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Supplemental information

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ROLE OF CAMK2D IN NEURODEVELOPMENT AND ASSOCIATED CONDITIONS

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Supplemental tables, methods and figures

Table S1. Primers used to isolate *CAMK2D*^{WT} from the human brain cDNA and tag it with AscI and PacI (restriction sites are indicated in capitals).

Location	Tag	Primers 5' >3'
5'	AscI	FW 5' – gaatCCGGCGCGCCaccatggcttcgaccacaacctg
3'	PacI	RV 5' – ggattcTTAATTAAttacttgatgggtactgttg

Table S2. Primers used during mutagenesis

Amino acid change	Nucleotide change	Primers 5' > 3'
p.Ser79Asn	c.236G>A	FW 5' – TATTGTGCGACTTCATGATAACATATCAGAAGAGGGCTTTC RV 5' – GAAAGCCCTCTTCTGATATGTTATCATGAAGTCGCACAATA
p.Pro139Leu	c.416C>T	FW 5' – TTCACAGGGACCTGAAGCTTGAGAATTTGCTTTTAGC RV 5' – GCTAAAAGCAAATTCTCAAGCTTCAGGTCCCTGTGAA
p.Gly210Arg	c.628G>A	FW 5' – CTCTATATTCTACTTGTGAGGTATCCACCCTTCTGGG RV 5' – CCCAGAAGGGTGGATACCTCACAAGTAGAATATAGAG
p.Gln274Pro	c.821A>C	FW 5' – CACCCATGGATCTGTCCACGTTCTACTGTTGCT RV 5' – AGCAACAGTAGAACGTGGACAGATCCATGGGTG
p.Arg275His	c. 824G>A	FW 5' – CCCATGGATCTGTCAACATTCTACTGTTGCTTCCA RV 5' – TGGAAGCAACAGTAGAATGTTGACAGATCCATGGG
p.Leu291Phe	c. 872G>T	FW 5' – GGAGACTGTGGAGTGTTGGCGCAAGTTCAATGCCC RV 5' – GGGCATTGAACTTGCGCCAACACTCCACAGTCTCC

Clinical synopsis of the patients

Individual #1 is the first child of healthy, non-consanguineous parents of Belgian ancestry. Family history shows relative macrocephaly in the mother (59 cm; +2,2 SD) and a paternal cousin of the mother with autism spectrum disorder. She was born after an uneventful pregnancy at 39 6/7 GW; the delivery was with vacuum extraction. Meconial amniotic fluid was noted. She didn't cry immediately, but recovered quickly. Her birth weight was 3750 gram, her height 51 cm. Her motor developmental milestones were delayed; she could sit at 8-9 months, she didn't crawl and started to walk unsupported at 23 months.

Her speech development was normal. She started primary school in regular education. She switched to special education, focused on her motor disability. She developed epilepsy at the age of 5,5 years, for which she is treated with Depakine. Clinically, the seizures are well-controlled; a 24 hour-EEG however still shows frequent epileptic activity. Her concentration skills, as well as motor skills appeared more impaired after the start of seizures. She started to fall frequently. A diagnosis of atactic dystonia was made. Fine motor skills are better than gross motor skills. Parents report a stagnation of her development.

Social emotional-development was abnormal; she was overly sociable to strangers, while she preferred playing alone at school. At the age of 11 years, she was diagnosed with autism spectrum disorder.

She has an obsession with food; she eats a lot and keeps asking for food. She displays no food-seeking behavior. She wears glasses because of myopia and astigmatism. Hearing tests were normal. Her sleeping pattern is normal. At the age of 11 years, multidisciplinary developmental testing showed a tIQ of 52 with a disharmonic profile with better performance in verbal comprehension and decreased performance in reasoning skills. Her verbal skills were tested at the level of 7 y and 11 months, with better expressive language compared to comprehension of language. Motor evaluation confirmed a atactic-dystonic pattern.

Clinical examination at 11.5 years showed a height of 161,9 cm (+1.69 SD), a weight of 48,85 kg (+0.91 SD) and a head circumference of 59.1 cm (+3.4 SD). Dysmorphic features comprised of a long face with high forehead, an upsweep in the frontal hair line with a local spot of frizzly hair, irregular dental implantation, small and low-set ears, long fingers and hypo- and hyperpigmentations on the forehead, upper part of the thorax and backside of the neck. A right-convex scoliosis was seen. Neurological evaluation showed asymmetry of the mouth when laughing, a broad-based gait, bilateral pes cavus, a mild tremor and dysmetria of the hands at coordination tests, impaired balance and normal reflexes. Brain MRI at the age of 8 years showed symmetric mild ventricular dilatation and periventricular white matter abnormalities.

