**Supplementary information.**

**Supplementary Note 1. Case reports.**

*Case 1, pedigree J*

The index patient, a 4-year-old girl, second of two children of healthy non-consanguineous parents, presented with delay in speech development and cognition. She was able to speak 50 words in two-word sentences and showed an IQ between 62-70. Motor development was appropriate for age. The family history is unremarkable with the exception of a cousin of the mother exhibiting behavioral problems. She showed signs of aggression and auto-aggression with a focus on intolerance to frustration. The patient was born after 40+1 weeks of unremarkable gestation by a vacuum-assisted vaginal delivery with APGAR 10/10. Her birth weight was 3120 grams, birth length was 51 cm and head circumference was 34 cm. Early postnatal development was without complications.

Last physical examination at the age of 4 years and 6 months revealed a friendly girl with severe developmental delay, sleeping difficulties and reduced pain perception. Her weight was 15.9 kg (-0.7 SD), height was 104.7 cm (-0.5 SD) and head circumference was 47.8 cm (- 2.1 SD). Brain MRI at the age of 4.5 years revealed no abnormalities. No facial dysmorphisms were apparent.

Trio-whole exome sequencing revealed a heterozygous, *de novo LRRC7* mutation: chr1:69760284T>C; NM_001370785.2: c.194T>C; p.Leu65Ser. The *de novo* occurrence was confirmed by Sanger sequencing in the patient and both parents.

*Case 2, pedigree K*

The proband is a 12-year-old female. She was born as the third child of healthy non-consanguineous parents. She has two unaffected brothers and one unaffected sister. The family history is unremarkable. The proband was born after 40 weeks of gestation by natural vaginal delivery. Her birth weight was 2480 grams (-1.75 SD), birth length was 49 cm and head circumference was 33 cm (-1.25 SD). APGAR scores were 8 and 10.

She showed a global development delay: she walked at 19 months and acquired speech later then her siblings. A global motor disorder and attention disorder were diagnosed following early scholar difficulties, leading to specialized scholarship. Later testing at 8 years old revealed a mild intellectual disability. There are no behavioural or relationship issues.

Last clinical examination at the age of 10 year old found a bicuspid aortic valve without cardiac complications. Her weight was 29.7 kg (-0.75 SD), height was 133 cm (-1.25 SD) and head circumference at 7 year old and 8 months was 49 cm (-2 SD). Facial features included low implanted ears, a high arched palate and dental diastema. Brain MRI at the age of 9 years revealed no abnormalities.

Trio-whole exome sequencing revealed a heterozygous, *de novo LRRC7* mutation: chr1:g.69760371A>G; NM_001370785.3: c.281A>G; p.(Asn94Ser). Sanger sequencing in the patient and both parents confirmed the *de novo* occurrence.

*Case 3, pedigree L*

This 6.5 year old boy was born as the first child of healthy non-consanguineous parents. He has a younger unaffected sister. The family history is unremarkable. The proband was born after 40 weeks of gestation by vacuum-assisted vaginal delivery. Her birth weight was 3735 grams, birth length was 52 cm and head circumference was 37 cm. APGAR scores were 10 and 10. Parental concerns began around the age of 2 with a language delay and behavioral problems (motor hyperactivity, difficulty with attention and concentration). Motor development was appropriate for age. Language developed

later and with speech therapy support (association of words at 3 years old, sentence at 4 years old). He presented moderate cognitive development ; testing reveals an IQ of 68-88 (WISC-IV). He did not have aggressive behavior disorder. He had sleeping and eating difficulties (oral disorder). He wore glasses for hyperopia. Brain MRI at the age of 5.5 years revealed no abnormalities.

At last physical examination at the age of 8 years and 9 months, her weight was 37 kg (+2.7SD), height was 144 cm (+3 SD) and head circumference was 56 cm (+2.2 SD). No facial dysmorphisms were apparent.

Trio-whole exome sequencing revealed a heterozygous, *de novo LRRC7* mutation: Chr1:g.69760371A>G; NM_001370785.2: c.281A>G, p.(Asn94Ser). The *de novo* occurrence was confirmed by Sanger sequencing in the patient and both parents.

*Case 4, pedigree M*

This patient first presented to clinic at 4 years 11 months. She is the second pregnancy to non-consanguineous parents. She was born full term after an unremarkable prenatal period. Birth weight is 3458 grams. Birth length and head circumference are not recalled, but there were no concerns at delivery and she was discharged home with her mother. Delays were first noted around one year, including both speech and gross motor delays, as well as inattentiveness. Neurodevelopmental evaluation at age 4 years 5 months assessed her language to be at 18 months, with scatter to 36 months; cognition was assessed to be 18 months, with scatter to 24 months. Follow up Stanford-Binet testing revealed a nonverbal IQ of 62; verbal IQ could not be completed. She has some autistic behaviors but does not meet criteria for a diagnosis of autism. Additional features include 3 atypical febrile seizures that resolved by age 5 and aggressivity with intolerance to frustration. She underwent brain MRI at age 5 years that was normal.

Last physical examination was at the age of 7 years 3 months. She is overall non dysmorphic. Weight was 15.9 kg (30%ile), height was 105 cm (17%ile). Head circumference at 5 years 7 months was 49.5 cm (20 %ile).

Regarding family history, her older brother has a history of mild developmental delays for which he received services as a child and he was discharged. Both parents are neurotypical. Family history is also remarkable for both maternal grandparents having speech delay, and several distant paternal relatives with ADD/ADHD and autism spectrum disorder.

Metabolic labs and Chromosome microarray were completed and were non-diagnostic. Trio whole exome sequencing revealed a heterozygous, *de novo LRRC7* variant: Chr1:g.69792056G>A; NM_001370785.2: c.317G>A; p.(Cys106Tyr).

*Case 5, pedigree N*

This 11-year-old male was born to healthy non-consanguineous parents. The proband was born after 40+5 weeks of gestation by vaginal delivery. Pregnancy and birth were normal. His birth weight was 3718 grams and birth length was 54 cm. APGAR scores were 9 and 10. Motor development was appropriate for age. Learned first word at around 12 months of life but subsequent language development was severely delayed; he currently only forms short sentences with up to 5-10 words. Cognitive development is low within average; testing reveals an IQ of 70-77 (WPSSI-IV and WISC-V). The patient had onset of genetic generalized epilepsy at the age of 1.5 years and seizure type includes absence seizures. His weight at last examination was 33 kg (-1 SD) and height was 146.6 cm (-1 SD). Brain MRI at the age of 2 years revealed no abnormalities. No facial dysmorphisms were apparent.

Trio-whole exome sequencing revealed a heterozygous, *LRRC7* mutation inherited from an unaffected father: Chr1:g.69834856G>C; NM_001370785.2: c.577G>C, p.(Ala193Pro) The occurrence was confirmed by Sanger sequencing in the patient and the father.

*Case 6, pedigree O*

The proband is currently a 7 year old female born healthy to non-consanguineous parents. She was born at term following a pregnancy that was complicated by gestational diabetes and oligohydramnios. The family history was unremarkable.

She first presented to Neurology at 10 months of age with developmental delays, muscle weakness, febrile seizures, staring spells and abnormal eye movements and was noted to have nystagmus, hypotonia, mild weakness of the hip girdle muscles, unsteady gait and global developmental delays. An evaluation by Genetics shortly after found that in addition to the above, she was non-dysmorphic and had ptosis of the upper eyelids. Multiple EEGs and two brain MRIs (last one at age three) were normal.

After a non-diagnostic baseline genetic evaluation of a chromosomal microarray and a gene panel for neurological disorders, she was referred to the Undiagnosed Diseases Network at 3.5 years old. At that age, she was walking unsteadily with a walker/gait trainer and was unable to stand or take any steps independently. During the evaluation, she was noted to have a substantial speech delay with six single words. The Vineland Adaptive Behavior Scales-3$^{rd}$ Ed showed an adaptive composite score of 75. The Preschool Language Scales- 5$^{th}$ Ed (PLS-5) showed a total language score of 78 (7$^{th}$%) and an expressive communication score of 72 (3$^{rd}$%).

Now at 7 years old, she has made gains in her skills. She is currently able to stand independently, but gait is ataxic and she needs to hold onto the wall/objects while walking. She is also speaking in 3-4 word sentences though her intelligibility varies. She continues to have episodes of staring spells and nystagmus. The most recent physical exam was at 7 years 2 months of age, with unchanged neurological findings. The weight was 15.9kg (35.09lb, Z=-3.02, 0.13%) and height was 106.7cm (42.01in, Z=-3.11, 0.09%). The head circumference was last measured at 4 years 4 months and was 50.3cm (Z=0.09, 54%).

Trio exome and trio genome sequencing released a heterozygous, *de novo LRRC7* mutation: Chr1:g.69931520C>A; NM_001370785.3: c.661C>A, p.(Leu221Met). Sanger sequencing in the proband and both parents confirmed the *de novo* inheritance.

*Case 7, pedigree P*

The proband is a 9 year old male born to healthy, non-consanguineous parents at 40 weeks gestation following an uncomplicated pregnancy. Family history included a maternal grandfather with adult-onset cerebellar ataxia with associated cognitive decline.

Developmental delays were first noted by the parents around 9 months of age when he was not yet sitting up; he walked independently at 2 years of age. On neurological exam at 2 years, he had decreased axial and appendicular tone, hyporeflexia, and ataxic gait. Brain MRI showed mild superior vermis atrophy, and on repeat imaging at 3 1/2 years of age showed cerebellar sulcal prominence. EMG was normal.

Comprehensive ataxia panel, chromosome microarray, Fragile X testing, and research-based exome sequencing were normal. He was evaluated through the Undiagnosed Diseases Network (UDN) at 3

years 10 months of age. Height was 105.5cm (83%ile), weight was 18.7kg (89%ile), and head circumference was 52cm (81%ile). Developmentally, he was able to run, climb stairs, feed himself with utensils, and speak in multi-word sentences. On neurologic exam he had subtle ataxia, dysarthric speech, hypoactive reflexes and mild hypotonia. Neurodevelopmental evaluation demonstrated symptoms of ADHD. Ophthalmologic and audiology exams were normal.

