CASE REPORT

DOI: 10.5336/caserep.2020-75076

Co-existence of Mutations in *PRRT2* and *ABCC6* Genes in a Turkish Family

Gülçin BENBİR ŞENEL[a], Didem TEZEN[a], Şeyma TEKGÜL[b], Ayşe Nazlı BAŞAK[b], Hülya APAYDIN[a]

[a]Department of Neurology, İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, İstanbul, TURKEY
[b]Suna and İnan Kıraç Foundation, Neurodegeneration Research Laboratory, KUTTAM, Koç University Faculty of Medicine, İstanbul, TURKEY

ABSTRACT Paroxysmal kinesigenic choreoathetosis (PKC) is an inherited disorder with an autosomal dominant mode of inheritance, caused mostly by the mutations in *PRRT2* (proline-rich transmembrane protein-2) gene, located on chromosome 16. Pseudoxanthoma elasticum (PXE) is a hereditary metabolic disease with autosomal recessive inheritance resulting from the mutations in the *ABCC6* (ATP-Binding Cassette, Subfamily C, Member 6) gene, located also on chromosome 16. Here we present a female patient with familial paroxysmal kinesigenic dyskinesia and benign familial infantile convulsions (BFIC), in whom both a heterozygous truncating frameshift mutation in the *PRRT2* gene and a heterozygous missense mutation in the *ABCC6* gene were demonstrated. The co-existence of these two mutations has not been reported in the literature. Although the clinical symptomatology of PXE was not present in our patient, some family members of our index case had. Here we present a Turkish family with two different mutations on the same chromosome, namely *PRRT2* and *ABCC6* mutations. However, because these two mutations have separate parental inheritance and are not in *linkage disequilibrium*, the co-existence was reported as co-incidental.

Keywords: Paroxysmal kinesigenic choreoathetosis; *PRRT2* gene mutations; pseudoxanthoma elasticum; *ABCC6* gene mutations

Paroxysmal kinesigenic choreoathetosis (PKC), also called paroxysmal kinesigenic dyskinesia, constitutes the most common subtype of paroxysmal dyskinesias.[1]. It is a hyperkinetic movement disorder characterized by recurrent, short-lasting attacks of involuntary, choreic, ballistic or dystonic movements. Typically, these attacks are triggered by movement, and consciousness is not affected during the attacks. The onset of disease occurs usually between the ages 1 to 20 years, with a decrease in severity by increasing age.[2] Dramatic response to carbamazepine is very typical of PKC. Although sporadic cases were also reported in the literature, PKC is inherited in an autosomal dominant mode.[3] Mutations in several genes were associated with PKC, the most common one being the *PRRT2* (proline-rich transmembrane protein-2) gene located on chromosome 16.[4] Point and frameshift mutations in the *PRRT2* gene were reported to account for almost half of PKC cases.[5]

Pseudoxanthoma elasticum (PXE) is a genetically inherited metabolic disease. Clinical manifestations of PXE include cutaneous findings including characteristic yellow papules on the nape, lateral sides of the neck, in flexural areas, and in horizontal oblique mental creases on the chin; ophthalmological features such as the presence of angioid streaks in the retina; and vascular and systemic involvement.[6] It has an autosomal recessive inheritance pattern resulting from mutations in *ABCC6* gene located on chromosome 16.[7]

In this case report, we present a female patient with familial paroxysmal kinesigenic dyskinesia and benign familial infantile convulsions, in whom both a truncating frameshift mutation in the *PRRT2* gene

Correspondence: Gülçin BENBİR ŞENEL
Department of Neurology, İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, İstanbul, TURKEY
E-mail: drgulcinbenbir@yahoo.com

Peer review under responsibility of Turkiye Klinikleri Journal of Case Reports.

Received: 29 Mar 2020 ***Received in revised form:*** 02 Aug 2020 ***Accepted:*** 12 Aug 2020 ***Available online:*** 26 Nov 2020

and a heterozygous *ABCC6* gene mutation were demonstrated.

CASE REPORT

A 23-year old woman was admitted to our movement disorders unit complaining of contractions in her both upper and lower extremities since the age of six years. She stated that before these contractions, she had a kind of numbness feeling in her affected extremities. She denied any loss of consciousness around the attacks. Contractions were described as involuntary, irregular twisting and rotational movements of sudden onset, lasting for less than one minute. The frequency of attacks varied between once in two weeks to ten times in one day. She denied any triggering or alleviating factor, but noticed that the attacks may occur more frequently after walking for long distances. Any other associated symptoms were not present. She was right-handed and unmarried. Her systemic, dermatological and neurological examinations were normal. Intelligence quotient of the patient and detailed ophthalmological examination were also normal. We unfortunately could not observe the attacks described during hospitalization, but the patient and her family were asked to record attacks upon which the patient was diagnosed as paroxysmal kinesigenic choreoathetosis.