Individual #2 is now a 7-year-old female who was born at 37 weeks gestational age via vaginal delivery after an uncomplicated pregnancy. Birth weight was 5 lb 7 oz. There was no family history of cardiomyopathy. No consanguinity. She was admitted to the hospital at 3 months of age due to respiratory distress and cardiomegaly on chest x-ray, and ultimately diagnosed with dilated cardiomyopathy with severely reduced function, and suspected non-compaction. Genetics consulted and testing for chromosomal abnormalities, dilated cardiomyopathy panel, and biochemical studies (organic acids, acylcarnitine profile, and plasma amino acids) was non-diagnostic. Physical examination was remarkable for dysmorphic facial features including midface hypoplasia, hypotonic mouth, frontal bossing, and deeply set eyes. Her exam was also significant for hypotonia. No history of seizures. Cardiac transplant was required at 6 months of age due to persistent poor cardiac function. Following her heart transplant, she had several infections and neutropenia for which she was placed on a single agent (tacrolimus) for her immunosuppression regimen. She has done well from cardiovascular perspective without signs and symptoms suggestive of high-grade allograft rejection.

Brain MRI at 10 months of age showed mild prominence of subarachnoid spaces lateral and third ventricle. Development was delayed. She sat around 7 months of age and began walking at 35 months. She was diagnosed with autism at 3.5 years of age. She receives developmental therapies and communicates in short phrases.

The patient required GJ tube feedings in infancy, and she had episodes of intermittent short segment small bowel-small bowel intussusceptions distal to the feeding tube. Currently, the tube is only

used for medications and supplemental nutrition during illness. Her growth parameters have been largely normal post -infancy, with height and weight at 5-10th and 10-25th centile, respectively. Her most recent head circumference at age 4 y 10 months was 49.5 cm (25th centile).

Exome trio study was performed at age 2 years and this revealed a de novo variant in *CAMK2D* (c.236G>A; p.Ser79Asn). Cardiac explant pathology was notable for left ventricular hypertrophy and chamber dilation, non-compaction (coarse trabeculation and endocardial fibroelastosis, smaller than usual pulmonary and aortic outflow valve circumferences, and non-uniform mitral valve free edge edema and thickening. The right ventricle was normal in size. The myocardium was generally well-ordered with mild biventricular myo-cytolytic changes and myocardial hypertrophy much more prominent in left than right ventricle.

