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Novel COL4A2 mutation causing familial malformations of cortical development

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Abstract. – OBJECTIVE: This article aimed to describe a novel COL4A2 mutation and the phenotypic features of two family members presenting with epilepsy and cortical development malformations.

PATIENTS AND METHODS: The first patient is a 65-year-old woman with hematuria and adult-onset seizures. Brain MRI showed closed lip schizencephaly of right lateral sulcus associated with polymicrogyria of the surrounding cortex and areas of subcortical heterotopia. The second patient is a 40-year-old man, her son. He was born post-term with neonatal distress and psychomotor developmental delay with congenital left leg paresis and strabismus, as well as childhood-onset focal motor seizures. Brain MRI showed a right nucleus-capsular porencephalic cavitation with enlargement of the homolateral ventricle and a focal right occipital cortico-subcortical encephalomalacia. A small heterotopic band was also present in the frontal left subcortical region.

RESULTS: We tested both patients with a NGS panel for genetic epilepsies, which evidenced a missense mutation in *COL4A2* gene (c.2972G>A, causing the aminoacidic substitution Gly991Glu).

CONCLUSIONS: The phenotypic spectrum associated with COL4A2 mutations has not been extensively described in the literature. Testing for *COL4A* mutations is indicated in patients with malformations of cortical development, particularly in the presence of familial conditions, even in the absence of porencephaly or early hemorrhagic strokes.

Key Words:
Collagen 4a, Schizencephaly, Heterotopia, Malformations of cortical development

Introduction

Collagen 4 (COL4) protein is an abundant component of basement membranes, including those of the cerebral vessels. This protein consists of three heterotrimers (α1α1α2, α3α4α5, and α5α5α6) and is responsible for the strength and integrity of the membrane[1]. *COL4A1* and *COL4A2* genes, which are under the regulation of the same promoter, encode for the subchains α1 (*COL4A1*) and α2 (*COL4A2*). The heterotrimeric complexes are secreted in the extracellular matrix, forming a network providing the biomechanical stability of the basement membranes[2].

Families with autosomal dominant porencephaly and linkage to chromosome 13q34 were first described in 2004[3,4]. Subsequently, the observation of *Col4a1*-mutated mice with porencephaly due to early disruption of the vascular basement membrane[5] led to the identification of *COL4A1* mutation as a cause of this condition. Since the *COL4A2* gene bears a common function to *COL4A1*, it was hypothesized that a mutation in *COL4A2* may cause similar manifestations. An animal model of *Col4a2* mutation showing eye, brain and kidney abnormalities was described in 2007[6]. The first patients bearing *COL4A2* mutations were identified soon after[7]. Over the years, the spectrum of *COL4A1* and *COL4A2* mutations related disorders has broadened. At present, it includes other cerebrovascular lesions and malformation diseases (disorders of cortical development, i.e., hydranencephaly, schizencephaly) as well as lesions in various organs, including the kidneys, eyes, heart, and skeletal muscles[8].

The pathogenic mechanism causing cerebral damage in both *COL4A1* and *COL4A2* mutations is most often a germinal matrix hemorrhage leading to deep venous infarction with tissue necrosis and porencephalic cavitations. These disturbances may arise during late pregnancy[9], during delivery or soon after birth[3,9]. *COL4A2* mutations associated with malformations of cor-

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tical development have also been described[8], but the phenotypic spectrum and the pathogenesis are not completely clear.

We report the case of two related patients (mother and son) with a novel *COL4A2* mutation and unusual phenotype, including porencephaly and multiple cortical malformations. We have also performed a review of the existing literature on patients with *COL4A* mutations, selecting reports with adequate clinical and radiological data.