In her past medical history, she had benign familial infantile convulsions, and mitral valve prolapse. Except for potassium supplement, she denies current use of drugs or substances. She was first diagnosed as having epilepsy because of these contractions and has a history of multiple antiepileptic use. She was first given valproic acid, which was stopped because of the emergence of skin rash as a side effect. The second antiepileptic agent chosen was epdantoin, which was also stopped because of skin rash and lack of benefit. Then, levetiracetam was given, but it was also stopped because of lack of benefit. Her family history revealed a consanguinity (second degree-cousin marriage) between her parents. Her mother had similar contractions following running during early adulthood (in the second decade). She has an older sister and an older brother. Her older brother has similar contractions since the age of eight years with a frequency of once in two to three months. Her sister did not have similar complaints of contractions. Both siblings of the index case had the definitive diagnosis of PXE. The diagnosis was made in the second decade of their lives based on the typical dermatological features; the ophthalmologic and cardiac examinations were reported as normal. Her sister had frequent and recurrent nephrolithiasis, as well. Her brother is married and has a daughter, who was diagnosed to have benign familial infantile convulsions (Figure 1).

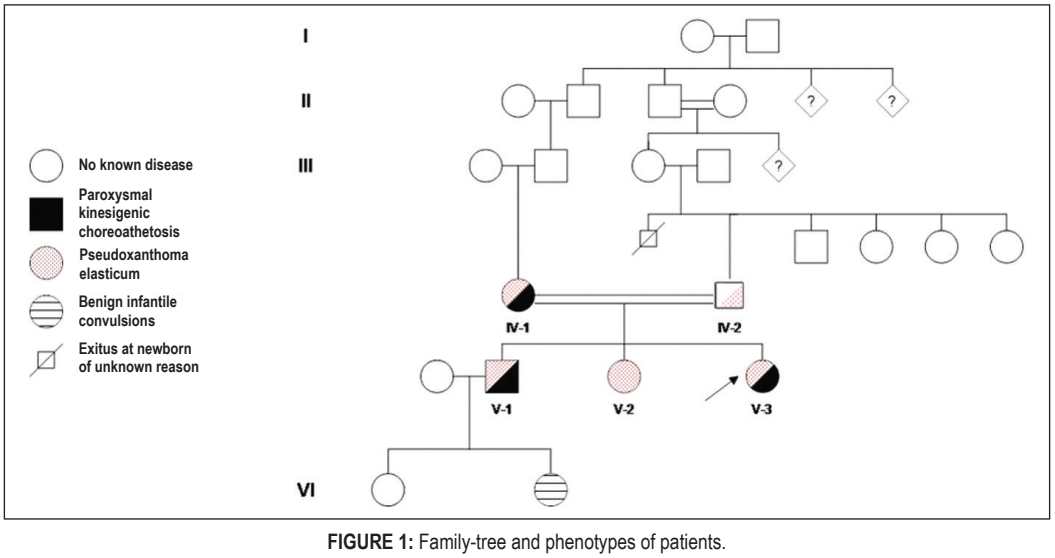

FIGURE 1: Family-tree and phenotypes of patients.

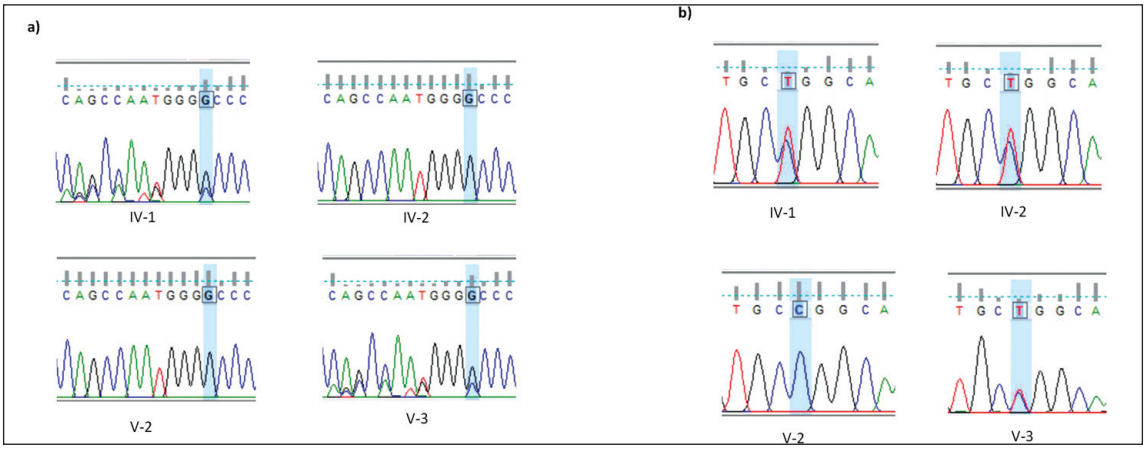

FIGURE 2: Sanger sequencing results of index case and family members a) PRRT2 p.Arg217ProfsTer8 (c.649dupC). b) ABCC6 p.Leu826Pro (c.2477T>C).

