygotic twins with a weight of 2700 grams and Apgar score of 10 after 5 minutes. In the neonatal period he had hypotonia with feeding problems and a heart murmur was diagnosed, which did not require further treatment. An IQ-test at the age of 11 years showed a global IQ of 51, with a better performance for verbal IQ compared to performancel IQ. PDD-NOS was diagnosed, and he had temper tantrums for which he was treated with aripiprazol. He was easily fatigued.

His twin brother had a cerebellar cyst, for which a VP-drain was placed. His twin brother and his other brother and sister had a normal development. His father was known to have behavioural problems and mood swings.

Physical examination at the age of 15 years showed a height of 161 cm (-2 SD), truncal obesity with a weight of 61 kg (+2 SD), BMI of 23.5 and a head circumference of 56 cm (-1 SD). Facial dysmorphisms included synophrys and a broad palate. Furthermore, inverted nipples, yellowish hand palms, tapered fingers, clinodactyly of fifth finger and lordosis were present.

Brain MRI showed no abnormalities. Karyotype analysis, metabolic screen, testing for Fragile X syndrome and Prader-Willi syndrome were normal. MIP re-sequencing revealed a *de novo* mutation in *PHIP* NM_017934.6:c.298_299del; p.(Leu100Ilefs*13).

Individual 2

This 11-year-old boy was born by caesarean section because of breech presentation after an uncomplicated pregnancy with Apgar scores of 8 and 9 after 1 and 2 minutes. He had bilateral cryptorchidism, strabismus, hypermetropia and hypermobility of the ankles. He started walking at 18 months and spoke his first words at 9 months. His development was delayed with a total IQ of 64 (verbal 64, visual 62 and performance 74) at the age of five years. At the age of seven years his IQ was 74. ADHD and a developmental coordination disorder (DCD) were diagnosed.

Physical examination at the age of 11 years showed a height of 153.4 cm (+0.5 SD), truncal obesity with a weight of 44 kg (+1 SD), BMI of 18.7 and head circumference of 56 cm (+0.2 SD). He had synophrys, arched eyebrows, full and long eyelashes, epicanthus, upturned nose, flat and long philtrum, serrated teeth, full earlobes, full helices of the ear and prominent antihelices. Fingers were tapered and

clinodactyly of the fifth fingers was present. Several café-au-lait spots (~1cm) were see on the thorax and a larger one was present on his right hip.
A MRI of the brain and ears showed a mildly enlarged cerebellum, agenesis of the left vestibular system and hypoplasia of the right vestibular system. A 250k SNP array showed a paternally inherited 360 kb deletion of 21q21.1 which did not contain any genes and was considered to be clinically not relevant. *DMPK1*, *FMR1* and *NF1* analysis showed normal results. MIP re-sequencing revealed a *de novo* mutation in *PHIP* NM_017934.6:c.2902C>T; p.(Arg968*).

Individual 3

This 42-year-old woman was born after an uncomplicated pregnancy and delivery. She had delayed speech development and attended special education. She had mild ID and was able to read and write. She had a shy personality. She had surgery for increased intraocular pressure.
Physical examination at the age of 42 years showed a height of 160 cm (-0.7 SD), weight of 112 kg (>>+2.5 SD weight to height), BMI 44 and a head circumference of 56.5 cm (+0.7 SD). Facial dysmorphism consisted of synophrys, upslanting palpebral fissures, broad nasal bridge and tip, long philtrum, high palate and long ears. She had a café-au-lait spot on her back (<1 cm). Her hands were small with tapered fingers. There was clinodactyly of the 4th and 5th toes.
Analysis for Prader Willi syndrome and Fragile X syndrome revealed no abnormalities. A mutation in *MIB1* p.Cys109* was identified by MIP capture. This mutation was not present in her mother. MIP re-sequencing revealed a mutation in *PHIP* NM_017934.6:c.1900C>T; p.(Gln634*). This mutation was not present in her mother. Paternal DNA was not available.

Individual 4

This 52-year-old man had mild ID. Information on the neonatal period and early development is lacking. He attended regular elementary school, but with difficulties. During adolescence, psychiatric problems, including borderline personality disorder and automutilation, became apparent and he lived in several facilities for patients with developmental and psychiatric problems. He had problems with impulse control and depression.
He had arthrosis of his knees, high blood pressure, chronic respiratory disease and possible cataract. Family history was unremarkable.
Physical examination at the age of 43 years showed a height of 175 cm (-1.2 SD), weight of 99.2 kg (> + 2.5 SD), BMI of 32.4 and head circumference of 57 cm (-0.5 SD). He had full eyebrows, large, fleshy ears

and a short neck with low posterior hairline. He had truncal obesity and thoracic kyphosis. His hands were broad with short, tapering fingers and bilateral clinodactyly of the fifth fingers. His skin showed acne and multiple lesions due to automutilation.
Endocrinological investigation because of a possible diagnosis of Klinefelter syndrome showed a high FSH of 25 U/L, normal LH of 7.1 U/L and low testosterone of 5.0 nmol/l. However, chromosomal analysis showed a normal male karyotype 46,XY. DNA-analysis for Fragile X syndrome was normal.
MIP re-sequencing showed a mutation in *PHIP* NM_017934.6:c.774dup; p.(Pro259Thrfs*9).

Individual 5

This 14-year-old boy was born at term by cesarean section with a birth weight of 2850 grams (- 1.5 SD) and normal Apgar scores. Pregnancy was complicated by HELLP syndrome. He could roll at the age of 9 months, sit at the age of 13 months and walk at the age of 2 years. He spoke his first words when he was 9 months, stopped talking for a year and spoke 2-3 word sentences at the age of 3 years and 10 months. He had no behavioural problems, but does have tics. He had recurrent urine infections due to vesico-ureteral reflux. He also had mild hip dysplasia and required adenoidectomy because of recurrent ear infections. An inguinal hernia required surgery and he had a frenulotomy. He had a hypermetropia of +4. Physical examination at the age of 14 years showed a height of 155 cm (-1.5 SD), a weight of 51.5 kg (+1.7 SD), BMI of 22.7 and a head circumference of 54.5 cm (-0.3 SD). He had a synophrys, full eyebrows, long upslanting palpebral fissures, epicanthal folds, periorbital fullness, an upturned nose with thick alae nasi and a full nasal tip. He had a broad mouth with full lips, prominent central incisors, prominent philtrum and normal ears. He had short, tapering fingers with clinodactyly of both fifth fingers and a single palmar crease of his left hand. He had short, broad feet and short toes, with clinodactyly of the third toes and a sandal gap on both sides.
Chromosomal analysis, MLPA interstitial deletion and duplications, DNA investigation for Angelman syndrome and mtDNA analysis for MELAS syndrome were normal. Brain MRI and EEG showed no abnormalities. MIP re-sequencing revealed a *de novo* mutation in *PHIP* NM_017934.6:c.328C>A; p.Arg110Ser.

Individual 6

This 23-year-old man was born via caesarean section at 32 weeks because of pre-eclampsia. His birth weight of was 1150 grams (-1.7 SD). The neonatal period was complicated by an infection and feeding problems. He started walking at the age of 4 years and spoke his first words at 3 years. He had an

inguinal hernia. He had a tonsillectomy because of recurrent upper airway infections and a visual impairment (visual acuity of 0.4), strabismus and nystagmus. He was analyzed for possible seizures, but epilepsy could not be confirmed. At the age of 23 years he lived in an assisted living facility and he worked in forestry. He did not have behavioural problems.
His sister (Individual 7) had a mild to moderate ID. Two half-brothers (same father) had a delayed development. Mother attended special education and her two sisters had a mild ID.
Physical examination at the age of 23 years showed a height of 171.7 cm (-1.7 SD), truncal obesity with a weight of 91.8 kg (> +2.5 SD weight to height), BMI of 31.1 and a head circumference of 56.5 cm (-0.7 SD). Facial dysmorphisms included high and small forehead, asymmetric face, full eyebrows, mild hypertelorism, telecanthus, prominent nose, long philtrum, thin lips and a small indentation in the uvula. He had long, simple and protruding ears. There was clinodactyly of the second and fifth fingers.
A metabolic screen, karyotype, 250k SNP array, *FMR1* and *ARX* analysis showed normal results. MIP re-sequencing revealed a mutation in *PHIP* NM_017934.6:c.340+2T>C; p.(?). This mutation was not present in his mother. Paternal DNA was not available.