Patients and Methods

Patient 1

The first patient is a 67-year-old woman. Her medical history is positive for breast cancer (in remission for 20 years) and chronic microhematuria. She had two generalized tonic-clonic seizures at age 22. She started taking phenobarbital (PB) 100 mg/day with complete remission thereafter. She came to our observation at 66 years of age. Her physical and neurological examinations were unremarkable. The neuropsychological examination was normal. Electroencephalogram (EEG), recorded at age 67, was also within normal limits. Her family history was positive for chronic microhematuria (her mother and son). Magnetic Resonance Imaging (MRI) (Figure 1, Letters A-C) showed closed lip schizencephaly of the right lateral sulcus (A) associated with polymicrogyria of the surrounding cortex. Some areas of nodular heterotopia were also visible in the adjacent white matter (B), and in the left subcortical white matter (C); the anterior horn of the left lateral ventricle was dysmorphic (not shown). We

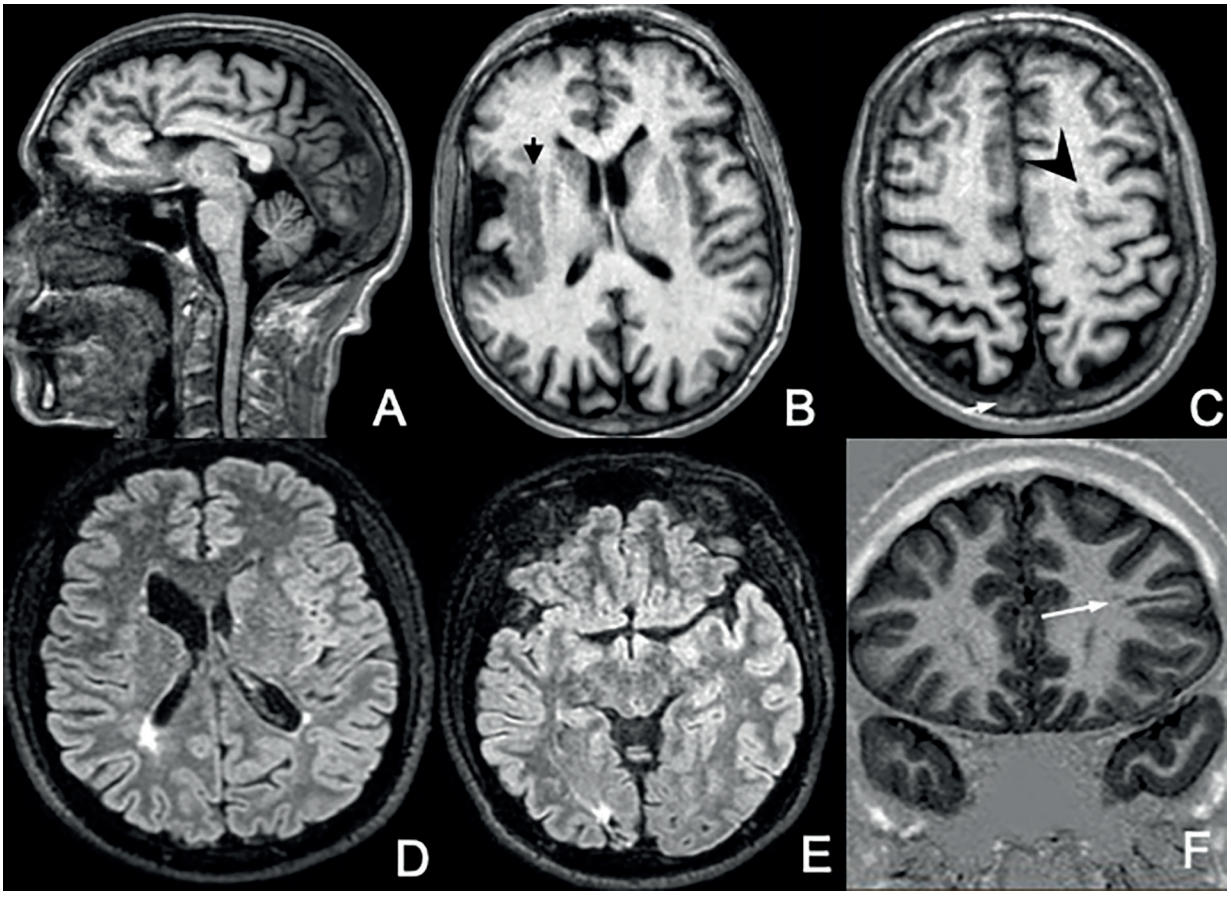

Figure 1. Magnetic resonance imaging findings of the two patients. Letters **A-C** correspond to patient 1 and letters **D-F** correspond to patient 2. **A,** Sagittal T1-weighted image showing left frontal closed-lip schizencephaly. **B,** Axial T1-weighted image showing polymicrogyria adjacent to schizencephaly and areas of nodular heterotopia in the right white matter (*black arrow*). **C,** Axial T1-weighted image showing nodular heterotopia in left subcortical white matter (*arrowhead*). **D,** Axial FLAIR image showing porencephaly with enlargement of right lateral ventricle as well as leukoaraiosis. **E,** Axial FLAIR image showing right occipital cortico-subocortical encephalomalacia. **F,** Coronal inversion recovery image showing a thin band of heterotopia (*white arrow*).

performed a Next Generation Sequencing panel for genetic epilepsies, including 221 genes (**Appendix**). The analysis evidenced a novel missense mutation in *COL4A2* gene (c.2972G>A, causing the aminoacidic substitution Gly991Glu). Two other missense mutations were also detected in the *CACNA1H* and *PIGA* genes. Echocardiogram, abdomen ultrasound, and ocular examination were within normal limits, except for low-grade myopia.

Of note, her mother, who is in her nineties and bedridden, has chronic microhematuria and hemiparesis due to a previous cerebrovascular accident. She refused to undergo genetic analysis or brain imaging.

Patient 2