At 5 years, 10 months of age, delays were most evident in fine motor skills. He was diagnosed with ADHD and started on stimulant medication. On exam his height was 115.3cm (55%ile) and weight was 20.8kg (55%ile). He did not have hypotonia, gait abnormalities or ataxia, but deep tendon reflexes were hard to elicit. At 8 years of age an EEG revealed benign Rolandic epilepsy, but he has not had seizures; on ophthalmologic exam he had hypometric saccades, with normal visual function, optic nerves and retina. Currently, at 9 years of age he has low average to borderline cognition, dyslexia and dysgraphia and receives additional instruction for math and reading.

Trio genome sequencing through the UDN revealed a heterozygous, *de novo* variant in LRRC7: NM_001370785.3:c. 887T>C; p.Leu296Pro. The variant was confirmed by Sanger sequencing.

*Cases 8 – 10, pedigree Q*

The proband is a 6-year-old male and born 34 weeks gestation as the third child of healthy non-consanguineous parents. Both siblings are affected. His full sister has ADHD, autism spectrum disorder, a Chiari 1 malformation (unique feature of the family), migraines, learning disabilities, eczema, asthma, and anxiety. His full brother had skin tags as a baby at the right nipple, sores, cerebral palsy, an overactive bladder (less severe than the proband), developmental and speech delay, seizures, ADHD, autism spectrum disorder, eczema, asthma, and a 2q23.3 deletion of uncertain significance which was not identified in the proband.

Last physical examination at the age of 6 years of age revealed a child with developmental delay who did not speak. He showed reduced pain perception. His weight was 24kg (0.65 SD) and height was 122cm (0.7 SD). Brain MRI at the age of 5 years revealed no abnormalities. No facial dysmorphisms were apparent. The patient was diagnosed with developmental delay, autism spectrum disorder, ADHD, selective mutism, feeding difficulties necessitating a gastrostomy/jejunostomy tube, GERD, generalized seizures, hydronephrosis that is now resolved, high-grade vesicoureteral reflux that is now resolved, spastic diplegic cerebral palsy, strabismus, sleep apnea, sleep disturbances, eczema, and limited sweating. The patient underwent genetic testing via a chromosomal microarray which returned normal and did not identify his brother's 2q23.3 VUS deletion. The patient then underwent whole exome sequencing as a "quad" including his mother and two siblings (father is not available), which revealed a variant of uncertain significance in the LRRC7 gene; chr1:g. 70028372G>A; NM_001370785.2:c.1995+1G>A. Both siblings are heterozygous for this variant, but the mother tested negative for the variant.

*Case 11, pedigree R*

This female patient, now 20 years old, is the seventh of eight children of a healthy mother. The siblings have different fathers. The patient´s father has a learning disability. Both younger half-siblings on the father's side show intellectual disability. One maternal half-brother has a PMP22-associated hereditary neuropathy. Contact with the father broke off shortly after birth of our patient when the father was convicted as a sex offender.

Birth and pregnancy in our patient were unremarkable. Weight at birth was 3180g, length 50 cm. Head circumference at birth and APGAR ist not known. Head circumference at the age of 17 years was 56.5 cm (SDS 0,93). Length 172 cm (ADS 0.75). She became obese (BMI 37 kg/m²) from the age of 10 years.

She had a delay in development in the areas of cognition, speech and motor skills. She could not read and write and could not orient herself outside the home. Motor skills are clumsy, but she can swim and ride a bicycle. She has an impulse control disorder, becomes aggressive quickly. Cognitive testing at the age of 17 showed an IQ of 63 (SON-R 6-40). The patient does not have facial abnormalities or other dysmorphia and other diseases. An MRI of the brain at age 9 years was unremarkable. At that age, she had a focal increase in excitability on EEG. Epileptic seizures have not occurred at any time.

Single exome sequencing revealed a heterozygous *LRRC7* variant: Chr1:g.70036578C>T, NM_001370785.2: c.2242C>T, p.(Gln748*). The mother was tested for the variant using Sanger sequencing which revealed it is not maternally inherited. The father is unavailable for testing. A prior SNP-Array was unremarkable.

*Case 12, pedigree S*

The patient, now 13 years of age, is the only child of his parents. There are also 2 paternal half-brothers and 2 maternal half-brothers. The father is reported to have a learning disability. A diagnosis of autism is established in one of the maternal half-brothers. The parents are no longer together and contact with the father has been lost.

There were no prenatal or birth complications. The birth weight was 3912g and the birth length was 51.2 cm. The head circumference at birth and APGAR scores are not known.

Initial concerns about the patient first came about at 2 years of age due to delayed speech and regressed language skills. Interventional therapies were then initiated and the patient was noted to have hypotonia and increased joint laxity prompting the use of foot and ankle orthotics. The patient began to gain weight rapidly by 4 years of age and developed a number of explosive and impulsive destructive behaviors. The patient experiences intense outbursts with food. He has been found to create holes in the wall to hide food wrappers and requires close supervision as he has been found eating animal food and food out of public garbage cans. The patient had been diagnosed with autism and ADHD by 5 years of age. Medications for ADHD had been trialed over several years with little perceived clinical benefit. The patient had also been retained in 1st grade [6 years of age] but did not advance in either domain of reading or writing. Neurocognitive testing has not been accomplished to the knowledge of the family, though his medical records also indicate a suspicion of an underlying comorbid intellectual disability.

The head circumference at the age of 11 was 60 cm [>99th%tile, +4.7 SD]. Length 166.5 cm [98th%tile]. At the time the patient had been notably obese with a BMI of 40.6.

Exome sequencing revealed a heterozygous LRRC7 variant: chr1: 70038741, NM_001370785.2: c.2803dupC, p.(L973Pfs*8). The mother was tested for the variant using Sanger sequencing which revealed it is not maternally inherited. The father is unavailable for testing. A prior SNP-Array was unremarkable. Fragile X analysis also returned as normal.

*Case 13, pedigree T*

This 7-year-old male was born to healthy non-consanguineous parents. The proband was born at term. Pregnancy and birth were normal. Feeding problems started in the neonatal period. In the first months he was referred to the pediatric gastroenterologist because of multiple food allergies and reflux. Motor

development was delayed, he started to walk independently from the age of 2 years. Speech development was also delayed, nowadays he speaks in sentences. Cognitive development is average; testing reveals an TIQ of 91, VIQ of 97 and PIQ of 87. He visits a regular school until now. His weight at last examination was 22.3 kg (+0.76 SD) and height was 117 cm (-0.87SD). His behaviour is sometimes challenging. He is hyperactive, impulsive and has low concentration. No facial dysmorphisms were apparent. He has some café-au-lait spots on the skin.

Trio-whole exome sequencing revealed a heterozygous, de novo *LRRC7* mutation: Chr1:g.70038876C>T; NM_001370785.2: c.3052C>T; p.Arg1018*.

*Case 14, pedigree U*

The patient is currently a 14 year old boy. He was born to a G2 P1>2, 29- year old mother. There was not exposure to bleeding, gestational diabetes, hypertension, infection, medications, drug/alcohol exposure, toxic exposure, or preterm labor during the pregnancy. Prenatal testing was not performed. Ultrasounds during the pregnancy were normal. Vaginal delivery at 38 weeks gestation was uncomplicated. Birth weight was 7 pounds 8 ounces and birth length was 21 inches. Apgars were 8 and 9. He stayed in the hospital for two days and then went home with mom. Neonatal course was otherwise unremarkable. He was initially referred to genetics clinic at 5.5 years of age for evaluation of developmental delays, low tone and behavioral concern. Initial concerns were noted around 6 months of age when the patient seemed to be making limited eye contact and was not yet sitting. He was evaluated by endocrinology for mildly elevated TSH in 11/2013. Repeat TSH in 4/2014 was elevated with positive TPO antibodies, therefore autoimmune hypothyroidism was diagnosed. Other symptoms have included macroglossia, bilateral pes planus, gait concerns (noted to have mild trendelenberg, mild external tibial torsion). He was found on previous brain MRI to have basal ganglia calcifications and it was felt that his basal ganglia calcifications may be a benign finding that are unrelated to an underlying condition. Repeat brain MRI was normal without evidence of basal ganglia calcifications. The patient is noted to have a large appetite and current behavioral concerns include outbursts and physical aggression. He currently has diagnoses of autism, ADHD, dyslexia, math learning disability. His most recent growth parameters on record demonstrate weight at the 68%, height at the 80% and head circumference at 71% Physical exam did not show any dysmorphisms.

A chromosomal microarray was ordered and revealed a 320 kb duplication of 1q21.1; this was inherited from his unaffected father. Fragile X testing was also performed and was normal. He also had testing for urine organic acids, urine oligosaccharides, lysosomal enzymes, amino acid quantitation, acylcarnitine profile, serum homocysteine and lactate; all tests were non-diagnostic. Genetic testing with a large neurodevelopmental panel demonstrated a heterozygous *de novo LRRC7* variant, c.3078dupA, p.Val1027Serfs*5.

*Case 15, pedigree V*

This patient was 4 year 7 month old male who presented to Genetics clinic with a history of ADHD, autism and developmental delay. Birth and newborn history is unavailable due to adoption at the age of 8 months. The patient and his twin sister were reported to be like newborns at this age and unable to hold up their heads, roll over, or sit unassisted; however, neglect likely contributed to failure to meet early developmental milestones. His first tooth erupted at age 18 months. On physical exam he was noted to have mild bitemporal narrowing with a long face, mild fifth finger clinodactyly with increased laxity of hands. The head circumference was 52 cm (75%); height was 109.2cm and weight was 18.1kg. His speech was confined to short 1-2 words. There are three biological siblings, one of whom is a twin with microcephaly; the biological mother and father have learning disabilities, in addition to a paternal aunt and paternal grandmother. Whole exome sequencing revealed a heterozygous variant in *LRRC7:* chr1:g. 70039428T>G: c.3604T>G, p.(Tyr1202*).

*Case 16, pedigree W*

This 26 year old male is the only child of healthy non-consanguineous parents. The family history is unremarkable. The proband was born in the 38th week of gestation. His birth weight was 3540 grams, birth length was 50 cm and head circumference was 36,5 cm. APGAR scores were 10 and 10. After birth there was a muscular hypotonia noticeable. As an infant he showed absence seizures. Early motor development was appropriate for age (sitting age 6-9 months, walking age 12 months). Expressive language development was delayed (first words at age 2 years); at the age of 6 years he used word combinations but no sentences. Brain MRI at the age of 4 years revealed no abnormalities. Testing at the age of 14 years revealed an IQ of 70 (CFT 20-R).