Individual 7

This 26-year-old woman is the sister of Individual 6 and was born premature. Information on gross milestones is lacking. She had a mild ID and mood disorders for which she was treated with valproic acid. She lived with her parents. She had strabismus, but no other health issues.
Her brother (Individual 6) had a moderate ID. Two half-brothers (same father) had delayed development. Her mother attended special education and her two sisters had a mild ID.
Physical examination at the age of 26 years showed a height of 160.1 cm (-1.7 SD), weight of 119.0 kg (>> +2.5 SD weight to height), BMI of 46.5 and head circumference was 55.5 (0 SD).
She had a high forehead, full eyebrows, mild hypertelorism, straight nose, long philtrum, thin lips and normal uvula. Her ears were large with uplifted earlobes andshe had normal extremities.
Sanger sequencing revealed a mutation in *PHIP* NM_017934.6:c.340+2T>C; p.(?). This mutation was not present in mother. Paternal DNA was not available.

Individual 8 (previously reported by De Ligt et al. as Trio 5)

This 12-year-old girl was born after an uneventful pregnancy with a birth weight of 3980 grams. Delivery was complicated by meconium stained amniotic fluid but she had normal Apgar scores of 9 and 9 at 1 and 5 minutes. She had neonatal feeding problems. She had a broad based walking pattern.

Family history was unremarkable; she had one healthy brother.
Psychomotor development was delayed. She could roll at 10 months of age, sit without support at 12 months of age and could walk at 24 months of age. She spoke her first words at 5 years of age. At the age of 10 years and 5 months her developmental level was the equivalent of that of a 2-3-year-old child. She showed stereotypic behaviour, anxiety and sometimes had abnormal breathing.
Physical examination at the age of 12 years showed a height of 149.5 cm (+0.5 SD), weight of 56.6 kg (+2.5 SD), BMI of 25.4 and a head circumference of 57.6 cm (> + 2.5 SD). She had straight eyebrows, strabismus, blepharophimosis, mild ptosis, a long philtrum, full lips and thick helices and earlobes. She had tapered fingers, clinodactyly of fifth fingers and long toes.
MRI of the brain showed slightly enlarged gyri and sulci and an atypical large cavum septum pellucidum. 250k SNP array, metabolic screening and analysis of *FMR1* and *MECP2* were normal. Whole exome sequencing revealed a *de novo* mutation in *PHIP* NM_017934.6:c.3447T>G; p.(Tyr1149*).

Individual 9

This 5-year-old girl was born after an uneventful pregnancy. From the age of 8 weeks hypotonia was noted. She is still hypotonic (mostly axial) and she is easily fatigued. Psychomotor development was delayed, having walked at 21 months. She had some speech therapy and attended regular education. She was social, but had problems with changes, was sensitive to sounds and was easily upset.
Family history is unremarkable, with one healthy brother.
Physical examination at the age of 5 years and 7 months showed a height of 114.5 cm (-0.2 SD), weight of 20.9 kg (+0.5 SD), BMI of 15.9 and head circumference of 49.7 cm (-0.5 SD).
She had upslanting palpebral fissures, blepharophimosis, almond shaped eyes, upturned nose, prominent columella and thin upper lip. She had clinodactyly of the fifth fingers and short toes with syndactyly of the 2nd and 3rd toes on both sides. She was hypermobile. Skin examination showed 1 café-au-lait spot on the thorax and an area of hypopigmentation on the left arm.
MRI of the brain showed no abnormalities. SNP array and metabolic screening were normal. Whole exome sequencing revealed a *de novo* c.805C>T (p.(Pro269Ser)) mutation in the *SSBP3*-gene, which was thought not to be causal, and a *de novo* mutation in *PHIP* NM_017934.6:c.919_923del; p.(Ile307fs).

Individual 10

This 12-year-old boy was born after an uneventful pregnancy and delivery with a birthweight of 3500 grams. At the age of 6 months his developmental delay became apparent: he sat at the age of 1.5 years,

walked at the age of 2 years and he spoke his first words at the age of 2.5 years. At age 5 years his IQ was 60. He showed hyperactive and obsessive behaviour and had angry periods. At the age of 12 years he displayed complex behaviour problems for which he was treated with methylphenidate, clonidine, melatonin and promethazine. He had a benign tremor of his hands.
He had non-consanguineous parents and three healthy siblings.
Physical examination at the age of 12 years, showed a height of 150.5 cm (-1 SD), weight of 49 kg (+2 SD) and BMI of 21.6. Head circumference at the age of 5 years was 51 cm (-0.5 SD). He had a full, round face with almond shaped eyes, upslanting palpebral fissures, epicanthal folds, a short nose with full nasal tip, broad chin and large ears with thick helices and earlobes. He had short and broad hands, with tapering fingers and short fifth fingers. He had a café-au-lait spot on the back and a hyperpigmentation on his right lower leg.
Previously performed brain CT, EEG, chromosomal analysis, 250K SNP array and metabolic screening were normal. Also investigations for Fragile X, Börjeson-Forssman-Lehmann and Prader-Willi syndromes revealed no abnormalities. Whole exome sequencing revealed a *de novo* mutation in *PHIP* NM_017934.6:c.328C>T; p.(Arg110Cys).

Individual 11

This 5-year-old boy was born prematurely by caesarean section. He had normal Apgar scores, but had feeding problems during the first week of life. Gross milestones were delayed; he walked at the age of 20 months. At 3.5 years he only spoke words, no sentences, and his development was delayed by 1 year.
He had recurrent upper airway infections and an adenoidectomy.
He had 1 healthy brother, 1 healthy sister and 1 sister wild mild developmental delay, epilepsy, cortical heterotopia and a skull defect. She was not tested for the *PHIP* mutation.
Physical examination at the age of 4.5 years showed a height of 110.8 (-0.5 SD), a weight of 22.35 (+2 SD) and BMI of 18.2. His head circumference was measured for the last time when he was 3.5 years old (49 cm (-1 SD)). He had full eyebrows and a synophrys. Hands and feet were normal, except for a single palmar crease on the left side. Skin investigation showed a depigmented macule on the chest.
Chromosomal analysis, SNP-array, analysis for Fragile X syndrome and metabolic screening were normal. Brain MRI showed no abnormalities. Whole exome sequencing revealed a *de novo* mutation in *PHIP* NM_017934.6:c.3571C>T; p.(Gln1191*).

Individual 12

This 5-year-old girl was born at term after a pregnancy complicated by HIV exposure with a birth weight of 2755 grams. The neonatal period was complicated by feeding problems. She was not able to roll over at the age of 8 months, but could walk at the age of 14 months. She had speech problems which improved after adenectomy and speech therapy. She attended regular school and had behavioral problems. She had postnatal growth retardation, panhypopituitarism due to hypoplasia of the hypophysis for which she was treated with growth hormone from the age of 1 year. She had hypothyroidism, recurrent airway infections, feeding problems and was susceptible to hypoglycemia (more than expected in a child with panhypopituitarism).

Family history was unremarkable. Father was not available for segregation analysis.