Individual #3 is a 4 year 9-month-old boy of Ethiopian descent with global severe developmental delay who has been known to the genetics clinic since late pregnancy. His mother, 27 years old G3P1 had an uneventful pregnancy until she developed cholestasis of pregnancy at 35 weeks GA, secondary to maternal hepatitis B infection. An anatomical ultrasound was reported as normal and repeated at the time of maternal disease diagnosis. The fetal heart was abnormally enlarged, and a suspicion of transposition of the great arteries was suspected; pericardial effusion was noted. The fetal growth was estimated to be at 50th-75th%, and the biophysical profile was 6/8. A fetal echo showed biventricular cardiomyopathy, dilated RV and LV, with moderately reduced systolic function.
Myocardium appeared thickened, and ventricles globular. Abnormal filling
with monophasic inflow, both LV and RV, and increased A-wave reversal in IVC
and ductus venosus were noticed. There was moderate MR and TR, with a peak gradient of MR 45
mmHg, and TR 45 mmHg. In a follow up US, there was oligohydramnios, umbilical artery
Dopplers were reassuring, MCA Dopplers showed redistribution, and DV Dopplers showed
reversal of the A-wave. A fetal MRI confirmed cardiomegaly with no additional findings. A postnatal plan was created with immediate access to ECMO and PCICU, and the mother was delivered by C/S at 36 weeks GA. Neonatal diagnosis was dilated cardiomyopathy with biventricular noncompaction, and the baby was listed for cardiac transplant. A VAD implantation, followed by ABO incompatible heart transplantation took place at 3 weeks of age, followed by repair of ascending aorta and dilatation of the superior vena cava stenosis. Post surgery he developed chylothorax, and clot in the lower left extremity. A medical genetics consult was done at day 1 of life, but limited given the ICU admission; however, a microarray and WES trio were ordered. The CMA was reported as normal and WES as negative; *CAMK2D* was mentioned as a candidate gene, and a Genematcher submission and connection followed. Mitochondrial DNA analysis on cardiac tissue found a variant m.12880T>C (MT-ND5, p.Phe182Leu) with 16% heteroplasmy. More investigations revealed urine and buccal heteroplasmy of 19%. The same mitochondrial variant is present in an asymptomatic, maternally-related family member at a heteroplasmy level of 28%. CoQ was trialed for a while and discontinued as no improvement was noticed. Post-transplant he was followed closely, and hypotonia, distinctive facial features (not ethnic) and global developmental delay became gradually evident. Proximal renal tubulopathy resolved in the first few months of life, but mild proteinuria has persisted over time; he had recurrent respiratory infections, showed GI intolerance (had a G-tube), and failure to thrive. Global developmental delay was clear by 1 year of age when he was not able to sit independently, smiled occasionally, babbled, and cooed, but was difficult to engage. Growth parameters were at 5th % for weight, 19th % for length, and 54th % for head circumference. By 4 years 7 month his disproportionate growth showed: weight at the 40th %, height at the 2nd %, and head circumference at the 74th%. He continued to have hypotonia, and frequent URTIs that enhance his chronic vomiting (containing mucus, not feeds). He has continued to be stable from the cardiac standpoint; is able to cruise the furniture, crawl up the stairs, and is nonverbal, but makes lots of sounds. He is completely G-tube dependent for his feeds and has oral aversion. He helps with dressing, has good vision and hearing, recognizes his name and follows limited one-step commands. He appears distinctive with prominent forehead, deep-set eyes, and midface hypoplasia.

Individual #4 is now a 6 year old male who was initially referred for genetic evaluation at age 6 months due to hypotonia. Pregnancy was full term without complications, and patient was admitted to neonatal

intensive care for 5 days after birth due to maternal fever, tachypnea and apnea-like episodes. He had macrocephaly and hypotonia at birth. He began having subclinical seizures which were noted on electroencephalogram, and he was diagnosed with central hypothyroidism. Whole exome sequencing was performed which identified a variant of uncertain significance in *CAMK2D*, but compound heterozygous variants in another gene were thought to be a more likely explanation. Subsequent analysis of those variants has shown they are not causative for his findings, and that *CAMK2D* is his diagnosis. Additional clinical findings include cortical visual impairment, constipation, gastroesophageal reflux necessitating gastrostomy tube, mild sleep apnea, and brain MRI showed enlarged ventricles and thin corpus callosum. Physical examination notable for coarse facial features, large head, and low-set ears.

Individual #5 is a now young adult female who presented with multiple congenital anomalies and neurodevelopmental disorder. She has a history of congenital heart disease including a large ventricular septal defect and coarctation of aorta requiring multiple surgeries, as well as dilated cardiomyopathy with heart failure. In terms of neurodevelopment, she has profound intellectual disability and is essentially nonverbal. She has behavioral abnormalities including irritability, anxiety, and autistic features. From a neurologic standpoint, she has a history of cerebral palsy with mixed hypotonia and hypertonia, as well as epilepsy. A brain MRI was abnormal, demonstrating diffusely decreased brain volume and prominent CSF spaces. She has a history of GI abnormalities including Chilaiditi syndrome, eosinophilic esophagitis, and dysphagia which necessitated enteral nutrition. She has skeletal abnormalities including kyphoscoliosis, clinodactyly, and bilateral hallux valgus. She additionally has been noted to have strabismus, microcephaly, short stature, and dysmorphic features including midface hypoplasia with prognathism, facial asymmetry, epicanthus inversus, and downslanting palpebral fissures. She has a history of atopy including severe allergies, asthma, and eczema.

Individual #6 was initially evaluated in pediatric genetics clinic at age 10 years, after coming to attention due to his father and brother's diagnoses of dilated cardiomyopathy requiring heart transplant; his father was deceased at the time of the genetic evaluation and his brother was stable. Cardiac workup for this patient revealed dilated cardiomyopathy as well as an atrial septal defect and partial anomalous venous return (PAPVR). Review of his neurodevelopmental history was notable for developmental delays, learning disabilities, behavioral differences including ADHD, trichotillomania and repetitive behaviors. He had received early intervention services with continued serviced into school age with special education. This patient's physical exam was notable for the following: craniosynostosis that was repaired in infancy; wide, prominent forehead; alopecia secondary to trichotillomania; midface hypoplasia; hypertelorism; bulbous nose; short fourth and fifth metacarpal; and disproportionate growth including acromelic shortening.