The second subject is a 40-year-old man who was born at 42+3 weeks of pregnancy and underwent neonatal distress. He experienced a psychomotor developmental delay with congenital left leg paresis and strabismus. Right after birth he had two generalized tonic seizures, but no treatment was initiated. Approximately at 4 years of age he started to experience focal aware seizures, described as "seeing something yellow" followed by eye rolling and lips cyanosis. Rarely, seizures evolved into bilateral tonic-clonic. In the following years, he was treated with PB, valproic acid, carbamazepine, and clobazam in various combinations, all with suboptimal response. At age 23, when he came to our observation, he was having 1-2 focal aware seizures per month and refused any therapeutic change. Physical and neurological examination did not reveal any abnormality besides the left leg paresis and strabismus. EEG performed at age 34 showed a global slowing of background activity and frequent spike-wave complexes over the left frontotemporal region. MRI (Figure 1, letters D-F) showed a right nucleus-capsular porencephalic cavitation with enlargement of the homolateral ventricle (D) as well as a focal right occipital cortico-subcortical encephalomalacia (E). A thin band of heterotopic gray matter was also present in the frontal left subcortical region (F). Multiple hyperintense spots in the T2-fluid attenuated inversion recovery (FLAIR) sequences in the white subcortical and periventricular matter were visible (D). He underwent an echocardiogram, abdomen ultrasound, and ocular examination that were within normal limits, with the exception of high-grade myopia. The direct sequencing of the *COL4A2* gene identified the same mutation as his mother's. On the contrary, no mutations were detected in *CACNA1H* or *PIGA* genes, excluding a pathogenic significance of these mutations in his mother.

Methods

We reviewed all English-language papers published in peer-reviewed journals. We performed a PubMed search with the following keywords: "COL4"; "COL4A1"; "COL4A2". Selection criteria were novelty, importance, originality, quality, and relevance to the scope of this review. We retrieved 107 articles. Seventy-two were excluded (46 because not pertinent, 9 because they were reviews and not original articles, 17 because reporting experimental data without clinical reports). Thus, 35 articles were included in the review. Of these, 27 reported patients with COL4A1 only, 5 reported patients with COL4A2 only, and 3 reported both COL4A1 and COL4A2-mutated patients.