Physical examination at the age of 5 years and 8 months showed a height of 105 cm (-2.3 SD), weight of 26.8 kg (+4.5 SD) and BMI of 24.3. Head circumference at the age of 4 years was 50 cm (0 SD). She had a long, triangular shaped face with a prominent forehead and prominent chin. She had full eyebrows, mild upslanting palpebral fissures, telecanthus, epicanthal folds, upturned nose with low nasal bridge, long prominent philtrum and thin upper lip. Ears were large with upturned lobules, thick helices and a pre auricular tag left. She had small hands with clinodactyly of the fifth fingers bilaterally and small feet with cutaneous syndactyly of the second and third toes bilaterally. She had 1 café-au-lait spot on the chest. Analysis for Silver Russell syndrome (methylation H19 and UPD7) showed no abnormalities. SNP-array and DNA analysis of *POU1F1*, *PROP1* and *LHX1* were normal. Metabolic screening was normal. Brain MRI showed hypoplasia of the adenohypophysis and an ectopic location of the neurohypophysis, but no other abnormalities. Whole exome sequencing revealed a mutation in *PHIP* NM_017934.6:c.1653+1G>A; p.(?). The mutation was not present in mother. Paternal DNA was not available.

Individual 13

This 14-year-old girl is the only child of two unrelated and healthy parents and was born at term after an uneventful pregnancy with normal birth parameters. At the age of 13 months developmental delay was noted. She went to a school for children with special needs. Her total IQ at the age of 6 years was 69. She did not present with any behavioral problems. She had reduced vision in her left eye.

Family history is negative regarding congenital malformations and/or ID.

Physical examination at the age of 14 years showed a height of 162 cm (-0.5 SD), weight of 72 kg (+2.5 SD), BMI 27.4 and head circumference of 56 cm (+0.7 SD). She had some coarsening of the face, a high

forehead, straight full eyebrows, an upturned nose with thick alae nasi, long philtrum, large ears with thick helices and ear lobules. She had tapering fingers.
Metabolic work-up and brain imaging were normal. Standard karyotyping revealed a translocation t(X;6)(p22.11;q13) with the breakpoint on 6q13 located in the *PHIP* gene **(Supplemental Figure 2)**.

Individual 14

This 21-year-old female is the only child of two unrelated, healthy parents and was born at term after an uneventful pregnancy and delivery. At the age of 2 years, mild psychomotor delay was noticed. She attended a school for children with moderate ID and at the age of 21 years she went to a daycare center. At the age of 12 years valproic acid therapy was initiated for panic attacks and episodes of hyperventilation. She was treated for a bilateral hip subluxation and strabismus. She developed a scoliosis during childhood. She had an ataxic gait.
Family history was unremarkable.
Physical examination at the age of 21 years showed a height of 156 cm (-2.2 SD), weight of 76.6 kg (>+2.5 SD), BMI of 31.5 and a head circumference of 55.5 cm (0 SD). She is not dysmorphic.
Array CGH showed a *de novo* deletion on chromosome 6 (chr6:g.(?_76509712)_(81615059_?)del(hg19)) **Supplemental Figure 2**) including several known genes involved in recessive disorders, as well as *PHIP*.

Individual 15

This 17-year-old male was born at term after an uneventful pregnancy and delivery with a birth weight of 3060 grams (- 1 SD). He was hypotonic short after birth. He could sit at the age of 12 months and walk at the age of 21 months. He had language delay and behavioural problems, with auto and hetero aggressiveness, and mild ID. He required surgery for unilateral cryptorchidism at age 6. He suffered from a femoral epiphysiolysis aged 15 after an accident. He had sleeping problems and suffered from fatigue.
Physical examination at the age of 17 years showed a height of 187 cm (+2.5 SD), a weight of 97 kg (+4 SD), a BMI of 27.9 and a head circumference of 57 cm (0 SD).
He had a large forehead with normal eyebrows, hypotelorism with enophthalmos, mild epicanthal folds, a nose with full nasal tip, low hanging columella and thick alae nasi. He had large ears and a broad mouth with full lips, large central incisors and a normal philtrum. He had short, tapering fingers with clinodactyly of both fifth fingers. He had syndactyly of the second and third toes and a sandal gap on both sides.

Chromosomal analysis, MLPA interstitial deletion and duplications, CGH array, gene analysis of *FMR1*, *MED12*, *PHF6*, and metabolic analyses were normal. Brain MRI showed no abnormalities. Whole exome sequencing revealed a *de novo* mutation in *PHIP* NM_017934.6:c.3892C>T; p.(Arg1298*).

Individual 16 (previously reported by Grozeva et al. Hum Mutat 2015 as Individual UK10K_FINDWGA5411669)

This 25-year-old man was born at 36 weeks gestation with a birth weight of 2145 grams. His development was delayed. He crawled at the age of 10 months, walked at the age of 15 months and spoke his first words at 16 months. At age 8 years, he was assessed as having mild-moderate ID with a performance IQ of 57 and verbal IQ of 88. He developed food foraging behaviour and as an adult, had anxiety and bipolar disorder. He had strabismus and bilateral cryptorchidism.

Family history was unremarkable apart from a paternal half-brother with similar features.

Physical examination at the age of 10.5 years showed a height of 147.5cm (+1.5 SD), weight of 56 kg (>+3.0 SD), BMI of 25.5 and head circumference of 55.7 cm (+1.7 SD). He had a high forehead, narrow bifrontal diameter, depressed nasal bridge, thickened and anteverted nares, highly arched palate, mild tongue-tie, dental crowding, large ears with large fleshy earlobes, moderate gynaecomastia, sloping shoulders, mild "hump" of the upper back, bilateral 5th finger clinodactyly, unilateral single transverse palmar crease, bilateral clinodactyly 3-5th toes and deep set toe nails with partial cutaneous 2-3 toe syndactyly on the right foot.

CT brain at the age of 8 years showed no abnormalities. Karyotype, Fragile X, methylation studies for Prader-Willi syndrome, and metabolic screening were normal. Borjeson-Forssman-Lehmann syndrome was suspected, but a mutation in *PHF6* was not found. Whole exome sequencing revealed a mutation in *PHIP* NM_017934.5:c.1050delT; p.(Phe349fs31). The mutation was not found in mother. Paternal DNA was not available.

Individual 17

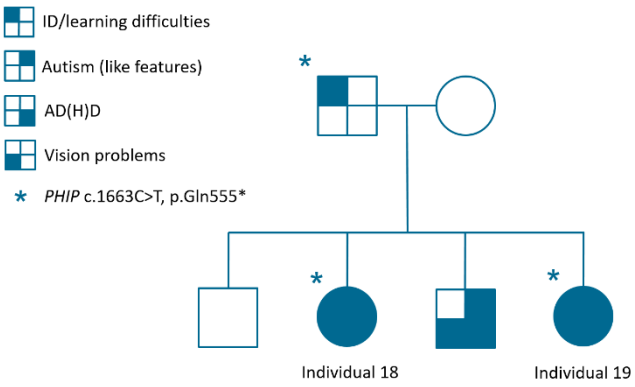
This 11-year-old male was born with a birth weight of 3699 grams. Development was normal with a FSIQ of 96 and adaptive IQ of 88. He was diagnosed with autism and had attention problems with anxious and withdrawn behaviour. Gastrointestinal reflux was diagnosed at the age of 10 years and he had recurrent ear infections.

Physical examination at the age of 11 years showed a height of 141 cm (-0.5 SD), weight of 34.2 (-0.35 SD), BMI of 17.2 and head circumference of 55.5 cm (+1 SD). There was no facial dysmorphism.

EEG and brain imaging were normal as were SNP-array and metabolic screening.

Whole exome sequencing revealed a *de novo* missense mutation in *TBC1D8B* and a *de novo* mutation in *PHIP* NM_017934.6:c.3787C>G; p.(Gln1263Glu).

Individual 18



This 15-year-old girl was born at term after an uneventful pregnancy and delivery. The neonatal period was unremarkable. Delayed psychomotor development was noted early. She had motor problems, including difficulties with coordination. Assessment of cognitive level showed a level at the lower end of the normal range. Neuropsychiatric assessment resulted in diagnoses of autism and ADD. She also had dyslexia. She attended regular education until grade 6. From grade 7 she attended a school for children with neuropsychiatric disorders. She had strabismus in early childhood and had hypermetropia (+7D) and astigmatism. There was a history of recurrent epistaxis with no known cause. She suffered from fatigue.