Individual #7 was initially evaluated in pediatric genetics clinic at age 16 years, after coming to attention due to her father and brother's diagnoses of dilated cardiomyopathy requiring heart transplant; her father was deceased at the time of the genetic evaluation and her brother was stable. She was subsequently evaluated and also diagnosed with dilated cardiomyopathy at the age of 15 years. Upon genetic evaluation, additional history was reviewed and included findings of disproportionate short stature, atrial septal defect (repaired), dysmorphic facial features, myopia, developmental delay and intellectual disabilities. She attended school within a special education program in a 12:1:1 classroom. Upon exam, notable physical findings included the following: disproportionate short stature with acromelic shortening; wide, prominent forehead; midface hypoplasia; hypertelorism; bulbous nose with depressed/flat nasal bridge; short philtrum; and brachydactyly.

Individual #8 was the second child to non-consanguineous parents, delivered at 39 weeks following induction of labor for reduced fetal movements, with a birth weight was 3.6kg. He was admitted to the special care nursery for observation for 5 hours after delivery and was subsequently discharged home on day 3 of life. At 3 weeks of age he presented to the emergency department with poor feeding, vomiting and respiratory distress. He was diagnosed with dilated cardiomyopathy on echocardiogram and was transferred to the pediatric intensive care unit for further management. His condition deteriorated and he

required intubation and ionotropic support. Clinical trio genome sequencing was performed as part of the Acute Care Genomics study (Victorian Clinical Genetics Services, Australia; PMID 37291213) and identified a *de novo* missense variant, NM_001321569.1:c.873G>C, NP_001308498.1:p.Leu291Phe. He died at 8 weeks of age at home after his parents elected for palliative care.

GestaltMatcher analysis

We performed the GestaltMatcher approach (Hsieh et al. 2022; Hustinx et al. 2023) to analyze the facial similarities among the 15 individuals with *CAMK2A* (four images), *CAMK2B* (five images), *CAMK2D* (ten images), and *CAMK2G* (four images) who consented to the facial analysis (Supplementary Table 3). In addition to the *CAMK2D* individuals recruited in this study, we collected the facial photos from two publications of *CAMK2A* and *CAMK2B* (Küry et al. 2017) and *CAMK2G* (Proietti Onori et al. 2018), and one unpublished *CAMK2A* patient. With model ensemble and test-time augmentation, we encoded each image into 12 512-dimensional vectors, and the average of 12 cosine distances between two images quantified the facial phenotypic similarity between two images. When the distance is smaller, two images show higher facial phenotypic similarity, which means they are close in the phenotype space. We first performed the cohort-level analysis to validate whether the individuals of *CAMK2D* are similar to each other and similar to the other three genes. We further analyzed the similarities on the individual level.

Facial similarity of *CAMK2D*. To validate the similarities of *CAMK2D* individuals, we first calculated their mean pairwise distance and random sampled 100 times. Individuals 4 and 5 have multiple images, so we make sure the images from the individual will not be sampled together to avoid bias. The distribution is shown in Figure S1A (orange). We compared the distribution to two distributions (same and random) built from the 1,555 images from different subjects with 328 syndromes from GestaltMatcher Database (GMDB) (Lesmann et al. 2023). For each of the 328 syndromes, we randomly selected a sub-cohort and calculated the mean pairwise distance 100 times to build the "same" distribution (in blue color in Figure S1A). We further built the "random" distribution (distribution in red color in Figure S1A) by randomly sampling a sub-cohort (not limit them within the same syndrome) and calculating their mean pairwise distance 100 times. We performed a five-fold cross-validation on Receiver Operating Characteristic (ROC) analysis to obtain the threshold for distinguishing the same and random distributions. The threshold c was chosen by the highest Youden index, resulting in c=0.909, corresponding to a sensitivity of 0.862 and a specificity of 0.792. When more than 50% of the cohort's distribution is below the threshold, we classify it as having a similar facial phenotype. Ultimately, 63% of *CAMK2D* distribution was below the threshold, indicating a moderate facial gestalt presenting in *CAMK2D* individuals (Figure S1A).