Since the age of 4 years he has been overweight (weight above the 97 th centile). He eats everything and especially likes sweets. At the age of 5 years Prader-Willi syndrome was excluded. He has low satiety and his appetite has been even increasing during the last years.

At the age of 16-17 he showed a period of self-injuries due to relationship problems. At the age of 26 he could read single letters and few simple words. He needs guidance in everyday life. He has an impaired balance (one-leg stand not possible) and difficulties in spatial perception. The proband spends excessive time sleeping. According to his parents he is emotionally unbalanced and shows verbal aggression under stress.

The last examination at the age of 26 years and 4 months revealed a friendly young man with an intellectual disability. His weight was 127 kg (+3.44 SD), height was 179 cm (-0.24 SD) and head circumference was 58.8 cm (+1.18 SD).

Exome Pool-Seq sequencing revealed a heterozygous LRRC7 mutation: chr1:g. 70039454T>G: c.3630T>G, p.(Tyr1210*). The mutation and the *de novo* occurrence was confirmed by Sanger sequencing in the patient and both parents.

Cases 17 - 19, pedigree X

*Case 17*

This 5 year old boy is the eldest of two siblings of non-consanguineous parents. He has a 1 year old sister who is symptomatic (case 18). He was born after 42 weeks of gestation by vaginal delivery. His birth weight was 4340 grams, birth length was 53 cm and head circumference was 37 cm. APGAR scores were 10 and 10. He presented with bronchiolitis at 4 months, without hospitalization. He is followed for a family atopic condition and in ophthalmology for a divergent strabismus. He evolved with a global developmental delay. Walking was acquired at 23 months. Last physical examination was done at the age of 5 years. His weight was at +0.75 SD, height at +1 SD and head circumference – 1 SD. The somatic examination was unremarkable. Morphological criteria were found with bitemporal retraction, microcephaly, hypoplasia of the *alae nasi* with a prominent nasal root and a columella above the *alae nasi*. The philtrum is marked with a hat mouth.

Trio-whole exome sequencing revealed a heterozygous *LRRC7* mutation: chr1:70076289T>G ; NM_001370785.2: c.4443T>G; p.Tyr1481*. The variant is inherited from the father, and also identified in his sister (case 18), confirmed by Sanger sequencing in the siblings and both parents.

*Case 18*

This 1 year old girl was born as the second child of non-consanguineous parents. She has an older affected brother (case 17). The pregnancy was marked by the observation at 23 weeks of gestatio of a short corpus callosum. A fetal MRI was done at 31 weeks of gestation confirming this corpus callosum. An amniocentesis was done in this sense showing a normal karyotype. CMV serology was

also negative. Gestational diabetes was associated with the pregnancy and was treated by diet alone. She was born at term at 39 WG + 5 days by non-instrumental vaginal delivery with an Apgar of 10/10. She weighed 3kg270 for a height of 51cm and a head circumference of 33cm.

Last physical examination was done at the age of 1 year. She weighed 9kg for a height of 73cm and a head circumference of 42cm. Morphological criteria were found with bitemporal retraction, microcephaly, hypoplasia of the *alae nasi* with a prominent nasal root and a columella above the *alae nasi*. The philtrum is marked with a hat mouth and narrow tapered palpebral fissures. There is no other abnormality. The neurological examination was normal with axial tonus within normal limits. Cardiopulmonary auscultation is unremarkable. She stands with support. There is no sleep disorder or specific eating disorder.

Sanger sequencing revealed a heterozygous *LRRC7* mutation: chr1:70076289T>G ; NM_001370785.2: c.4443T>G; p.Tyr1481*. The variant is inherited from the father, and also identified in her brother (case 17) identified by trio-whole exome sequencing.

Case 19

The father of cases 17 and 18 presented with global developmental delay and evolved with a mild to moderate intellectual disability with care in special education.

Case 20, pedigree Y

This 7-month-old male was born to non-consanguineous parents. The proband was born at 37 weeks due via emergency C-section due to severe oligohydramnios. He was retained in the NICU for four hours due to fluid aspiration at delivery. The proband birth weight was 3118 grams and birth length of 49.53 cm. Head circumference and APGAR scores are unknown. He was discharged from the hospital at day of life 2. The first three weeks of life, there was growth failure due to pyloric stenosis that was surgically corrected. The proband was enrolled in the research study due to involuntary leg movements that occurred when he slept that also involved eye fluttering. He also exhibits episodes of “zoning out”. EEG was reported normal and no other abnormalities are described.

There is family history of seizures and/or intellectual disability (ID). The biological mother is noted to have recurrent pregnancy losses of unknown cause (2 miscarriages, one full term), one due to a “chromosome abnormality” but no testing was performed. Both parents suffer from attention deficit hyperactivity disorder, oppositional defiant disorder, and bipolar disorder. The mother also reports history of anxiety and post-traumatic stress disorder. Maternal history also indicates history of bipolar disorder and substance abuse of both of her parents, ADHD and unspecified learning disability in the maternal grandmother. The maternal grandfather passed away due to drug overdose. There is paternal family history of depression, seizures, and/or intellectual disability. A paternal cousin with both seizures and ID harbored with a maternally inherited missense variant in DEPDC5 (NM_0012428962:c.2632A>C p.(Lys787Gln) that was not observed in the proband (case 20).

Duo-whole genome sequencing reveal a heterozygous LRRC7 mutation: chr1:g. 70121859T>A; NM_001370785.2: c.4700T>A, p.(Leu1567Gln). The variant was confirmed by Sanger sequencing in the patient and the biological father.

*Case 21, pedigree Z*

The proband is a 6 yo female born at full term to non-consanguineous parents. Mother had no prenatal care. No known history of teratogen use. After birth, cleft lip and palate were found that were repaired. Birth parameters were within normal percentiles. Developmental history is unknown in the first 3 yo of life. At age 3 years, she moved to live with the maternal grandparents who became

legal guardians. At age 3, she had no words, no babbling. At age 4 years she was diagnosed with autism spectrum disorder. First words started between 3-4 years. Currently, at age 6y, she can talk in short sentences in 3-5 words. Medical history includes strabismus, which is treated with glasses. Behavioral concerns started at age 6y, which include tantrums, episodic crying. Brain imaging was normal, and EEG performed due to suspected staring episodes was non-diagnostic. Growth parameters at age 6 y are normal except for short stature. On physical exam, mild dysmorphism including secondary findings to cleft lip and palate repair, hypertelorism and esotropia on the left were observed.

Family history is positive for a brother with autism and vision problems. Mother had some reading problems during school years but finished high school. Father finished high school and has a diagnosis of anxiety and depression. Mother has concerns of depression. The siblings were adopted by the grandparents.

The proband underwent genetic testing which included CMA, proband WES and mitoNGS. Parental samples were used for segregation of variants of unknown significance. Genetic testing showed a duplication of 661 kb on chromosome 14 that was inherited from the father. This copy number variant is of unknown significance. In addition, the proband was found to inherit a frameshift variant in LRRC7 from her mother: chr1:g.70038198delC; NM_001370785.2: c.2374del; p.Arg792Valfs*7. Her brother was not tested for the variants. Other genetic tests were non-diagnostic.

*Case 22, pedigree #*

Individual 22 is a female child who was initially conceived as a gemellar pregnancy with a vanishing twin. The patient, now an adolescent, was born at 38 weeks of gestation via natural vaginal delivery. Her birth parameters were within the normal range, with a weight of 3040g, height of 50cm, and OFC of 33cm. She began walking independently at the age of one. She exhibited a delay in language development, using her first words at two years of age. Concerns regarding the patient's learning abilities arose at the beginning of preschool as her progresses were judged delayed compared to her peers'. At the age of four, the patient encountered difficulties in fine motor skill issues as graphism and occasional clumsiness. Physical examination revealed no dysmorphic features, and the neurological examination was unremarkable. Despite efforts to integrate the patient into a regular preschool environment during her first year at school, she was eventually redirected to an adapted class and later an institution. Furthermore, she displayed behavioral issues such as difficult interactions. The patient was described as an irritable child. During her follow-up as a teenager, the patient began experiencing auditory and visual hallucinations, which required psychiatric management. There were no reported instances of hetero- or autoaggressivity. The patient exhibited limited social interactions. She also had insufficient sleep.

Overall, she had a limited intellectual functioning with psychiatric features but she managed to attain a certain level of independence. At her latest clinical examination at the age of 19, she weighed 61 kg, had a height of 159 cm, and an OFC of 55 cm, within the average range. She developed skills in serigraphy and engaged professionally in this activity.

Initial investigations, including a brain MRI, did not reveal any abnormalities. A psychometric evaluation conducted at eight years of age indicated a limit intellectual functioning, with a total IQ of 71, verbal IQ of 77, and performance IQ of 73. Her etiologic workup, which included standard karyotype, 22q11 FISH, and an extended metabolic screening, was unremarkable. CGH array revealed an heterozygous de novo 100kb deletion arr[GRCh37] 1p31.1(705835088-70682550)x1 affecting the last exon of *LRRC7* and *SRSF11* gene.