This girl is the second child of this family.

The oldest sibling was a 20-year-old male. He had a diagnosis of dyslexia and the parents reported difficulties with social interaction, but further medical investigations or assessments were not performed. He attended normal high school. This brother was not tested for the mutation in *PHIP.*

Her younger brother was 13 years old. He had difficulties with social interaction from early on and severe sleeping difficulties with insomnia were noted. Neuropsychiatric assessment resulted in diagnoses of autism/Asperger syndrome and ADHD. He also had dyslexia. Psychomotor development was not clearly delayed and no formal assessment of cognitive level had been performed. He also had strabismus in early childhood, hypermetropia (+6D) and astigmatism. He also had a history of recurrent epistaxis with no known cause. He did not have the mutation in *PHIP*.

Her 11-year-old sister did have the mutation in *PHIP* and is described below as Individual 19.

The father has attended normal education, but with difficulties and now holds a job as a janitor. The father had the mutation in *PHIP*. The mother is healthy. No other known cases within the extended family.

Physical examination at the age of 15 years showed a height of 168 cm (0 SD), weight of 68 kg (+1.5 SD) and BMI of 24.1. Facial features comprised high forehead, periorbital fullness, prominent cheekbones, thick alae nasi, full lips and large ears with thick helices. She had tapering fingers and bilateral fifth finger clinodactyly.

Previously performed array-CGH showed no abnormalities.

Recurrency screening revealed a mutation in *PHIP* NM_017934.6:c.1663C>T, p.(Gln555*).

Individual 19

This 11-year-old girl is the younger sister of individual 18. She was born after an uneventful pregnancy and delivery with a birth weight of 3475 grams. The neonatal period was unremarkable. Psychomotor development was delayed and assessment of cognitive level showed an extremely uneven profile, although the overall level is within the low normal range. Verbal function was above normal while perception and memory was clearly below average. She attended special education from grade 1. She had mild motor problems and difficulties with coordination. Neuropsychiatric assessment has resulted in a diagnosis of ADHD. She did not fulfil the criteria for autism but had a diagnosis of autism like symptoms. She also had dyslexia. A possible diagnosis of Tourette syndrome was considered. She had hypermetropia (+8D), astigmatism and strabismus. There is a history of recurrent epistaxis with no known cause. She suffered from fatigue.

Physical examination at the age of 11 years showed a height of 140 cm (-1 SD), weight of 34 kg (-1 SD) and BMI of 17.3. Facial features comprised ptosis, thin upper lip and large ears.

Previously performed array-CGH showed no abnormalities.

Recurrency screening revealed a mutation in *PHIP* NM_017934.6:c.1663C>T, p.(Gln555*).

Individual 20

This 5-year-old girl was born at term after a pregnancy which was complicated by an external version because of an abnormal position. The delivery was complicated by meconium stained fluid. Her birth weight was 3760 grams. The neonatal period was unremarkable. She was able to sit unsupported at the age of 11 months and walked at the age of 25 months. She had motor and speech delay and attended special education. She had periods of sudden tiredness, sleeping problems, hypermetropia, amblyopia and problems with depth perception.

Family history was unremarkable.

Physical examination at the age of 5 years showed a height of 104.1 cm (-0.63 SD), weight of 17.2 kg (-0.1 SD), BMI of 15.9 and head circumference of 49.5 cm (-0.25 SD). She had a flat face, straight eyebrows with a tendency to synophrys, epicanthal folds, low nasal bridge, full nasal tip, high arched palate, prominent chin, thick helices and ear lobules, folded left ear helix, sacral dimple, bilateral clinodactyly of the fifth fingers and bilateral cutaneous syndactyly of the second and third toes.
Previously performed SNP-array showed a paternally inherited duplication in Xp22.3. Whole exome sequencing revealed a *de novo* mutation in *PHIP* NM_017934.6:c.3801_3805del; p.(Ile1268fs).

Individual 21

This 6-year-old boy was born at term by caesarean section because of decreased fetal movements with a birth weight of 2630 grams. He had Apgar scores of 9 and 9 after 1 and 5 minutes, respectively. He was admitted to the neonatal care unit because of feeding difficulties and hypoglycaemia due to his low birth weight. He had hypotonia, was often tired and gross milestones were delayed. He walked independently from the age of 3.5 years and spoke 2-word sentences from the age of 2.5 years. His IQ was 73. Psychological examination showed features of autism. He had constipation and eczema.
Mother had hyperlaxity of the joints. Family history is otherwise unremarkable.
Physical examination at the age of 6 years showed a height of 114 cm (-1.7 SD), weight of 17.7 kg (+0.5 SD), BMI of 13.6 and head circumference of 52 cm (-1 SD). Facial features comprised hypertelorism, epicanthal folds, upturned nose and everted ears with thick helices. He had tapering fingers and hyperlaxity of the joints.
Brain MRI showed no abnormalities. SNP-array showed a paternally inherited duplication in 8q22.3 without clinical significance. Whole exome sequencing revealed a *de novo* mutation in *PHIP* NM_017934.6:c.820C>T; p.(Gln274*).

Individual 22

This 47-year-old woman was born after an uncomplicated pregnancy and delivery. She had delayed speech development, mild ID and attended special education. She was able to read and write, albeit at a low level. She required medications for behavioural problems including lack of anger control with aggression.
She had hypermetropia from child hood on. She had a normal eating and sleeping pattern, but suffered from fatigue. She had type 2 diabetes for which she did not use medication.

Her father was deceased and had learning difficulties at a young age. Her mother and two uncles were known to have arched feet of unknown cause.

Physical examination at the age of 47 years showed a height of 159.5 cm (-1.8 SD), weight of 114 kg (>>+2.5 SD), BMI of 44 and a head circumference of 54.5 cm (-0.3 SD). Facial features included a full round face, full eyebrows, upslanting palpebral fissures, full upturned nasal tip, small mouth with down turned corners, high palate, broad large chin and low set narrow ears with large earlobules. Her hands were short and broad with tapered fingers and clinodactyly of the relatively short fifth fingers. She had short, broad feet with short toes and partial bilateral 2-3 cutaneous syndactyly and clinodactyly of the fourth and fifth toes.

SNP array showed no abnormalities. Whole exome sequencing revealed a mutation in *PHIP* NM_017934.6:c.4060A>T; p.(Arg1354*). Parental DNA was not available.