Facial similarity among *CAMK2D*, *CAMK2A*, *CAMK2B*, and *CAMK2G*. We investigated the similarities between the individuals with two different disease-causing genes. We built two control distributions, the "same" and "different." The "same" distribution was built by sampling the individuals with "the same disorder" into two groups, and we calculated the mean pairwise distance between the individuals of these two groups (blue distribution in Figure S1B, C, and D). The "different" distribution was built by sampling two groups from two different disorders (red distribution in Figure S1B, C, and D). The threshold c=0.896 with a sensitivity of 0.903 and a specificity of 0.802 was obtained by the five-fold cross-validation of ROC analysis. When more than 50% of the distribution of two disorders is above the threshold, we classify them as not having similar facial phenotypes. On the other hand, when there is more than 50% of the distribution below the threshold, we classify them as having a similar facial phenotype. In Figure S1B, C, and D), when comparing to *CAMK2D*, the distributions of all the other three genes were more than 50% above the threshold (*CAMK2A*: 92.4%, *CAMK2B*: 98.9%, and *CAMK2G*: 97.8%).

We further investigated the facial similarities on the individual level by the pairwise comparison analysis. We compared 23 images of 15 individuals with *CAMK2D, CAMK2A, CAMK2B, and CAMK2G* to 7,459 images with 449 different disorders from GMDB by performing the leave-one-out cross-validation to simulate the real-world scenario. For example, by testing the image of Ind 5-4, we put the remaining 22 images in the space with the other 7,459 images and calculated the ranks of 22 images to Ind 5-4. With this analysis, we could visualize the similarity of each pair of individuals compared to the control cohort. Figure S2 shows that Ind 4-1 was at the 48th closest position to Ind 5-4. Moreover, G2-1 was in the 31st position to Ind 4-1, and A-1 was in the 13th position to Ind 5-6.

Therefore, with all the results, although the facial phenotype of *CAMK2D* was not similar to *CAMK2A*, *CAMK2B*, and *CAMK2G* on the cohort level analysis, some pairs of individuals still showed a high degree of similarity, such as (Ind 4-1 and G-1) and (Ind 5-6, A-1). In addition, the four individuals of *CAMK2D* showed a moderate degree of facial similarity. However, more images from different individuals might be required in the future for the comprehensive analysis of a larger cohort.

Table S3. The cohort in GestaltMatcher analysis. GMDB patient ID and photo ID can be used to visualize the photo in GMDB. The label is the ID used in Figure S2. The labels of the CAMK2D images are the same as those in Figure 2H.

GMDB Patient ID	GMDB Photo ID	Label	Gene	Variant	PMID or source
3202	4415	A1	CAMK2A	p.(Glu109Asp)	29100089
3203	4417	A2	CAMK2A	p.(Pro212Leu)	29100089
3204	4419	A3	CAMK2A	p.(Pro235Leu)	29100089
7277	11641	A4	CAMK2A	p.(Gly301Glu)	Unpublished
3205	4420	B1	CAMK2B	p.(Arg29*)	29100089
3206	4426	B2	CAMK2B	p.(Glu110Lys)	29100089
3207	4428	B3	CAMK2B	p.(Pro139Leu)	29100089
3208	4431	B4	CAMK2B	p.?	29100089
3209	4438	B5	CAMK2B	p.Lys301Glu	29100089
6686	10342	Ind 1	CAMK2D	p.?	This paper
9686	15622	Ind 2	CAMK2D	p.(Ser79Asn)	This paper
9550	15189	Ind 4-1	CAMK2D	p.(Gly210Arg)	This paper
9550	15190	Ind 4-2	CAMK2D	p.(Gly210Arg)	This paper
6685	10325	Ind 5-1	CAMK2D	p.(Gln274Pro)	This paper
6685	10327	Ind 5-2	CAMK2D	p.(Gln274Pro)	This paper
6685	10332	Ind 5-3	CAMK2D	p.(Gln274Pro)	This paper
6685	10330	Ind 5-4	CAMK2D	p.(Gln274Pro)	This paper
6685	10335	Ind 5-5	CAMK2D	p.(Gln274Pro)	This paper
6685	10336	Ind 5-6	CAMK2D	p.(Gln274Pro)	This paper
3210	4445	G1-1	CAMK2G	p.(Arg292Pro)	30184290
3210	4446	G1-2	CAMK2G	p.(Arg292Pro)	30184290