**Supplementary Methods.**

**Supplementary Table 1.**

***C. elegans* strains**

| **Strain** | **Genotype** |
|---|---|
| VC2010 | *C. elegans* wild-type |
| FX30134 | *tmC3* [egl-9(tmIs1228)] V, inversion balancer |
| SU93 | *jcIs1* [ajm-1::GFP + unc-29(+) + rol-6(su1006)] IV |
| UDN100047 | *let-413(udn25)*, control edit L248L #1 |
| UDN100049 | *let-413(udn27)/tmC3*, variant edit L248P #1 |
| UDN100050 | *let-413(udn28)/tmC3*, variant edit L248P #2 |
| UDN100052 | *let-413(udn30)*, control edit L173L #1 |
| UDN100054 | *let-413(udn32)*, variant edit L173M #1 |
| UDN100055 | *let-413(udn33)*, variant edit L173M #2 |
| UDN100062 | *let-413(udn71)/tmC3*, deletion/insertion allele |
| UDN100118 | *let-413(udn25)/tmc3; jcIs1*, control edit L248L #1 |
| UDN100084 | *let-413(udn27)/tmC3; jcIs1*, variant edit L248P #1 |
| UDN100117 | *let-413(udn71)/tmC3; jcIs1*, deletion/insertion allele |

**Supplementary Table 2**

**Single stranded oligonucleotides for editing in *C. elegans***

| Name | Sequence (5' to 3') | Description |
|---|---|---|
| let-413.L183_gRNA2 | CTCAATTCCACAATCGACAG | Guide RNA for L173 control and variant edits |
| let-413.L248_gRNA | ATATTCAAGTCTGTGAGATT | Guide RNA for L248 control and variant edits |
| L173Mrep_R | GCTTCAAGTTCATTTTGTCCAAGATCGAGCTCTTCAAGTTTTCTCAtTTCgACgATCGACAGAGGAATTGTTCGGAGAAGATTGTCTCGAGCTTCGAGAA | Homologous recombination repair template for L173M variant edit |
| L173Lrep_R | GCTTCAAGTTCATTTTGTCCAAGATCGAGCTCTTCAAGTTTTCTCAATTCgACgATCGACAGAGGAATTGTTCGGAGAAGATTGTCTCGAGCTTCGAGAA | Homologous recombination repair template for L173L control edit |
| L248Prep_R | CCAAATGAACTAGGCAATTCGATTATCTCATTTATAGAAATATTCggGTCaGTcAaATTTGGCATTCTGCCAAGATTTTCAGGTAGTCGAATAATTTGGT | Homologous recombination repair template for L248P variant edit |
| L248Lrep_R | CCAAATGAACTAGGCAATTCGATTATCTCATTTATAGAAATATTCAAGTCaGTcAaATTTGGCATTCTGCCAAGATTTTCAGGTAGTCGAATAATTTGGT | Homologous recombination repair template for L248L control edit |

**Supplementary table 3.**

**Oligonucleotides used for cloning LRRC7 expression constructs**

| Name | Sequence (5' to 3') | Description |
|---|---|---|
| Densin_Irr_F | TTTGGATCCATGCAGTGCCTGGAGATGACCACC | cloning of LRR domain constructs |
| Densin_Irr-R | TTTGTCGACTCAACGGGGCTGCTGGGGAAACATG | cloning of LRR domain constructs |
| L94S_F | GAGGAAGAGATCATCTCGGTGTCGGATTACTCCCACTGCAGCCTG | mutagenesis L65S |
| L94S_R | CAGGCTGCAGTGGGAGTAATCCGACACCGAGATGATCTCTTCCTC | mutagenesis L65S |
| N56S_F | GAGCTCTATCTAGATGCCAGTCAGATTGAGGAGCTACCC | mutagenesis N94S |
| N94S_R | GGGTAGCTCCTCAATCTGACTGGCATCTAGATAGAGCTC | mutagenesis N94S |
| C106Y_F | CCCAAGCAATTGTTCAACTATCAAGCTCTAAGGAAACTAAG | mutagenesis C106Y |
| C106Y_R | CTTAGTTTCCTTAGAGCTTGATAGTTGAACAATTGCTTGGG | mutagenesis C106Y |
| A193P_F | GCCTTCCTCGAATTTCTTCCACCTAATTTTGGAAGACTTGTC | mutagenesis A193P |
| A193P_R | GACAAGTCTTCCAAAATTAGGTGGAAGAAATTCGAGGAAGGC | mutagenesis A193P |
| L221M_F | CTACCAAAGTCAATGCACAAGATGGCCCAGCTGGAAAGACTTGAC | mutagenesis L221M |
| L221M_R | GTCAAGTCTTTCCAGCTGGGCCATCTTGTGCATTGACTTTGGTAG | mutagenesis L221M |
| L296P_F | GGATGTGAAGCCCTCGAGGACCCCTTACTATCATCCAATATGTTG | mutagenesis L96P |
| L296P_R | CAACATATTGGATGATAGTAAGGGGTCCTCGAGGGCTTCACATCC | mutagenesis L96P |

**Supplementary Table 4.**

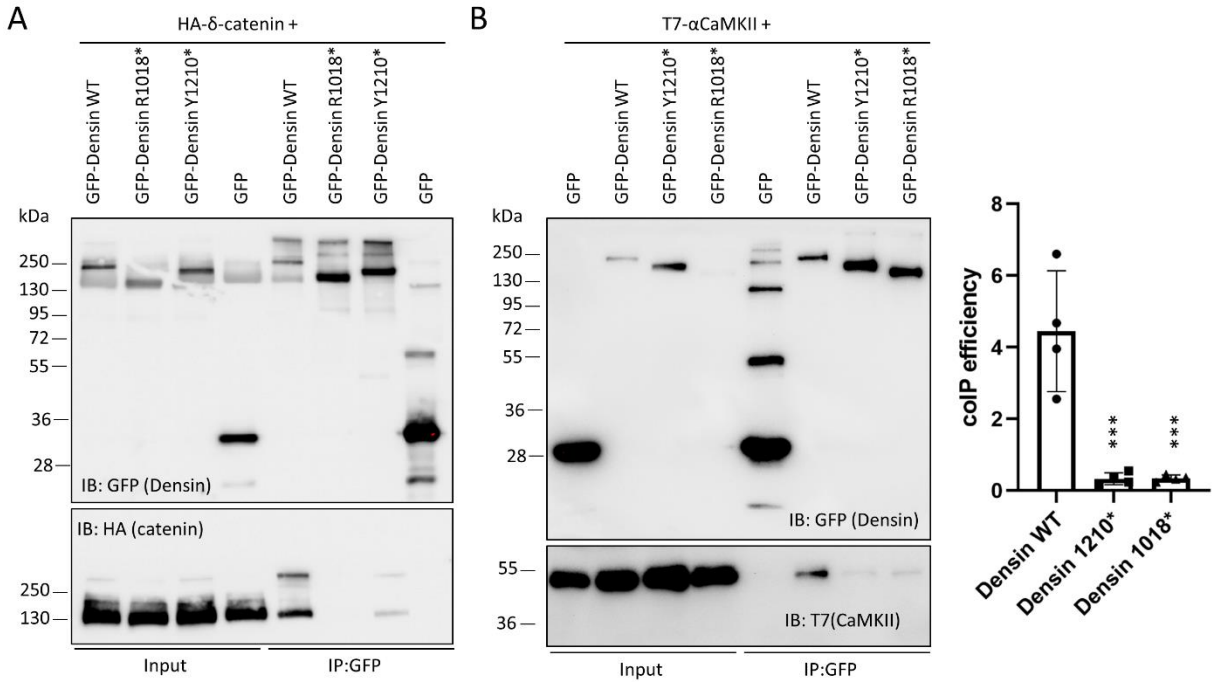
| Rank | BioID with LRR domain of LRRC7 | Uniprot accession |
|---|---|---|
| **1** | Leucine-rich repeat-containing protein 7 (LRRC7) | Q96NW7 |
| **2** | Erbin | Q96RT1 |
| **3** | ATP-dependent RNA helicase DDX3X | O00571 |
| **4** | Zinc finger CCCH-type antiviral protein 1 | Q7Z2W4 |
| **5** | Band 4.1-like protein 2 | O43491 |
| **6** | ATP-dependent RNA helicase DDX3Y | O15523 |
| **7** | Insulin receptor substrate 4 | O14654 |
| **8** | 4F2 cell-surface antigen heavy chain | P08195 |
| **9** | Afadin | P55196 |
| **10** | Hemoglobin subunit beta | P68871 |
| | | |
| **Rank** | **BioID with full length LRRC7** | **Uniprot accession** |
| **1** | Leucine-rich repeat-containing protein 7 (LRRC7) | Q96NW7 |
| **2** | Erbin | Q96RT1 |
| **3** | Keratin | Q7Z794 |
| **4** | Myosin-9 | P35579 |
| **5** | Dermcidin | P81605 |
| **6** | Myosin-10 | P35580 |
| **7** | Desmocollin-1 | Q08554 |
| **8** | CCR4-NOT transcription complex subunit 1 | A5YKK6 |
| **9** | Immunoglobulin heavy constant alpha 1 | P01876 |
| **10** | Actin, alpha skeletal muscle | P68133 |

**BioID screens for interaction partners of the LRR domain of Densin-180.** The BioID screen was performed in 293T cells transfected with plasmids coding for BioID fusions of either Densin-180 full-length or, the LRR domain, or the empty pBio-N1 control plasmid. After purification of biotinylated proteins and analysis by mass spectroscopy in three independent experiments, identified targets were ranked by calculating the difference between signal strength in Densin samples vs control samples. Erbin and DDX3 were top hits in most experiments (see Fig. 7 for further analysis). Afadin and, in some cases, its associated protein Nectin-2 were also high on the list and chosen for further analysis. Typical non-specific contaminants such as keratins were ignored.