Results

The clinical findings in patients with COL4A1 and COL4A2 mutations reported in the literature are depicted in Table I.

Discussion

We described a family with a novel *COL4A2* missense mutation affecting two generations, causing an aminoacidic substitution Gly>Glu in the protein's collagenous domain. The pathogenic role of this mutation is supported by its segregation with the phenotype in the family herein reported. Moreover, most pathogenic mutations of *COL4A1* and *COL4A2* genes described in the literature are missense and consist of the substitution of a Gly residue in the collagenous domain[42], like the present c.2972G>A mutation.

The phenotypic spectrum of *COL4A* genes mutations is broad, and the description of new features is still ongoing. In particular, mutations in the *COL4A1* gene have been more widely described and are related to different phenotypes. The first descriptions of early-onset familial porencephaly[30,43] have been subsequently joined by many reports of different clinical pictures, not necessarily including porencephaly. In particular, the hereditary angiopathy, nephropathy, aneurysms, and muscle cramps (HANAC) syndrome[13], as well as Axenfeld-Rieger anomaly,

Table I. Review of the findings in patients with COL4A mutations reported in the literature. SVD = small vessel disease.

							Brain MRI features												Ophtalmological findings				Renal findings			Muscle abnormalities	
Paper	N. patients	Males/ Females	Asymptomatic	Seizures	Intellectual disability	Focal neurological signs	Porencephaly	Hemorrhage	SVD (leukoaraiosis)	SVD (lacunar infarct)	SVD (microbleeds)	SVD (Wirchov-Robin)	SVD (aneurysms)	Cerebral calcifications	Schizencephaly	Polymicrogyria	Dysplasia	Heterotopia	Cataract	Strabismus	Myopia	Abnormal retinal vessels	Hematuria	Proteinuria	Malformations	Raised CK	Myopathy
COL4A1 mutations																											
Gould et al[10]	6	5/1	0	0	0	0	0	2	6	0	1	6	0	0	0	0	0	0	0	0	0	6	0	0	NA	NA	NA
Breedveld et al[11]	7	3/4	0	1	1	7	7	0	6	0	0	0	0	0	0	0	0	0	NA	NA	NA	NA	NA	NA	NA	NA	NA
van der Knaap et al[12]	3	1/2	0	2	2	3	3	1	1	0	0	0	0	1	0	0	0	0	3	3	0	1	NA	NA	NA	NA	NA
Plaisier et al[13]	9	6/3	0	0	0	0	0	0	6	1	0	4	5	0	0	0	0	0	0	0	0	8	6	0	4	8	0
Sibon et al[14]	5	1/4	0	0	0	3	1	0	5	2	1	0	1	0	0	0	0	0	5	0	5	0	0	0	NA	NA	NA
Vahedi et al[15]	1	1/0	0	1	0	1	1	1	1	0	1	0	0	0	0	0	0	0	1	0	0	1	0	0	NA	NA	NA
de Vries et al[9]	2	1/1	0	0	1	1	2	2	1	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	NA	NA
Plaisier et al[16]	11	4/7	0	0	0	2	0	0	5	0	0	0	1	0	0	0	0	0	0	0	0	11	1	2	2	7	NA
Rouaud et al[17]	1	1/0	0	0	0	0	0	0	1	1	1	0	0	1	0	0	0	0	1	1	1	0	0	0	0	0	0
Shah et al[18]	2	1/1	0	0	0	2	0	1	1	0	1	0	1	0	0	0	0	0	2	0	0	0	0	0	NA	NA	NA
Livingston et al[19]	5	2/3	0	4	5	5	4	0	4	0	0	0	0	5	0	0	0	0	2	3	2	0	NA	NA	NA	5	0
Meuwissen et al[20]	4	3/1	0	2	0	1	4	3	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	1	NA	NA