The magnetic resonance imaging of the brain was normal. Electroencephalographic recordings showed bilateral, symmetrical, and generalized disorganization, infrequent sharp-and-slow-wave discharges over the right occipital region. She was given valproic acid, and phenytoin previously, which showed no benefit, but side effects like headache. She was then put on carbamazepine therapy (400 mg/day) with substantial benefit and total alleviation of symptoms. Genetic analysis was performed in our patients and her family including her parents and two siblings. Whole exome sequencing showed a heterozygous truncating frameshift mutation leading to p.Arg217ProfsTer8 (c.649dupC, exon 2) in the *PRRT2* gene (ENST00000567659.1) (see Figure 2a). Whole exome sequencing also revealed a heterozygous missense mutation in p.Leu826Pro (c.2477T>C, exon 19) in the *ABCC6* gene (ENST00000205557.7) (see Figure 2b). These mutations were examined in the parents and older sister of the patients by Sanger sequencing. Her brother having PKC and PXE denied participating at the genetic analysis. The same heterozygous *PRRT2* mutation was also shown to be present in the mother of our index case; the father and her older sister were free of the *PRRT2* mutation. Sanger sequencing showed as expected the *ABCC6* gene mutation in heterozygous form in both mother and father of the patient, and a homozygous mutation was present in her older sister.

A written informed consent was obtained from the index patient, and the family members who accepted to be genetically tested.

DISCUSSION

In this case report, we present a patient with familial paroxysmal kinesigenic choreoathetosis and a history of benign familial infantile convulsions. There was remote consanguinity between her parents, and both her mother and older brother also had paroxysmal kinesigenic choreoathetosis. None of her parents or siblings had benign familial infantile convulsions, but the daughter of his brother did. Genetic analysis demonstrated a recurrent heterozygous truncating frameshift mutation in the *PRRT2* gene in our patient and also in her mother. This mutation was reported as the most common mutation in benign familial infantile convulsions and paroxysmal kinesigenic choreoathetosis.[8,9]

PRRT2 is a transmembrane protein, expressed mainly in the cerebellum, basal ganglia and cortex; it binds to synaptosomal-associated protein-25 (SNAP-25), which is involved in vesicular exocytosis and neurite outgrowth.[4] Besides, symptoms including several movement disorders, exercise-induced dystonia, episodic ataxia, febrile seizures and headache disorders, such as hemiplegic migraines were reported in patients with *PRRT2* mutations, all of which were grouped within the *PRRT2* mutation spectrum disorders.[10] Most of the mutations discovered in the *PRRT2* gene were responsible from truncation of the protein, resulting in loss of function. The mutation described here, was reported to lead to nonsense-mediated decay, which generated a haploinsufficiency phenotype and genotype-phe-

notype discrepancy.[9,11] This phenomenon was also evident in the family of our patient; the mother of the patient had PKC only, our patient had PKC and benign familial infantile convulsions, the older brother had PKC, but his daughter had benign familial infantile convulsions.

In addition to the *PRRT2* mutation, a heterozygous missense mutation in the *ABCC6* gene was identified in our patient. The same heterozygous mutation was described in heterozygous form in both parents by Sanger sequencing and in homozygous mutation in the older sister, who was diagnosed to have PXE. This mutation was also previously reported in the literature.[12] Recently an update was published on mutation spectrum in *ABCC6* gene and genotype- phenotype correlations in PXE; which proposed renal (nephrolithiasis) and neurological (strokes) features to be included in the evaluation of the disease.[13] In the older sister of our patient, nephrolithiasis was thought to be related with PXE, as well.

In conclusion, although PKC and PXE co-existed in the same individuals at the same time (our index case and her mother), her father and older sister only had *ABCC6* mutation. These show that *PRRT2* and *ABCC6* mutations-although both are located at chromosome 16-had separate parental inheritance, which can't be explained by the *linkage disequilibrium*. The association of these two genes may therefore be just a coincidence. Nevertheless, we here aimed to attract some attention to this unique coexistence of mutations in the *PRRT2* and *ABCC6* genes in a Turkish family with paroxysmal kinesigenic choreoathetosis, benign familial infantile convulsions, and pseudoxanthoma elasticum.

Acknowledgments

We would like to extend our sincere gratitude to Suna and İnan Kıraç Foundation for their generous support. We also thank the Foundation, Koç University and its Translational Medicine Research Center KUTTAM for the inspiring working environment created.