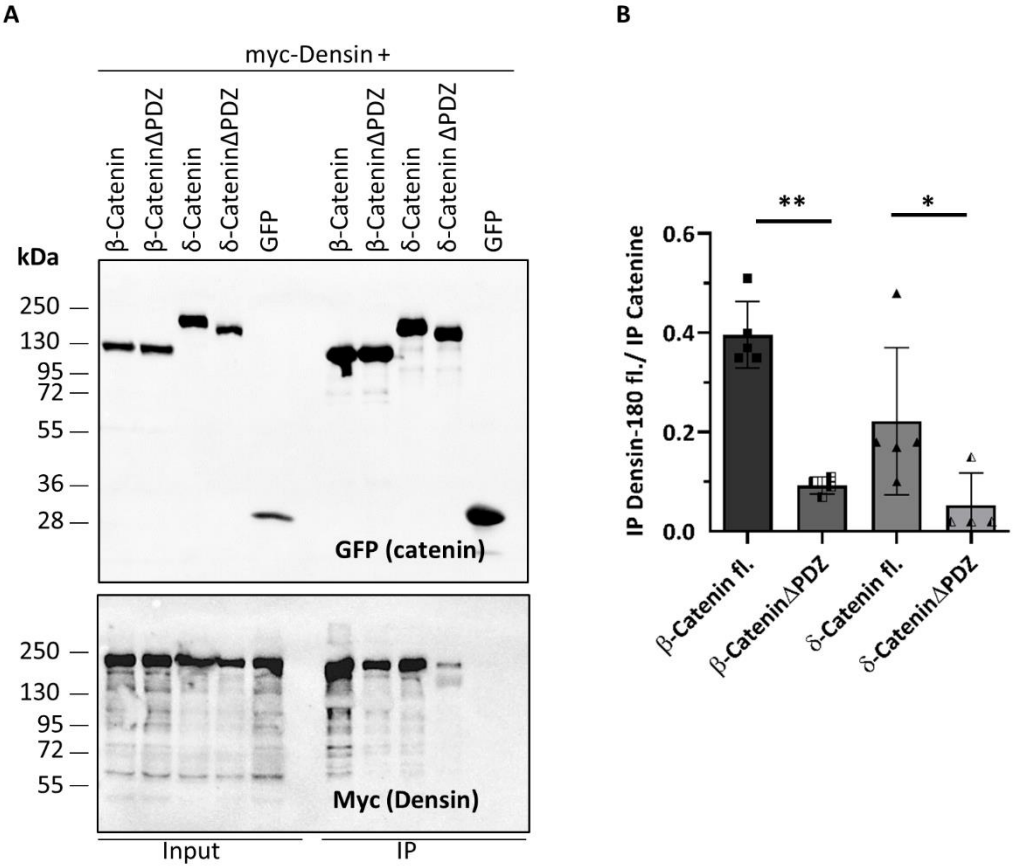
**Supplementary Note 2.**

**Yeast two hybrid screen for interaction partners of the LRR domain of Densin-180.** For screening, the cDNA coding for the LRR domain of rat Densin-180 was cloned into the pGBKT7 in frame with the DNA binding domain of Gal4. After transformation into the yeast reporter strain *Saccharomyces cerevisiae* CG1945 (Clontech) a human brain cDNA library in the Gal4 activation domain fish vector pACTII (Clontech) was screened for interacting proteins as described. Of a total of $1.1 \times 10^6$ transformants, 15 positive clones were identified by β-galactosidase filter lift assay. Two independent clones contained coding sequence for the C-terminus of the microtubule actin crosslinking factor MACF1, including two EF hands and the first half of the C-terminal GAR domain (growth-arrest specific 2 or Gas2-related); residues 6893-7150 and residues 6961-7150; Uniprot entry Q9UPN3-1). In addition, one clone encompassing the C-terminus of muscle β-spectrin (residues 2111-2328; NM_001024858.1) was obtained. Other clones were not in frame with the Gal4 activation domain and were not considered. The insert fragment of the longer MACF1 clone, and of the single β-spectrin clone were subcloned into pEGFP-C1 in frame with the EGFP coding sequence for further biological analysis (see below). In addition, the MACF1 insert was also subcloned into pmRFP-C1 and used for analyses in Fig. 8 of the main manuscript.

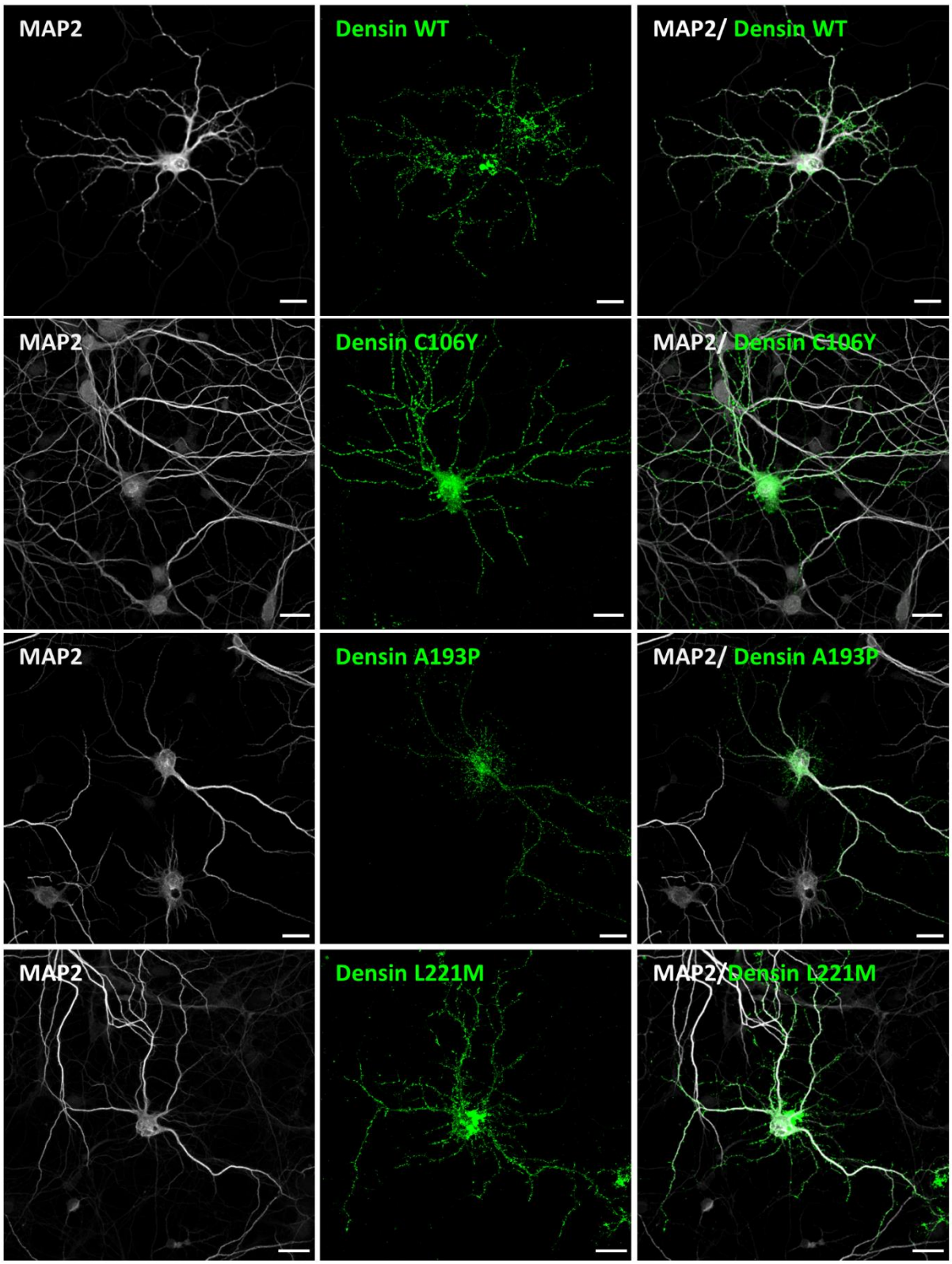
**Supplementary Figures**



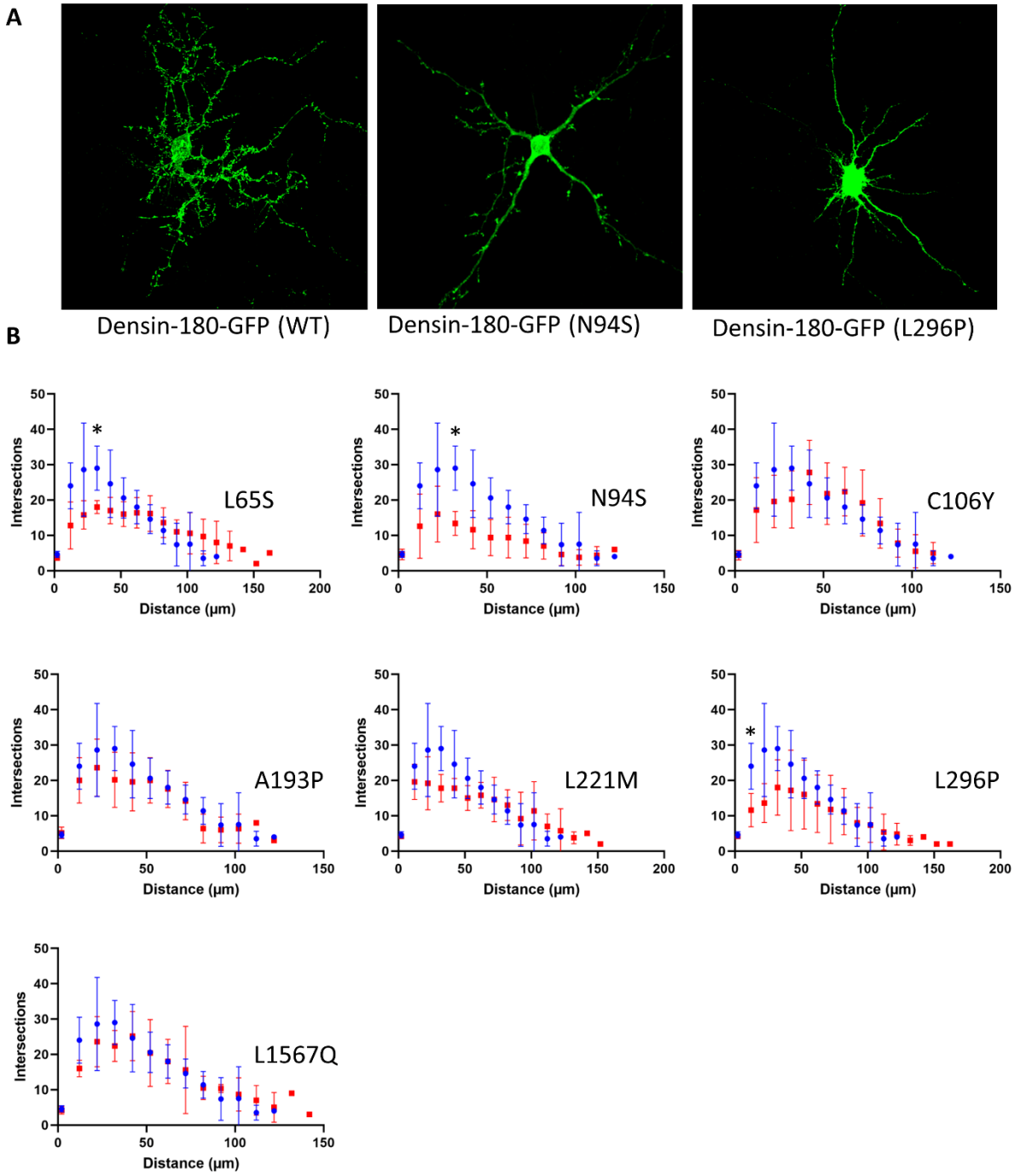

**Supplementary Figure 1. Functional analysis of LRRC7 deletion mutants.** 293T cells were cotransfected with constructs coding for GFP-tagged Densin-180 (WT or nonsense variants), or GFP alone, in combination with HA-tagged δ-catenin (A) or T7-tagged αCaMKII (B). GFP-tagged proteins were immunoprecipitated from cell lysates, and input and IP samples were analysed by Western blotting. Note that most if not all binding for δ-catenin is lost with the nonsense variants. Weak but consistent binding is maintained for αCaMKII for both variants (Y1210* and R1018*; see quantification), in agreement with the presence of a second binding site at amino acids 842-856 of Densin-180. ***, p<0.001; ANOVA (n=4). Data are shown as mean +/- SD. Source data are provided as a Source Data file.