Individual 23

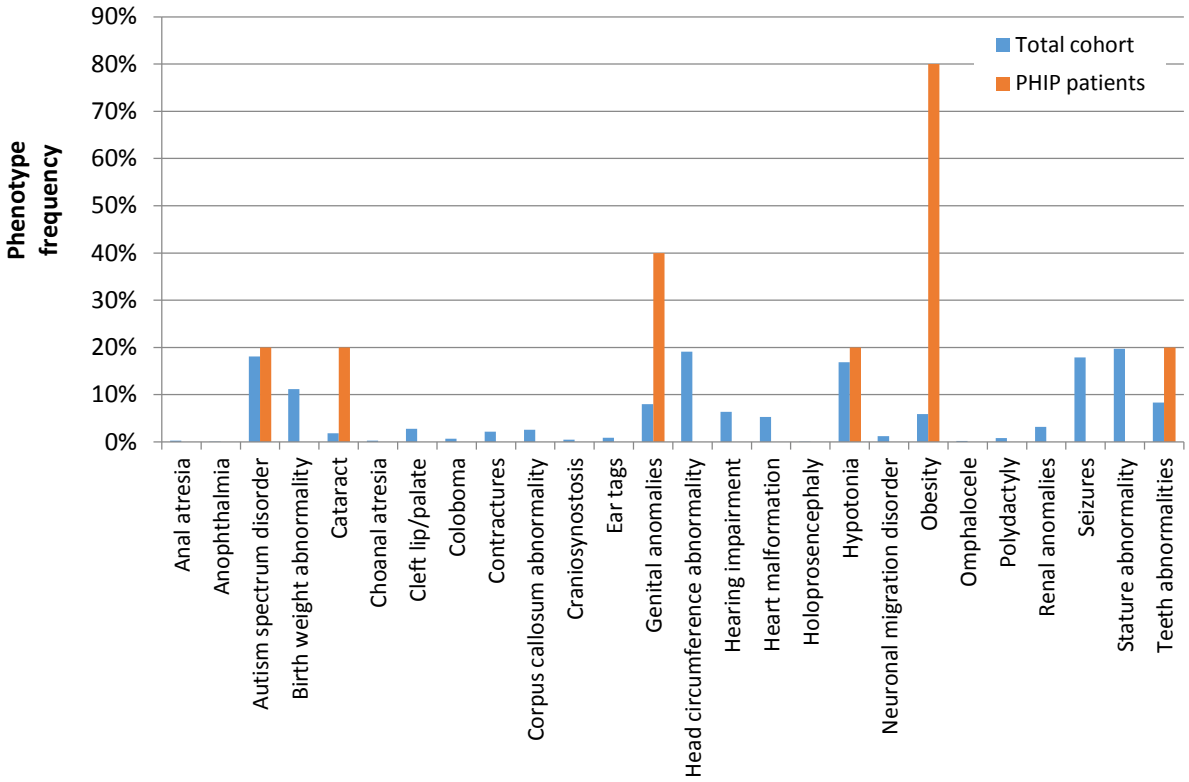
This 29-year-old woman was born at 38 weeks and 5 days by caesarean section because of breech presentation with a birth weight of 3150 grams. She was a very unsettled baby until transfer from breast feeding to bottle-feeding at the age of 4 months. Milk allergy was later diagnosed. She had frequent infections of the respiratory tract and middle ears. Her dentition was abnormal with several teeth placed in a double row. Four teeth have been extracted. As an adult, she has had a dental abscess eroding a tooth. She gained weight easily and complained of fatigue.

Early motor milestones were normal; she sat at the age of 7 months and walked at age of 10 months. She has been considered clumsy and was reported to have hyperactive reflexes. She received speech therapy in kindergarten because of language delay, which improved after frenulectomy. She attended special education from second grade. At the age of 21 years she was tested with WAIS-III and her total IQ was 65 with no significant differences between verbal and performance IQ. At the same age she was referred for psychiatric examination due to severe tantrums and challenging behaviour. Her most prominent symptoms were severe motoric hyperactivity, impulsivity and extreme restlessness and inattentiveness. As the symptoms could be traced back to early childhood, she was diagnosed with ADHD. Autistic features including difficulties with abstract thinking and decision-making were also prominent. Both treatment with methylphenidate and atomoxetine were effective, but were discontinued due to severe sleep problems, fatigue and headache. She lived alone with daily support. Family history was unremarkable.

Physical examination at the age of 29 years showed a height of 168.5 cm (-0.5 SD), weight of 76 kg (+2 SD), BMI of 26.8 and head circumference of 59.5 cm (> +3 SD). Her face was triangular with full eyebrows, synophrys, hypertelorism and downslanting palpebral fissures. She had anteverted and thick alae nasi, full lips and narrow ears. She had clinodactyly of the 4^{th} and 5^{th} fingers bilaterally, bilateral pes cavus, short toes and a short left hallux.

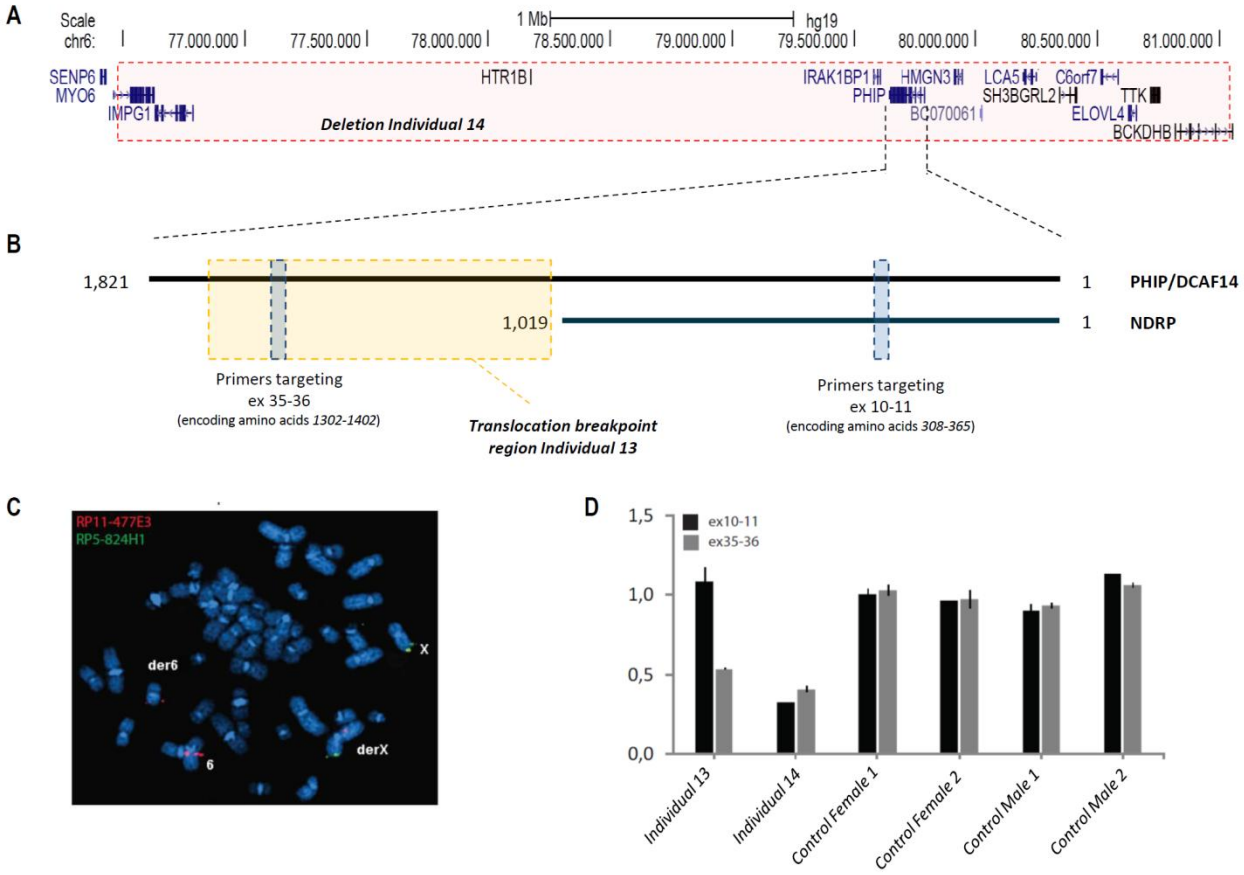
Cerebral MR at age 14 years showed no anomalies. Whole exome sequencing revealed a *de novo* mutation in *PHIP* NM_017934.6:c.4415_4418del, p.(Glu1472Alafs*22).