Data Availability Statement

The data that support the findings of our paper are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Ayşe Nazlı Başak, Hülya Apaydın;* ***Design:*** *Ayşe Nazlı Başak, Hülya Apaydın;* ***Control/Supervision:*** *Hülya Apaydın;* ***Data Collection and/or Processing:*** *Gülçin Benbir Şenel, Didem Tezen, Şeyma Tekgül;* ***Analysis and/or Interpretation:*** *Gülçin Benbir Şenel, Hülya Apaydın, Ayşe Nazlı Başak;* ***Literature Review:*** *Gülçin Benbir Şenel;* ***Writing the Article:*** *Gülçin Benbir Şenel;* ***Critical Review:*** *Hülya Apaydın, Ayşe Nazlı Başak;* ***References and Fundings:*** *Hülya Apaydın, Ayşe Nazlı Başak;* ***Materials:*** *Gülçin Benbir Şenel, Didem Tezen, Şeyma Tekgül, Ayşe Nazlı Başak, Hülya Apaydın.*

REFERENCES

1. Jankovic J, Demirkiran M. Classification of paroxysmal dyskinesias and ataxias. Adv Neurol. 2002;89:387-400. [PubMed]
2. Bruno MK, Hallett M, Gwinn-Hardy K, Sorensen B, Considine E, Tucker S, et al. Clinical evaluation of idiopathic paroxysmal kinesigenic dyskinesia: new diagnostic criteria. Neurology. 2004;63(12):2280-7. [Crossref] [PubMed]
3. Nagamitsu S, Matsuishi T, Hashimoto K, Yamashita Y, Aihara M, Shimizu K, et al. Multicenter study of paroxysmal dyskinesias in Japan--clinical and pedigree analysis. Mov Disord. 1999;14(4):658-63. [Crossref] [PubMed]
4. Chen WJ, Lin Y, Xiong ZQ, Wei W, Ni W, Tan GH, et al. Exome sequencing identifies truncating mutations in PRRT2 that cause paroxysmal kinesigenic dyskinesia. Nat Gen. 2011;43(12):1252-5. [Crossref] [PubMed]
5. Huang XJ, Wang T, Wang JL, Liu XL, Che XQ, Li J, et al. Paroxysmal kinesigenic dyskinesia: clinical and genetic analyses of 110 patients. Neurology. 2015;85(18):1546-53. [Crossref] [PubMed]
6. Plomp AS, Toonstra J, Bergen AA, van Dijk MR, de Jong PTVM. Proposal for updating the pseudoxanthoma elasticum classification system and a review of the clinical findings. Am J Med Genet A. 2010;152A(4):1049-58. [Crossref] [PubMed]
7. Miksch S, Lumsden A, Guenther UP, Foernzler D, Cristen-Zäch S, Daugherty C, et al. Molecular genetics of pseudoxanthoma elasticum: type and frequency of mutations in ABCC6. Human Mutat. 2005:26(3):235-48. [Crossref] [PubMed]
8. He ZW, Qu J, Zhang Y, Mao CX, Wang ZB, Mao XY, et al. PRRT2 mutations are related to febrile seizures in epileptic patients. Int J Mol Sci. 2014;15(12):23408-17. [Crossref] [PubMed] [PMC]
9. Lamperti C, Invernizzi F, Solazzi R, Freri E, Carella F, Zeviani M, et al. Clinical and genetic features of paroxysmal kinesigenic dyskinesia in Italian patients. Eur J Pediatr Neurol. 2016:20(1):152-7. [Crossref] [PubMed]
10. Zhao G, Liu X, Zhang Q, Wang K. PRRT2 mutations in a cohort of Chinese families with paroxysmal kinesigenic dyskinesia and genotype-phenotype correlation reanalysis in literatures. Int J Neurosci. 2018;128(8):751-60. [Crossref] [PubMed]
11. Ebrahimi-Fakhari D, Saffari A, Westenberger A, Klein C. The evolving spectrum of PRRT2-associated paroxysmal diseases. Brain. 2015:138(Pt 12):3476-95. [Crossref] [PubMed]
12. Plomp AS, Florijn RJ, ten Brink J, Castle B, Kingston H, Martín-Santiago A, et al. ABCC6 mutations in pseudoxanthoma elasticum: an update including eight novel ones. Mol Vis. 2008:14:118-24. [PubMed]
13. Legrand A, Cornez L, Samkari W, Mazzella JM, Venisse A, Boccio V, et al. Mutation spectrum in the ABCC6 gene and genotype-phenotype correlations in a French cohort with pseudoxanthoma elasticum. Genet Med. 2017:19(8):909-17. [Crossref] [PubMed]