**Supplementary Figure 2. Densin-180 interacts with β- and δ-catenin via their C-terminal PDZ ligand motifs. A.** 293T cells were transfected with constructs coding for myc-tagged Densin-180 in combination with GFP-tagged catenin variants, or GFP alone. In ΔPDZ constructs, early stop codons were introduced to remove the C-terminal PDZ ligand motifs. After cell lysis, GFP-containing proteins were immunoprecipitated using the GFP-trap matrix. Input and immunoprecipitate (IP) samples were analysed by Western blotting. B. Quantitative analysis of the data shown in A; shown is the ratio of Densin-180 IP signal over catenin signals in IP samples. *,**: $p<0.05$, 0.01, respectively, t-test (n=5 for β-catenin; n=4 for δ-catenin). Data are shown as mean +/- SD. Source data are provided as a Source Data file.

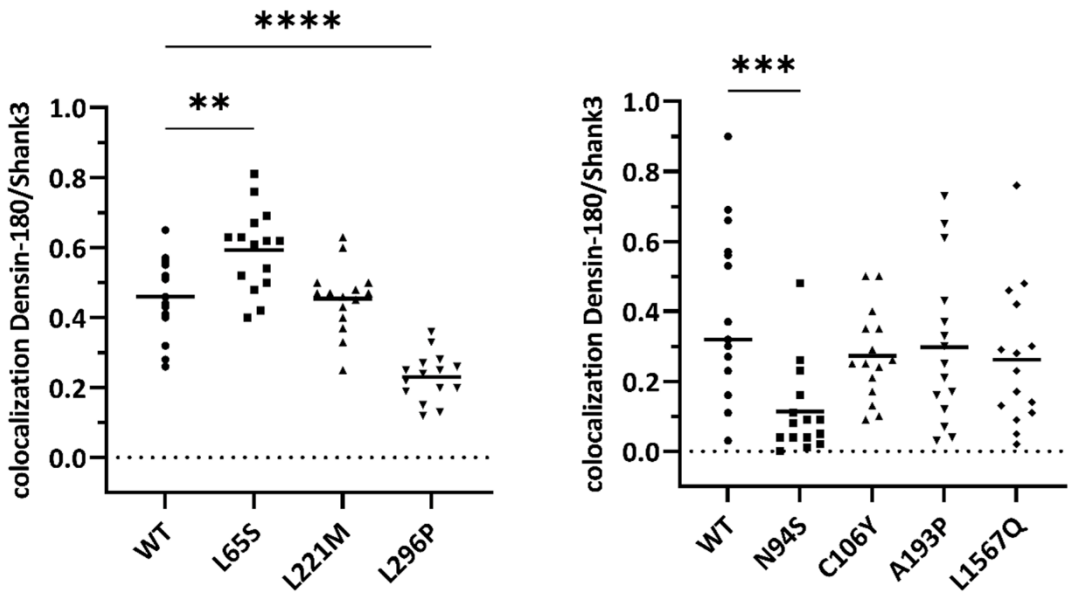



**Supplementary Figure 3. Expression of LRRC7 variants in hippocampal neurons.** Primary cultured hippocampal neurons were transfected with plasmids coding for Densin-180 variants. These neurons were quantitatively analysed in Figure 5c of the main manuscript.

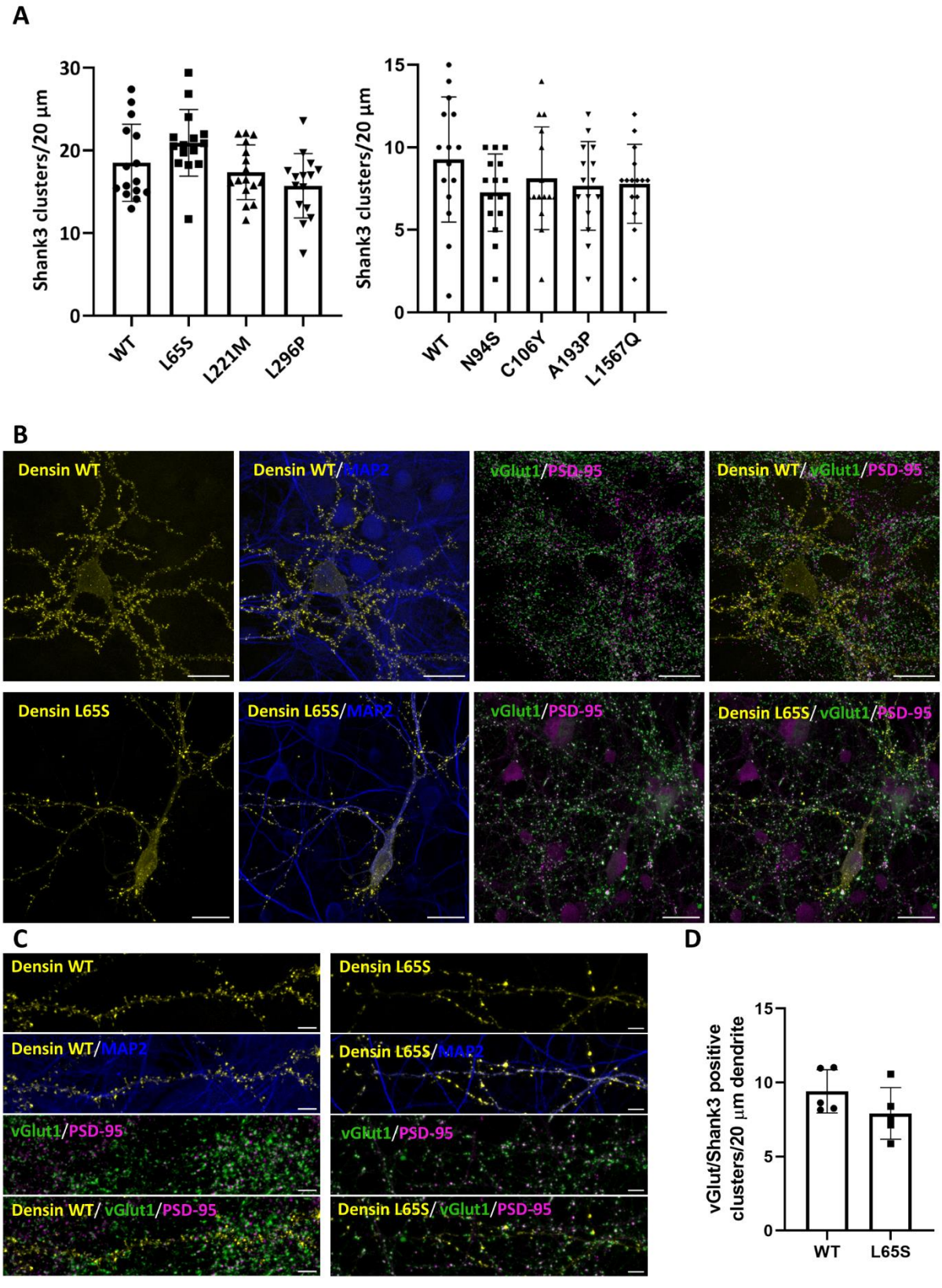



**Supplementary Figure 4**: **Sholl analysis of rat primary hippocampal neurons transfected with Densin-180 variants. A.** Representative images of neurons expressing GFP-Densin-180 WT and the N94S and L258P mutants. **B.** Plot of Sholl analysis for neuron arborisation upon transfection with Densin-180 WT compared to Densin-180 mutants; in each case the WT is shown in blue and the mutant in red. A sample of 5 hippocampal neurons was analyzed for each conditon. The number of intersections of the dendritic tree with concentric circles at increasing distances from the soma is shown, starting at 2 µm, and then increasing in steps of 10 µm. Error bars represent SEM. Neurons expressing the Densin-180 mutants L65S, N94S and L296P mutants exhibited significant differences from the WT at individual distances from the soma (*, significantly different from WT, $p<0.05$; two way ANOVA, followed by Dunnett's multiple comparisons test; n=5). Comparing the total mean number of intersections over all circles, only the N94S variant differs from WT (****, $p<0.0001$; two

way ANOVA, followed by Dunnett's multiple comparisons test). Source data are provided as a Source Data file.