Vermeulen et al[21]	2	NA	0	2	1	0	2	2	0	0	0	0	0	0	0	0	0	0	NA	NA	NA	NA	NA	NA	NA	NA	NA
Lichtenbelt et al[22]	1	NA	0	0	0	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	NA	NA
Shah et al[23]	7	4/3	0	3	3	6	3	1	6	0	1	0	0	0	0	0	0	0	5	0	4	0	0	0	1	1	NA
Tonduti et al[24]	3	2/3	2	0	0	1	0	2	3	0	0	0	0	2	1	0	0	0	3	0	0	0	1	0	2	3	0
Yoneda et al [25]	15	8/7	0	15	15	15	11	0	0	0	7	0	0	7	3	0	1	0	2	NA	NA	NA	2	0	0	6	1
Corlobe et al[26]	1	0/1	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	NA	NA
Takenouchi et al[27]	2	1/1	0	1	0	2	1	1	1	0	1	0	1	0	0	0	0	0	0	0	0	1	1	1	1	NA	NA
Decio et al[28]	2	2/0	0	1	0	1	0	0	1	0	1	0	0	0	0	0	0	0	1	0	0	0	1	0	0	2	2
Renard et al[29]	1	0/1	0	0	0	1	0	0	1	1	1	0	0	0	0	0	0	0	NA	NA	NA	NA	NA	NA	NA	NA	NA
Giorgio et al[30]	7	3/4	1	3	2	4	1	2	4	1	1	0	2	0	0	0	0	0	1	0	1	1	0	0	NA	1	NA
John et al[31]	1	0/1	0	1	0	0	0	0	1	1	1	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	NA
Meuwissen [32]	19	NA	4	9	7	9	10	4	6	2	0	0	0	2	1	0	0	0	6	0	0	1	0	0	0	1	2
Durrani-Kolarik et al[33]	1	0/1	0	0	1	0	1	1	0	0	0	0	0	0	0	0	0	0	1	0	1	0	NA	NA	NA	NA	NA
Smigiel et al[34]	1	0/1	0	1	1	0	0	0	0	0	0	0	0	1	1	0	0	0	1	0	0	0	0	0	0	NA	NA
Verdura et al[35]	18	12/6	8	0	9	10	0	0	18	16	4	0	0	0	0	0	0	0	NA	NA	NA	Na	Na	NA	NA	NA	NA
Vitale et al[36]	9	5/4	2	7	6	5	3	3	6	0	0	0	0	4	4	1	0	0	1	2	1	0	2	0	0	2	0
Zangaglia et al[8]	1	1/0	0	0	1	1	0	0	1	0	0	0	0	0	0	1	0	0	NA	NA	NA	NA	NA	NA	NA	NA	NA
Cavallin et al[37]	4	2/2	0	3	4	4	4	0	0	0	0	0	0	0	4	1	0	0	1	0	0	0	NA	NA	0	1	NA
Total	**151**	**69/62**	**17 (11%)**	**56 (37%)**	**59 (39%)**	**86 (57%)**	**59 (39%)**	**28 (18%)**	**86 (57%)**	**25 (16%)**	**22 (14%)**	**10 (7%)**	**11 (7%)**	**23 (15%)**	**14 (9%)**	**3 (2%)**	**1 (1%)**	**0**	**38 (31%)**	**11 (10%)**	**15 (14%)**	**31 (29%)**	**15 (13%)**	**4 (4%)**	**12 (13%)**	**37 (39%)**	**5 (8%)**
COL4A2 mutations																											
Verbeek et al[7]	6	2/4	3	0	3	3	3	0	2	0	0	1	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0
Yoneda et al[25]	2	2/0	0	1	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Meuwissen et al[20]	2	NA	0	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Gunda et al[38]	1	1/0	0	0	0	1	0	1	1	0	1	1	0	0	0	0	0	0	NA	NA	NA	1	0	1	0	NA	NA
Ha et al[39]	4	2/2	1	3	3	2	3	0	1	0	0	0	0	0	0	0	0	3	0	0	0	0	NA	NA	NA	NA	NA
Kollmann et al[40]	1	1/0	0	0	0	0	0	0	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
McGovern et al[41]	4	2/2	0	0	1	2	4	0	1	0	1	0	0	0	0	0	0	0	NA	NA	NA	NA	NA	NA	NA	NA	NA
Cavallin et al[37]	2	1/1	0	2	2	2	0	0	0	0	0	0	0	2	2	1	1	0	0	0	0	0	NA	NA	0	0	0
Present paper	2	1/1	0	2	1	1	1	0	2	1	0	0	1	1	2	0	2	0	1	2	0	2	0	0	0	0	0
Total	**24**	**12/10**	**4 (17%)**	**8 (33%)**	**13 (54%)**	**13 (54%)**	**13 (54%)**	**3 (12%)**	**8 (33%)**	**1 (4%)**	**2 (8%)**	**3 (12%)**	**1 (4%)**	**5 (20%)**	**4 (16%)**	**1 (4%)**	**3 (12%)**	**3 (12%)**	**1 (5%)**	**4 (21%)**	**0**	**3 (15%)**	**0**	**1 (7%)**	**0**	**0**	**0**