9663	15490	G2-1	CAMK2G	p.(Arg292Pro)	30184290
9663	15492	G2-2	CAMK2G	p.(Arg292Pro)	30184290

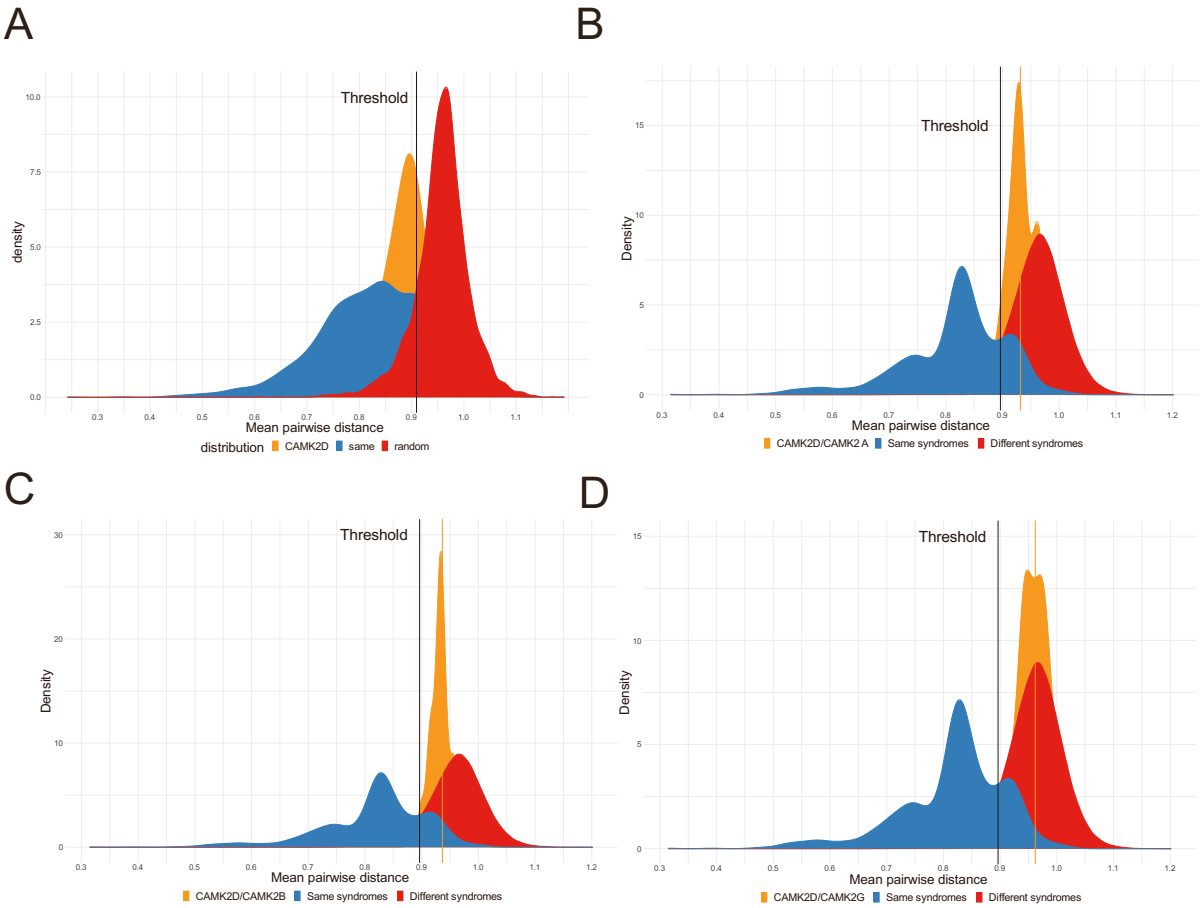

Figure S1. A) The distribution of mean pairwise distance. It shows three distributions: *CAMK2D* (orange), the random selection from the subjects with 328 disorders (red), and the selection with the same disorder (blue). The black vertical line is the threshold that classifies whether it is the same disorder or random selection. 63% of *CAMK2D* distribution are below the threshold; B) The mean pairwise distance distribution when comparing two groups: sampling from *CAMK2D and CAMK2A* (orange), sampling with the same disorder (blue), and sampling from two different disorders (red); C) orange distribution is sampled from *CAMK2D and CAMK2B*; D) orange distribution is sampled from *CAMK2D and CAMK2G*.