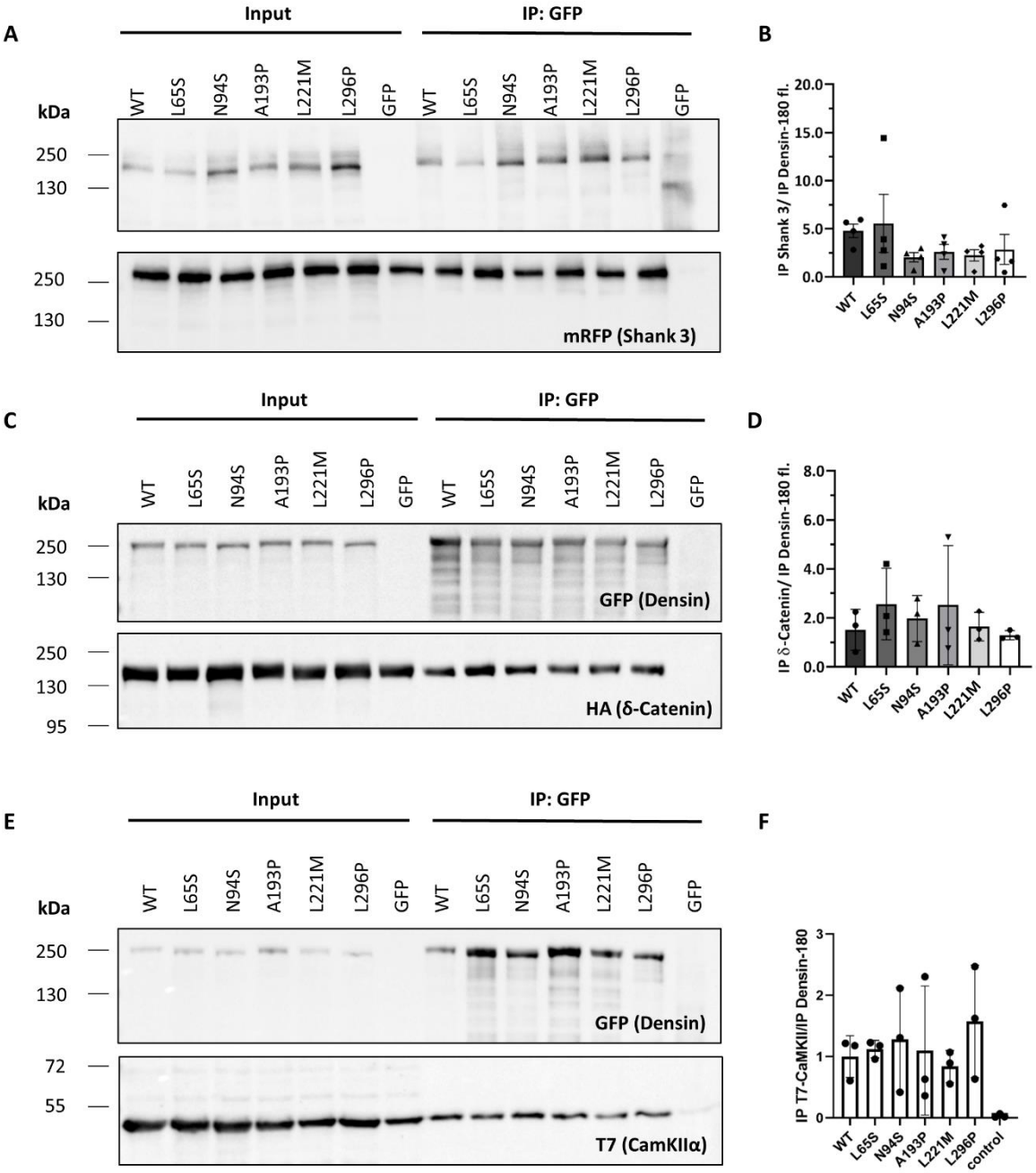



**Supplementary Figure 5. Colocalization analysis of GFP-Densin-180 and Shank3.** Dendritic segments of neurons expressing GFP-tagged Lrrc7 WT or variants were analysed for colocalization of the expressed GFP-tagged protein with the endogenous Shank3. Shown is the Pearson correlation coefficient for 15 neurons (three dendritic segments analysed per neuron) from three different preparations. ***, significantly different from WT, $p<0.001$, one-way ANOWA, followed by Dunnett's multiple comparisons test. Data are shown as mean +/- SD. Source data are provided as a Source Data file.

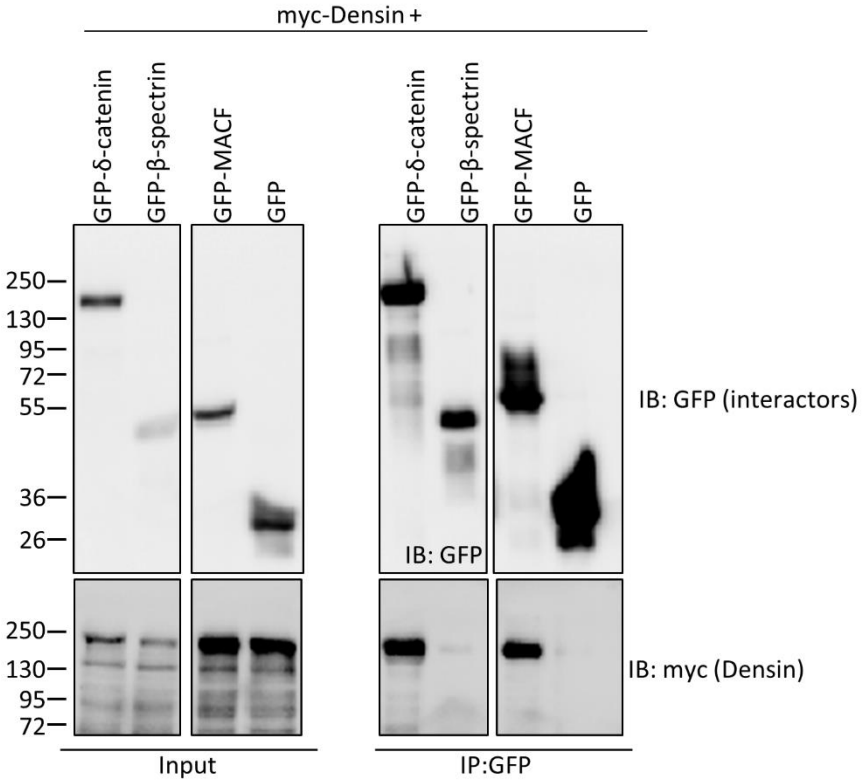



**Supplementary Figure 6. Postsynaptic clusters along dendrites.** A. Clusters of the Shank3 protein were counted along dendritic segments of neurons expressing WT or variant forms of GFP-tagged Densin-180. For each condition, 15 neurons from three different preparations (three dendritic segments per neuron) were analysed. B-D. Neurons expressing GFP-Densin-180 WT or L65S variant were immunostained for MAP (dendritic marker), Shank3 (postsynaptic) and vGlut (presynaptic). vGlut and Shank3 positive clusters were determined along dendritic segments (n=5 neurons from

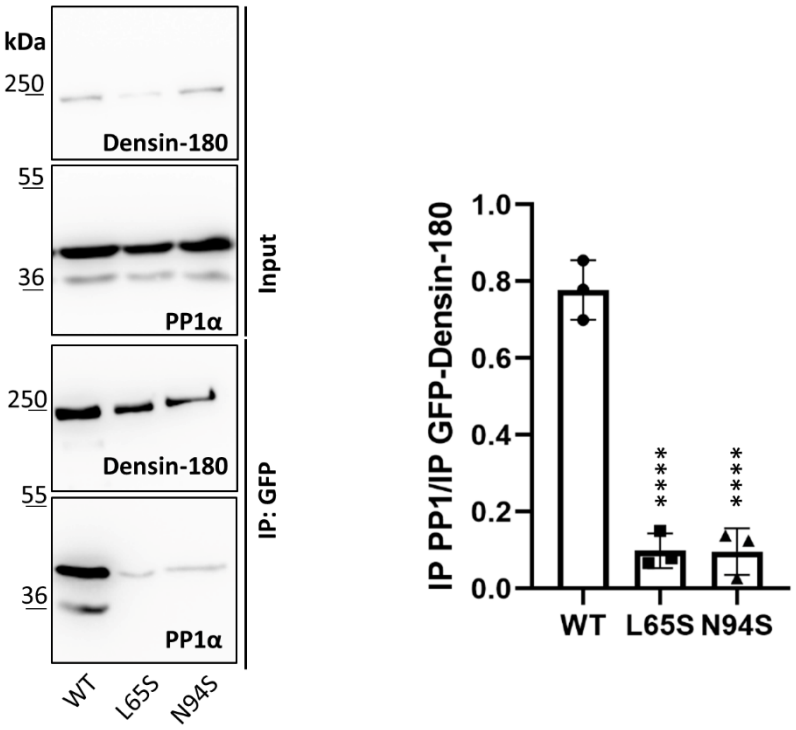
three different preparations). Scale bars: 20 µm (overview pictures), 5 µm (enlargements). Data are shown as mean +/- SD. Source data are provided as a Source Data file.