Supplemental Figure 1: Frequencies of 26 clinical features in 5 individuals with a LoF mutation in *PHIP* compared to 5 random individuals in the cohort of 3,275 individuals with ID



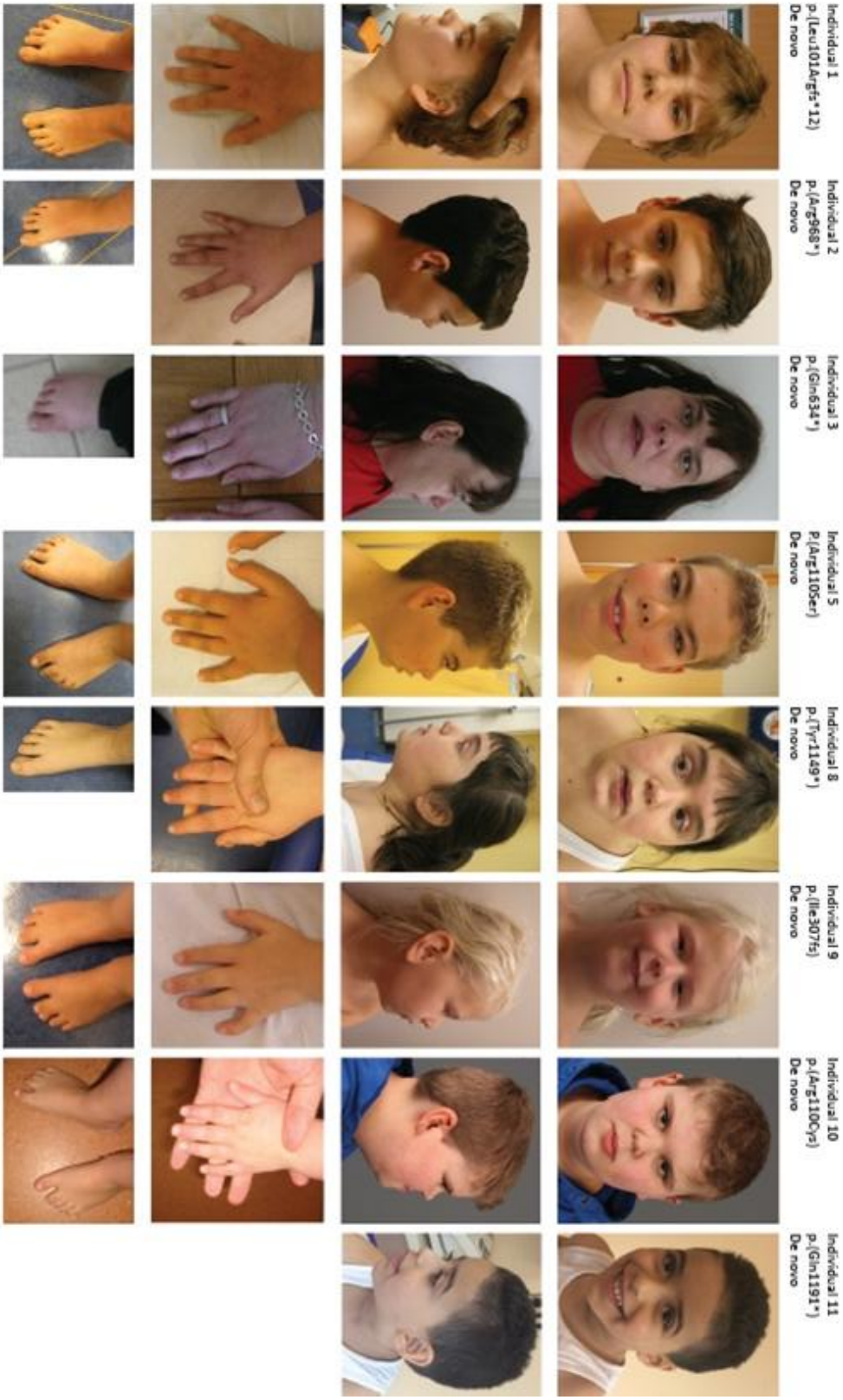
Frequencies of 26 clinical features in 5 individuals with a LoF mutation in *PHIP* compared to 5 random individuals in the cohort of 3,275 individuals with ID. Based on calculations of these 26 commonly assessed phenotype features as described by Vulto-van Silfhout at al. Hum Mutat 2017, we found that the phenotypic similarity between the 5 individuals with a LoF mutation in *PHIP* was much larger than by random chance (p=6.25e-05, permutation test).

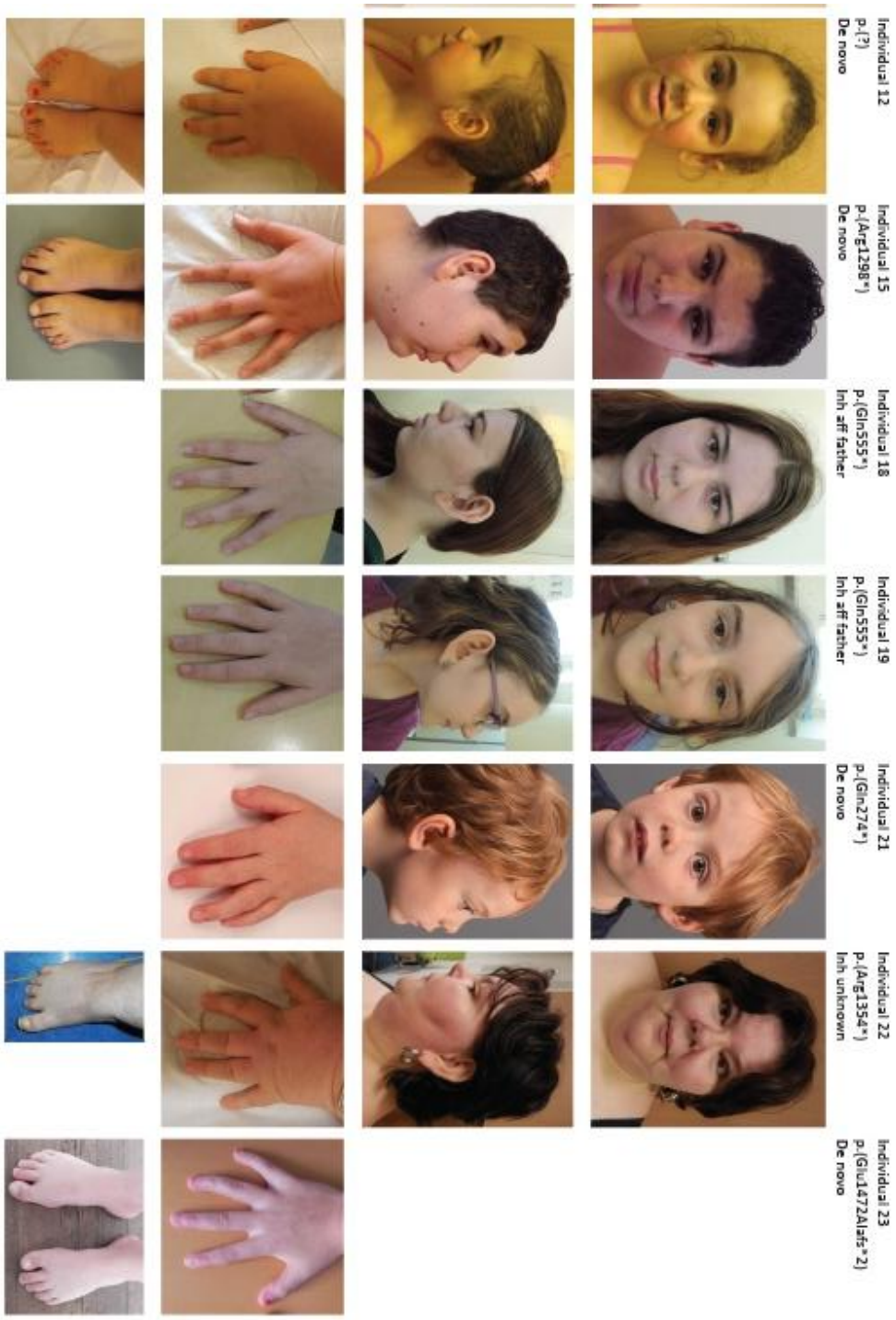
Supplemental Figure 2: Schematic representation of PHIP disruptions in Individuals 13 and 14