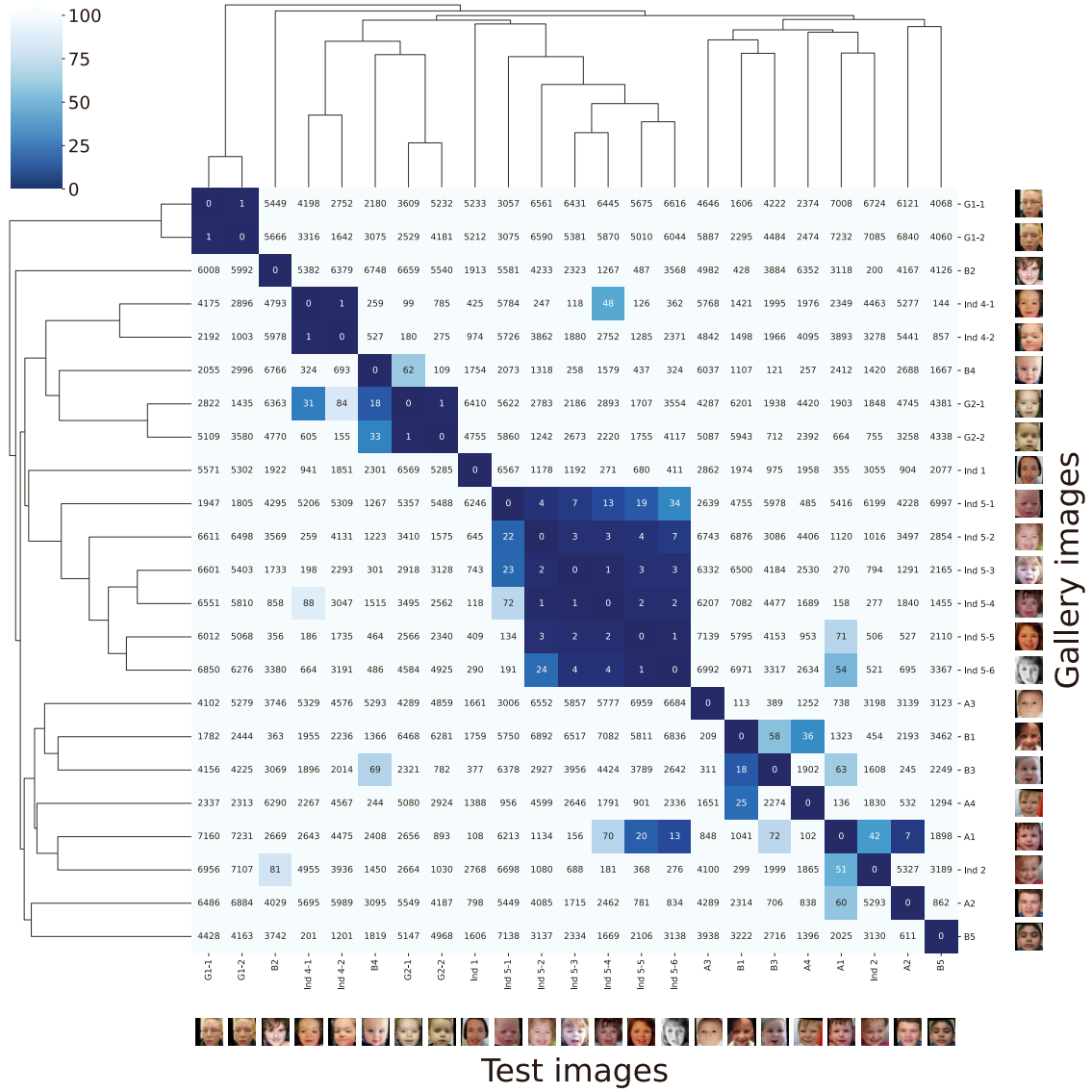

Figure S2. The pairwise rank matrix and hierarchical clustering of 23 images of 15 individuals with *CAMK2A, CAMK2B, CAMK2D* and *CAMK2G*. Each column is the result of testing one subject in the column and listing the rank of the rest of the 21 images in each row. For example, by testing Ind 5-4, Ind 4-1 was on the 48th rank, and G2-1 was on the 31st rank of Ind 4-1.

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