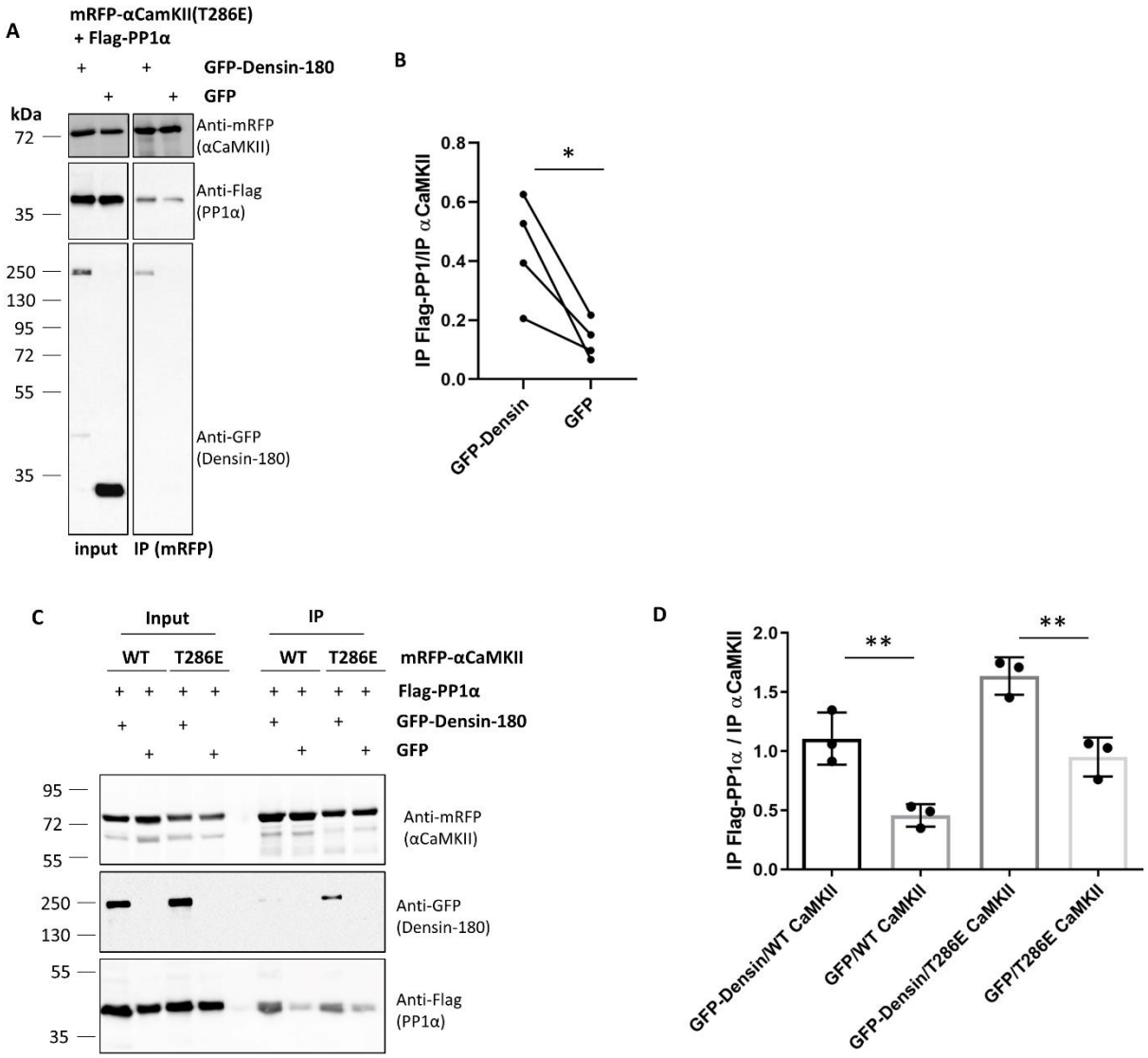

**Supplementary Figure 7. Missense variants in the LRR domain do not affect binding of Densin-180 to Shank3, δ-catenin and CaMKIIα.** 293T cells were transfected with plasmids coding for GFP-tagged variants of Densin-180 in combination with Shank3 (A,B), δ-catenin (C,D) or T7-tagged CaMKIIα (E,F). GFP-tagged proteins were immunoprecipitated (IP) from cell lysates, and input and IP samples were analysed by Western blotting. Panels B,D, and F show quantitative analyses of the blot data. No significant differences were detected between WT and mutants, using one-way ANOVA. Data are shown as mean +/- SD. Source data are provided as a Source Data file.



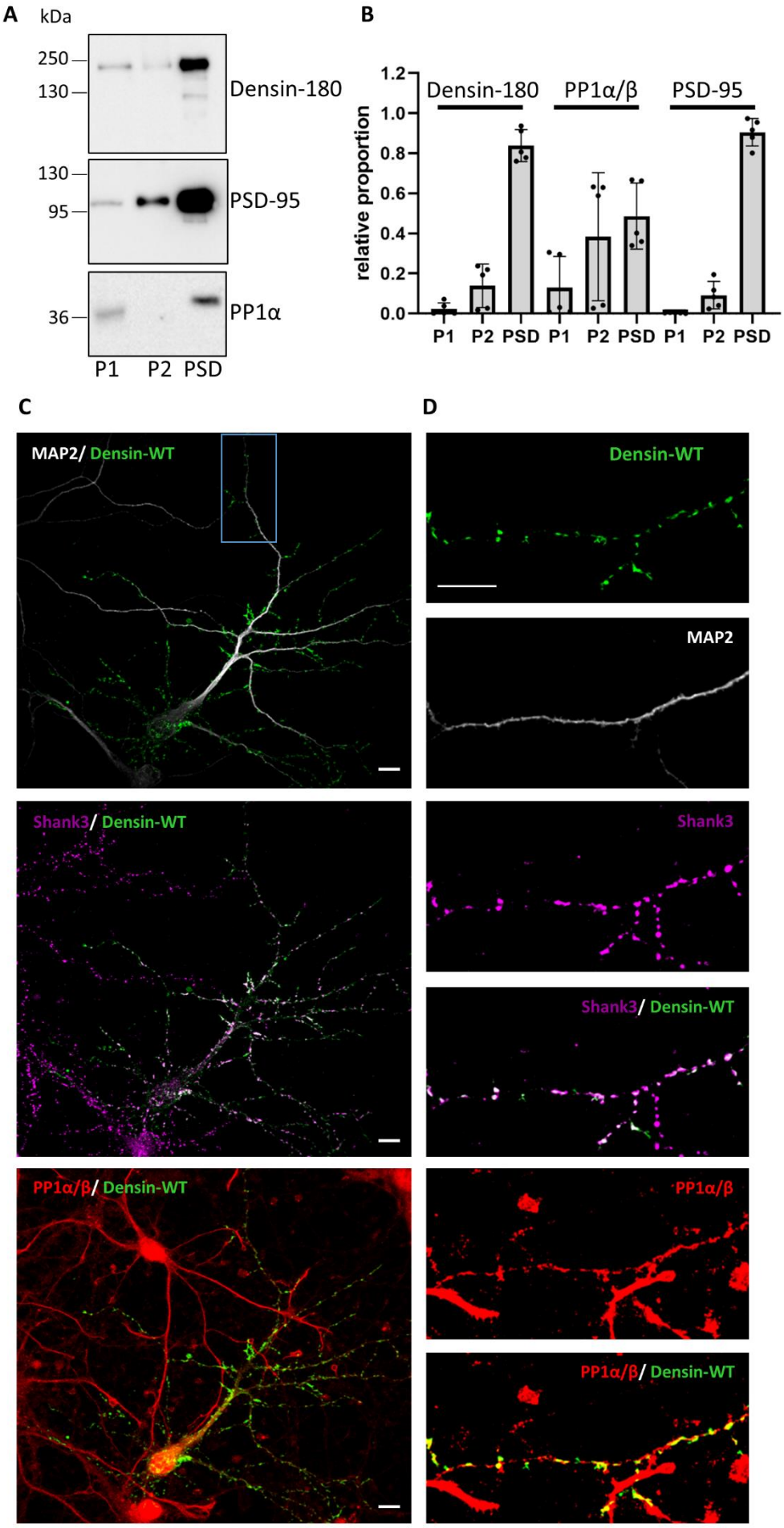

**Supplementary Figure 8. Screening of putative interaction partners of the Densin-180 LRR domain.** Putative interaction partners of the Densin-180 LRR domain obtained in the yeast two hybrid screen were coexpressed as GFP-tagged proteins with full length myc-tagged Densin-180 in 293T cells to verify interaction by coimmunoprecipitation. GFP-tagged δ-catenin was used as the positive control. Cells were lysed in IP buffer, and GFP-tagged proteins were immunocprecipitated from cell lysates using the GFP-trap matrix. Note that in this experiment, the MACF1 protein fragment showed strong interaction with Densin-180, similar to the δ-catenin positive control. The β-spectrin fragment interacted only weakly. The insert from the MACF1 clone codes for residues 6893-7150 of human MACF1 (Uniprot entry Q9UPN3-1; including two EF-hands and the first half of the C-terminal GAR domain (growth-arrest specific 2 or Gas2-related). This experiment was performed twice with similar results. Source data are provided as a Source Data file.




**Supplementary Figure 9. LRR variants interfere with binding of full-length Densin-180 to PP1α.** 293T cells were transfected with plasmids coding for GFP-tagged Densin-180 (full length, WT, and L65S and N94S variants) and Flag-tagged PP1α. After cell lysis, GFP-tagged proteins were immunoprecipitated (IP) using the GFP-trap matrix. Input and immunoprecipitate samples were analysed by Western blot, as indicated. Note that both the Flag-tagged (upper band) as well as the endogenous (lower band) PP1 are efficiently coimmunoprecipitated with WT Densin-180, but not with the two variants tested here. Quantification of the data for the larger band is shown on the right. ****, $p<0.0001$, ANOVA followed by Dunnett's multiple comparisons test (n=3). Data are shown as mean +/- SD. Source data are provided as a Source Data file.




**Supplementary Figure 10. Formation of a complex of αCaMKII, Densin-180 and PP1α. A.** 293T cells were transfected with plasmids coding for GFP-tagged Densin-180 (WT, full length) or GFP alone in combination with mRFP-tagged αCaMKII (T286E mutant) and Flag-tagged PP1α. After cell lysis, RFP-tagged proteins were immunoprecipitated (IP) using the RFP-trap matrix. Input and immunoprecipitate samples were analysed by Western blot, as indicated. **B.** Quantification of the data shown in A. For each data point, the signal of the IP Flag-PP1α sample was normalized to the signal intensity of the IP αCaMKII sample. Data points in four independent biological repeats were set into relation to each other, showing that in each experiment a more than twofold increase was observed upon coexpression of Densin-180. *, $p<0.05$, paired t-test. **C,D.** Experiments as described in A were repeated, with the inclusion of WT αCaMKII. Note that the amount of Densin-180 coprecipitated with the T286E αCaMKII variant is much higher than with the WT, where the coprecipitated Densin-180 is hardly detectable at short exposures. This is in agreement with the observation that the central binding site in Densin-180 is specific for the active kinase variant. Nevertheless, a significant increase in coprecipitation of PP1α can be observed for both variants, suggesting that the C-terminal binding site is more relevant for the scaffolding function of Densin-180 in this experiment. **, significantly different, $p<0.01$, ANOVA, followed by Sidak's multiple comparisons test. Data are shown as mean +/- SD. Source data are provided as a Source Data file.


A
kDa
250
130
Densin-180
130
95
PSD-95
36
PP1α
P1
P2
PSD
B
Densin-180
PP1α/β
PSD-95
relative proportion
1.2
1.0
0.8
0.6
0.4
0.2
0.0
P1
P2
PSD
P1
P2
PSD
P1
P2
PSD
C
D
MAP2/ Densin-WT
Densin-WT
MAP2
Shank3/ Densin-WT
Shank3
Shank3/ Densin-WT
PP1α/β/ Densin-WT
PP1α/β
PP1α/β/ Densin-WT

**Supplementary Figure 11. Densin-180 and PP1α are present at postsynaptic sites**. **A.** The postsynaptic density (PSD) fraction was prepared from mouse cortex using a series of centrifugation and sucrose gradient/ultracentrifugation steps. P1 and P2 refer to intermediate stages of the purification (P1, postnuclear supernatant; P2, complete membrane pellet). Equal amounts of protein were loaded and analysed by Western blotting using antibodies against Densin-180, the postsynaptic marker PSD-95 and PP1α/PP1β. **B.** Proportional signal intensity is plotted for five independent experiments. While PSD-95 and Densin-180 are highly enriched in the PSD fraction, PP1α/β is enriched but shows a more broad distribution, in keeping with the multiple functions exerted by this protein. Data are shown as mean +/- SD. **C.** Primary cultured hippocampal neurons were transfected with a plasmid coding for Lrrc7 WT. Neurons were costained with antibodies for Shank3 (postsynaptic marker), MAP2 (dendrite marker) and PP1α/β. **D.** Enlargment of a dendritic segment shown in C. Bars, 10 µm. Source data are provided as a Source Data file.

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