(A) Deletion identified in Individual 14, highlighted by a red box, was reported to be ~4 Mb (from BAC clones RP3-472A9 and RP11-707H15). The deletion was independently confirmed by FISH (data not shown), and comprised the coding sequence of 11 genes including *PHIP*. **(B, C, D)** In individual 13, a t(X;6) was identified, predicted to disrupt the coding sequencing of *PHIP* on chromosome 6. In **(B)**, the region containing the breakpoint is indicated by a yellow box. In addition, the location of the primer sets used for qPCR assaying the level of PHIP mRNA are indicated. **(C)** FISH used to characterize the breakpoints resulted in split signals for RP11-48D14 (chrX) and RP11-477E3 (chr6). RP11-477E3 contains only the coding sequence of *PHIP,* thereby confirming the disruption of *PHIP* coding sequencing. **(D)** *PHIP* mRNA expression levels were analyzed for both predicted isoforms in EBV-PBL cell lines derived from Individuals 13 and 14, and compared to those of 4 controls. Expression of the housekeeping genes *HPRT* and *GUSB* were used for normalization. A significant decrease was noticed for the short isoform in the two individuals resulting in about 50% of the levels observed in controls. As expected, expression of the long isoform in Individual 14 is also strongly reduced as a consequence of the full gene deletion. In Individual 13 however, there are normal expression levels of the ex 10-11 product but lowered ex 35-36 product, suggesting that the translocation only affects expression of the long isoform, encoding PHIP/DCAF14, and not NDRP.

Supplemental Figure 3: Photographs of individuals with a mutation in *PHIP.*

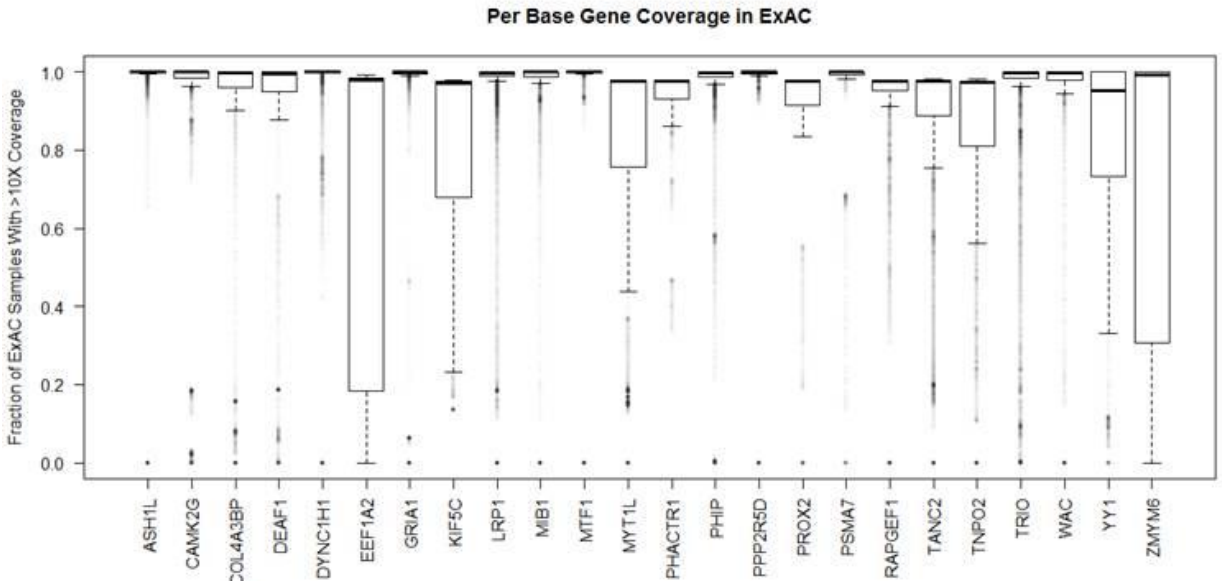




Photographs of 15 individuals with a mutation in *PHIP* of whom Individuals 18 and 19 were sisters. Shared facial features include a high forehead, full eyebrows/synophrys, characteristic upturned nose with thick alae nasi, a long philtrum, thin lips, large ears with thick helices and thick earlobes. Extremities showed tapering fingers, bilateral clinodactyly of the fifth finger and sometimes bilateral partial cutaneous syndactyly of the second and third toes.

Photographs are shown with informed consent of the individual or his/her parents.

Supplemental Figure 4: ExAC per base coverage statistics for all genes used in this study



This graph shows the ExAC per base coverage statistics for all genes shown in Table 1. This is based on CDS fraction of all genes. Boxplot outliers are partially transparent to help with visibility.

Most Genes are very well covered in ExAC, however there are a few genes with extended tails indicating some coverage holes in the ExAC data (these are: EEF1A2, KIF5C, MYT1L, TNPO2, YY1, ZMYM6).

Supplemental Table 1: Overview of relative contribution of known disease mechanisms to disease

Mutation consequence (DDG2P)	**# Disease caused by this mechanism**	**Relative contribution**
loss of function	1509	69%
all missense/in frame	349	16%
activating	112	5%
uncertain	144	7%
dominant negative	57	3%
cis-regulatory or promotor mutation	9	0.40%
5_prime or 3_prime UTR mutation	6	0.30%
increased gene dosage	2	0.10%
part of contiguous gene duplication	1	0.05%
Totals	***2189***	***100%***

Calculations are based on the DDG2P overview of known genotype-phenotype correlations and reported underlying pathophysiological mechanism (https://decipher.sanger.ac.uk/ddd#ddgenes).

Supplemental Table 2: LoF variants identified in 3,275 individuals with ID/DD

Genomic variant annotation	cDNA	Protein change	Mutation type	parental of origin
ASH1L				
Chr1(GRCh37):g.155448002_155448005del	NM_018489.2(ASH1L):c.4656_4659del	p.(Glu1553Asnfs*58)	frameshift	no parental DNAs available for testing
Chr1(GRCh37):g.155408307_155408308del	NM_018489.2(ASH1L):c.5638_5639del	p.(Asp1880Argfs*11)	frameshift	not in father, no maternal DNA available
CAMK2G				
Chr10(GRCh37):g.75574824C>T	NM_172171.2(CAMK2G):c.1620G>A	p.(Trp540*)	stop-gain	Inherited (maternal)
DEAF1				
Chr11(GRCh37):g.687910C>A	NM_021008.3(DEAF1):c.664+1G>T	p.(?)	splice site mutation	no parental DNAs available for testing
Chr11(GRCh37):g.653961C>T	NM_021008.3(DEAF1):c.1593+1G>A	p.(?)	splice site mutation	Inherited (paternal)
DYNC1H1				
Chr14(GRCh37):g.102446713_102446714dup	NM_001376.4(DYNC1H1):c.787_788dup	p.(Asp263Glufs*18)	frameshift	not in father, no maternal DNA available
GRIA1				
Chr5(GRCh37):g.152871760T>C	NM_001258021.1(GRIA1):c.2T>C	p.(Met1?)	start-loss	Inherited (maternal)
LRP1				
Chr12(GRCh37):g.57573606C>T	NM_002332.2(LRP1):c.5008C>T	p.(Arg1670*)	stop-gain	Inherited (maternal)
Chr12(GRCh37):g.57604623C>T	NM_002332.2(LRP1):c.12877C>T	p.(Arg4293*)	stop-gain	no parental DNAs available for testing
MIB1				
Chr18(GRCh37):g.19321737dup	NM_020774.3(MIB1):c.193dup	p.(Ala65Glyfs*17)	frameshift	no parental DNAs available for testing
Chr18(GRCh37):g.19345830C>A	NM_020774.3(MIB1):c.327C>A	p.(Cys109*)	stop-gain	not in mother, no paternal DNA available
Chr18(GRCh37):g.19379813C>T	NM_020774.3(MIB1):c.1249C>T	p.(Gln417*)	stop-gain	no parental DNAs available for testing
Chr18(GRCh37):g.19395649C>T	NM_020774.3(MIB1):c.1552C>T	p.(Arg518*)	stop-gain	Inherited (paternal)
Chr18(GRCh37):g.19399526del	NM_020774.3(MIB1):c.1748del	p.(Leu583Trpfs*23)	frameshift	Inherited (maternal)
Chr18(GRCh37):g.19399608G>C	NM_020774.3(MIB1):c.1827del	p.(Ser610Valfs*36)	frameshift	no parental DNAs available for testing
Chr18(GRCh37):g.19423090A>G	NM_020774.3(MIB1):c.1963-2A>G	p.(?)	splice site mutation	no parental DNAs available for testing
Chr18(GRCh37):g.19423155C>T	NM_020774.3(MIB1):c.2026C>T	p.(Arg676*)	stop-gained	**de novo**
Chr18(GRCh37):g.19423179G>T	NM_020774.3(MIB1):c.2049+1G>T	p.(?)	splice site mutation	no parental DNAs available for testing
Chr18(GRCh37):g.19433103_19433104dup	NM_020774.3(MIB1):c.2589_2590dup	p.(Glu864Valfs*31)	frameshift	Inherited (paternal)
Chr18(GRCh37):g.19437112del	NM_020774.3(MIB1):c.2687del	p.(Lys896Serfs*8)	frameshift	no parental DNAs available for testing
MYT1L				