have been described[8,14]. Ischemic or hemorrhagic stroke may occur at any age in these patients, from antenatal period to adulthood[10,18]. Two other phenotypic features have been highlighted: isolated small vessel disease and malformations of cortical development (MCD)[37,43]. Gould et al[10] first hypothesized the role of COL4A1 mutations in small vessel disease in 2006 by analyzing adult mice models of Col4a1 mutation. These animal models were prone to hemorrhagic stroke and subarachnoid hemorrhage due to focal damage of the vascular basement membrane, even in the absence of hypertension or head trauma. This finding was confirmed by the discovering of a missense *COL4A1* mutation in six members of a family with small vessel disease and hemorrhagic manifestations without porencephaly[10]. Subsequently, other adult patients with *COL4A1* mutations and small vessel disease (leukoencephalopathy, lacunar infarcts, microbleeds) were described[29,44].

Different kinds of MCD have also been reported in patients with the *COL4A1* mutations, including schizencephaly, which is the most frequent finding and is often asymmetrical[37]. Less frequent manifestations include gyral abnormalities, lissencephaly, and focal cortical dysplasia[32].

The phenotype associated with mutations of *COL4A2* gene is not as well characterized. In fact, those mutations have been reported only recently and in a smaller number of patients[7,25,38-41].

The most frequently reported findings in patients with *COL4A2* mutations include intracerebral hemorrhage and porencephaly[7,32,38,39] with onset ranging from antenatal period to adulthood, as well as leukoencephalopathy and intracranial aneurisms[7,32,38,40,41]. The paucity of published reports might depend both on the more recent discovery of *COL4A2* mutations and on the possibility of a milder phenotype, including asymptomatic cases[41]. Indeed, the COL4A heterotrimer is composed of two α1 chains and one α2 chain; thus, α2 chain is less represented. For this reason, it is conceivable that COL4A2 mutations may cause a milder phenotype or even be asymptomatic[25].

Our patients' phenotype is partially similar to what has been depicted in the literature. Only one of the patients, in fact, show porencephaly, which is the hallmark of the disease. An original finding is represented by subcortical heterotopia, which was present in both our patients. Periventricular, bilateral and extensive heterotopia associated with complex malformation disorder was reported only once in a patient with the *COL4A2* mutation[37]. Heterotopias are a subset of malformations of cortical development with a predominantly genetic origin, more rarely caused by antenatal infection or trauma[45]. While the other malformations of cortical development in our patients are probably vascular in origin, the pathogenesis of subcortical heterotopia is more obscure. The association of heterotopia with other clinical features typical of *COL4A* mutations might suggest a common mechanism. Indeed, the NGS panel performed on Patient 1 included all genes which have been associated with schizencephaly, porencephaly, and heterotopia, with negative results. Thus, other genetic causes of malformations of cortical development have been reasonably excluded.