Chr2(GRCh37):g.1920976C>T	NM_001303052.1(MYT1L):c.1618+1G>A	p.(?)	splice site mutation	**de novo**
Chr2(GRCh37):g.1906961A>C	NM_001303052.1(MYT1L):c.1923T>G	p.(Tyr641*)	stop-gain	**de novo**
PHIP				
Chr6(GRCh37):g.79770426_79770427del	NM_017934.6(PHIP):c.298_299del	p.(Leu100Ilefs*13)	frameshift	**de novo**
Chr6(GRCh37):g.79770383A>G	NM_017934.6(PHIP):c.340+2T>C	p.(?)	splice site mutation	present in affected sister, absent in mother, no paternal DNA available
Chr6(GRCh37):g.79735708dup	NM_017934.6(PHIP):c.774dup	p.(Pro259Thrfs*9)	frameshift	no parental DNAs available for testing
Chr6(GRCh37):g.79708088G>A	NM_017934.6(PHIP):c.1900C>T	p.(Gln634*)	stop-gain	not in mother, no paternal DNA available
Chr6(GRCh37):g.79680593G>A	NM_017934.6(PHIP):c.2902C>T	p.(Arg968*)	stop-gain	**de novo**
PROX2				
Chr14(GRCh37):g.75329960_75329963del	NM_001243007.1(PROX2):c.575_578del	p.(His192Argfs*31)	frameshift	no parental DNAs available for testing
TANC2				
Chr17(GRCh37):g.61432740_61432741dup	NM_025185.3(TANC2):c.2349_2350dup	p.(Cys784Serfs*22)	frameshift	Inherited (paternal)
TRIO				
Chr5(GRCh37):g.14290933A>T	NM_007118.3(TRIO):c.649A>T	p.(Arg217*)	stop-gain	Inherited (paternal), absent in affected brother
Chr5(GRCh37):g.14387728del	NM_007118.3(TRIO):c.3752del	p.(Asp1251Valfs*11)	frameshift	**de novo**
Chr5(GRCh37):g.14390409G>A	NM_007118.3(TRIO):c.4128G>A	p.(Trp1376*)	stop-gained	**de novo**
Chr5(GRCh37):g.14419959C>T	NM_007118.3(TRIO):c.5032C>T	p.(Arg1678*)	stop-gain	**de novo**
Chr5(GRCh37):g.14463023C>T	NM_007118.3(TRIO):c.5656C>T	p.(Gln1886*)	stop-gain	Inherited (paternal)
WAC				
Chr10(GRCh37):g.28872382C>A	NM_016628.4(WAC):c.329C>A	p.(Ser110*)	stop-gained	**de novo**
Chr10(GRCh37):g.28905193C>T	NM_016628.4(WAC):c.1648C>T	p.(Arg550*)	stop-gained	**de novo**
ZMYM6				
Chr1(GRCh37):g.35480655dup	NM_007167.3(ZMYM6):c.537dup	p.(Pro180Thrfs*13)	frameshift	not in mother, no paternal DNA available
Chr1(GRCh37):g.35480388A>T	NM_007167.3(ZMYM6):c.705T>A	p.(Cys235*)	stop-gain	no parental DNAs available for testing
Chr1(GRCh37):g.35476525del	NM_007167.3(ZMYM6):c.1175del	p.(Asn392Thrfs*30)	frameshift	no parental DNAs available for testing
Chr1(GRCh37):g.35472675G>A	NM_007167.3(ZMYM6):c.1690C>T	p.(Arg564*)	stop-gain	no parental DNAs available for testing
Chr1(GRCh37):g.35472675G>A	NM_007167.3(ZMYM6):c.1690C>T	p.(Arg564*)	stop-gain	no parental DNAs available for testing

All variants reported in this table are independently validated by Sanger sequencing. Mutation annotation is reported according to HGVS standards. Note: Individual #3 carried two de novo mutations (in MIB1 and PHIP), hence to total number of de novo mutation is 41 and the number of individual with de novo mutations is 40.

Supplemental Table 3: De novo mutations reported in denovo-db in the 24 candidate ID/DD genes

	Original cohort (n=110)		*ExAC constraint metrics*			
Gene ID	**#DNM**	**Mutation type of first reported mutation**	**pLI**	**z-Score missense**	**# total DNMs in denovo-db[3]**	**p-value[4]** *(likelihood of #DNM mutations given cohort size)*
ASH1L	*1*	missense[1]	1.00	3.05	2	0.191
CAMK2G	*1*	missense[1]	0.99	4.28	1	0.710
COL4A3BP	*1*	missense[1]	0.98	3.58	5	**9.94×10^{-9}**
DEAF1	*1*	missense[2]	0.00	2.74	3	**5.06×10^{-5}**
DYNC1H1	*1*	missense[2]	1.00	13.88	14	**6.54×10^{-20}**
EEF1A2	*1*	missense[1]	0.96	6.14	9	**3.78×10^{-21}**
GRIA1	*1*	missense[1]	1.00	4.24	1	0.812
KIF5C	*1*	missense[1]	1.00	3.3	3	**1.39×10^{-4}**
LRP1	*1*	missense[1]	1.00	10.62	5	**7.62×10^{-5}**
MIB1	*1*	missense[1]	0.00	3.51	0	1
MTF1	*1*	LoF[1]	0.99	2.42	0	1
MYT1L	*1*	LoF[1]	1.00	4.81	6	**1.32×10^{-10}**
PHACTR1	*1*	missense[1]	0.66	0.73	1	0.518
PHIP	*1*	LoF[1]	1.00	5.2	8	**3.96×10^{-12}**
PPP2R5D	*1*	missense[1]	1.00	4.26	15	**2.15×10^{-34}**
PROX2	*1*	missense[1]	0.00	-0.99	1	0.534
PSMA7	*1*	missense[1]	0.97	2.68	0	1
RAPGEF1	*1*	missense[1]	1.00	2.88	1	0.941
TANC2	*1*	missense[1]	1.00	1.62	1	1
TNPO2	*1*	missense[1]	1.00	6.43	5	**3.58 x 10-9**
TRIO	*1*	missense[1]	1.00	6.29	7	**4.46×10^{-9}**
WAC	*1*	LoF[1]	1.00	1.57	5	**5.98×10^{-9}**
YY1	*1*	missense[2]	0.97	4.9	5	**1.50 x 10-10**
ZMYM6	*1*	LoF[1]		NA	0	1
Sum					**98**	

1. De Ligt et al. NEJM 2012; 2. Vissers et al. Nat Genet 2010; 3.Turner et al. NAS 2017; 4. p-values calculated using the gene-specific de novo mutation rate and corrected for multiple testing.

Supplemental Table 4: Clinical features of individuals with mutation in *PHIP*

See separate excel table.