Conclusions

Our results allow to reaffirm that testing for *COL4A* mutations is indicated in patients with malformations of cortical development, particularly in the presence of familial conditions, even in the absence of porencephaly or early hemorrhagic strokes. The genetic testing may have implications on prognosis and on genetic counselling.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Appendix

NGS panel for genetic epilepsies: examined genes. AARS, ADAR, ADGRGI, ADSL, AFG3L2, AGA, ALDHSAT, ALDH7A1, ALG13, AMACR, AMT, APBA2, ARGI, ARHGEF2, ARHGEF9, ARX, ATPI A2, ATPIA3, ATP6AP2, BTD, CI0ORF2, CACNAIA, CACNAIH, CACNA2D2, CACNB4, CASK, CASR, CAV3, CDKL5, CERSI, CHD2, CHRNA2, CHRNA4, CHRNB2, CLCN2, CLN5, N6, CNTNAP2, COL4AI, COL4A2, CPT2, CSTB, CTSD, DCX, DEPDC5, DIAPHI, DNMI, DOCK7, DPYD, EEFIA2, EFHCI, EMX2, EPM2A, ERMARD, ETFA, ETFB, ETFDH, FH, FIG4, FLNA, FORLI, FOXGI, FOXPI, GABRY, GABRB3, GABRG2, GAMT, GBA, GCDH, GCHI, GLDC, GLI3,

GNAOI, GNAQ, GNE, GOSR2, GPHN, GRASP, GRINI, GRIN2A, GRIN2B, HCNI, HCN2, HCN4, HEPACAM, HESXI, HNRNPU, IQSEC2, ITPA, KATNBI, KCNAI, KCNA2, KCNBI, KCNCI, KCNE2, KCNJI0, KCNMAI, KCNQ2, KCNQ3, KCNTI, KCNT2, KCTD7, KDM6A, KIFIA, KIF2A, KIF5C, KMT2D, L2HGDH, LAMBI, LAMC3, LGII, LIAS, MAGI2, MBD5, MECP2, MEDI7, MEF2C, MOCSI, MTHFR, MTOR, NDEI, NDP, NECAPI, NEUT, NHL RCI, NPCI, NPC2, NPRL2, NPRL3, NRXNI, NSDHL, NUSI, OCLN, PAFAHIBI, PCDH19, PEXSL, PGKI, PHGDH, PIGA, PIGO, PIGQ, PLCBI, PNKP, PNPO, POLG, PPTI, PRICKLEI, PRNP, PRODH, PRRT2, PTEN, PTS, PURA, QARS, QDPR, RELN, RNASEH2A, RNASEH2B, ROGDI, RTTN, SACS, SAMHDI, SCARBI, SCARB2, SCNIA, SCNIB, SCN2A, SCN3A, SCN5A, SCN8A, SCN9A, SETBPI, SIKI, SLC12A5, SLC12A6, SLC13A5, SLC9A3 SLC20A2, SLC25A15, SLC25A22, SLC2AI, SLC35A2, SLC46AT, SLC6AI, SLC6A8, SLC9A6, SMS, SNAP25, SPATA5, SPTANI, SPTBN2, SRPX2, ST3GAL3, ST3GALS, STXIB, STXBPI, SUOX, SYNI, SYNGAPI, SZT2, TBCID24, TCF4, TNK2, TPPI, TREXI, TSCI, TSC2, TSEN15, TSEN2, TSEN54, TUBAIA, TUBA8, TUBB2B, TUBB3, TUBB4A, UBE3A, VLDLR, WDR45, WDR62, WWOX, ZEB2.

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