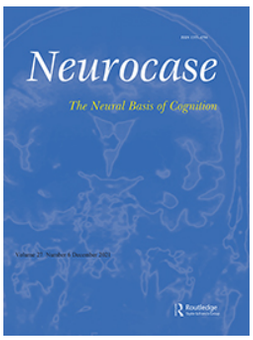

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Two cases with mitochondrial membrane protein-associated neurodegeneration: genetic features and long-term clinical follow-up

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ABSTRACT

Mitochondrial membrane protein-associated neurodegeneration (MPAN) is a rare neurological disease with childhood or adult onset. It is a subtype of clinically and genetically heterogeneous group of disorders, collectively known as neurodegeneration with brain iron accumulation . MPAN is generally associated with biallelic pathogenic variants in *C19orf12*. Herein, we describe genetic and clinical findings of two MPAN cases from Turkey. In the first case, we have identified the relatively common pathogenic variant of *C19orf12* in the homozygous state, which causes late-onset MPAN. The second case was homozygous for an essential splice-site variation.

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Introduction

Neurodegeneration with brain iron accumulation (NBIA) is an umbrella term used for a group of ultra-rare neurological movement disorders. NBIA subgroups are characterized by accumulation of iron deposits in the brain and progressive neurodegeneration. To date, 12 genes inherited in an autosomal dominant, autosomal recessive, or X-linked dominant fashion have been implicated in all known forms of NBIA disorders (Di Meo & Tiranti, 2018). Pantothenate kinase-associated neurodegeneration (PKAN; MIM:234200), phospholipase A2-associated neurodegeneration (PLAN; MIM:610217), mitochondrial membrane protein-associated neurodegeneration (MPAN; MIM614298), and neurodegeneration with brain iron accumulation 5 (BPAN; MIM 300894) are the four major classes of NBIA disorders (Hayflick et al., 2018; Di Meo & Tiranti, 2018).

MPAN is characterized by Lewy bodies in the basal ganglia and neocortex, neuronal loss, gliosis, as well as peripheral axonal spheroids (Schneider et al., 2013; Schulte et al., 2013). MPAN may have an childhood, adolescence, or early adulthood onset in which the following clinical features are usually common: lower limb spasticity, dystonia, optic atrophy, cognitive impairment, neuropsychiatric disturbances, as well as bowel/bladder incontinence (Hartig et al., 2011; Hogarth et al., 2013). In addition to these symptoms, parkinsonism, hallucinations, depression, anxiety, emotional fluctuations, and psychosis are predominantly observed among adult patients (Dogu et al., 2013; Hogarth et al., 2013).

Brain magnetic resonance imaging (MRI) of a MPAN case commonly shows iron deposits in substantia nigra and globus pallidus; yet during early stages of the disease iron accumulation may not be detectable on MRI (Hogarth et al., 2013). One of the MRI features of MPAN is quite similar to the diagnostic hallmark of PKAN; known in the literature as the "eye of the tiger" sign. It has been reported that hyper-intense streaking of the medial medullary lamina in T2 sequences have been observed in a few cases of MPAN (Hogarth et al., 2013; Horvath et al., 2012; Skowronska et al., 2015).

MPAN is a genetically defined disorder caused by pathogenic variations in Chromosome 19 open reading frame 12 (*C19orf12*) gene. Variations in this gene can also lead to autosomal recessive spastic paraplegia 43 (SPG43; MIM:615043) and juvenile amyotrophic lateral sclerosis (ALS; Sparber et al., 2018; Hogarth, 2015; Gregory & Hayflick, 2021). *C19orf12* codes for a mitochondrial membrane protein, which still has an unknown function. The common inheritance pattern of MPAN is acknowledged as autosomal recessive, given that various biallelic pathogenic variations in *C19orf12* have been associated with MPAN phenotype (Hartig et al., 2011; Hogarth et al., 2013). Nevertheless, heterozygous variants in *C19orf12* have also been described to cause this disease (Monfrini et al., 2018; Gregory et al., 2019). Herein, we report clinical and genetic findings of two probands whose phenotypes were compatible with MPAN. We have identified two distinct homozygous pathogenic variations in *C19orf12* using whole exome and/or Sanger sequencing methods.

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Supplemental data for this article can be accessed here.

Materials and methods

Patients and clinical assessments

Two unrelated individuals with a clinical diagnosis of MPAN have been included in this study. Physical and neurological examinations were performed and detailed information on family history was collected.

Case 1

A 37-year-old male patient born to first-degree cousins has been followed for dementia for 8 years. He was reported to be born after an uneventful vaginal delivery and his motor-mental developmental milestones were reported to be within normal limits. The patient has started to show signs of severe amnesia without rapid eye movement sleep behavior disorder, hallucinations, or psychotic findings since the age of 29. His amnesia was characterized by a high tendency to forget newly learned information. According to the family history, his paternal aunt, currently in her 50's, had recently been diagnosed with Alzheimer's disease and schizophrenia.

In his neurological examination, speech, cranial nerves, motor system, reflexes, sensory system, cerebellar tests, and gait were found to be in normal limits. Comprehension, speaking, reading, and writing abilities were also normal. The neuropsychological tests were suggestive for daily executive dysfunction with forgetting of newly learned information. Brain MRI of the patient was in accordance with the diagnosis of MPAN with iron deposits (Figure 1(A), 1(B)). There were no additional cortical MRI finding such as focal or generalized atrophy.

Case 2

A 24-year-old male patient has been followed up for 15 years. He was born in term to healthy, first-degree cousin parents. His initial developmental milestones were within normal limits. He was able to walk at 18 months. However, he developed tip toe walking at the age of 9. This was followed by falls during walking. He was wheelchair dependent after the age of 22. Forgetfulness started at around the ages of 17–18, followed by decline in cognitive and visual function in his 20s. At the age of 19, he

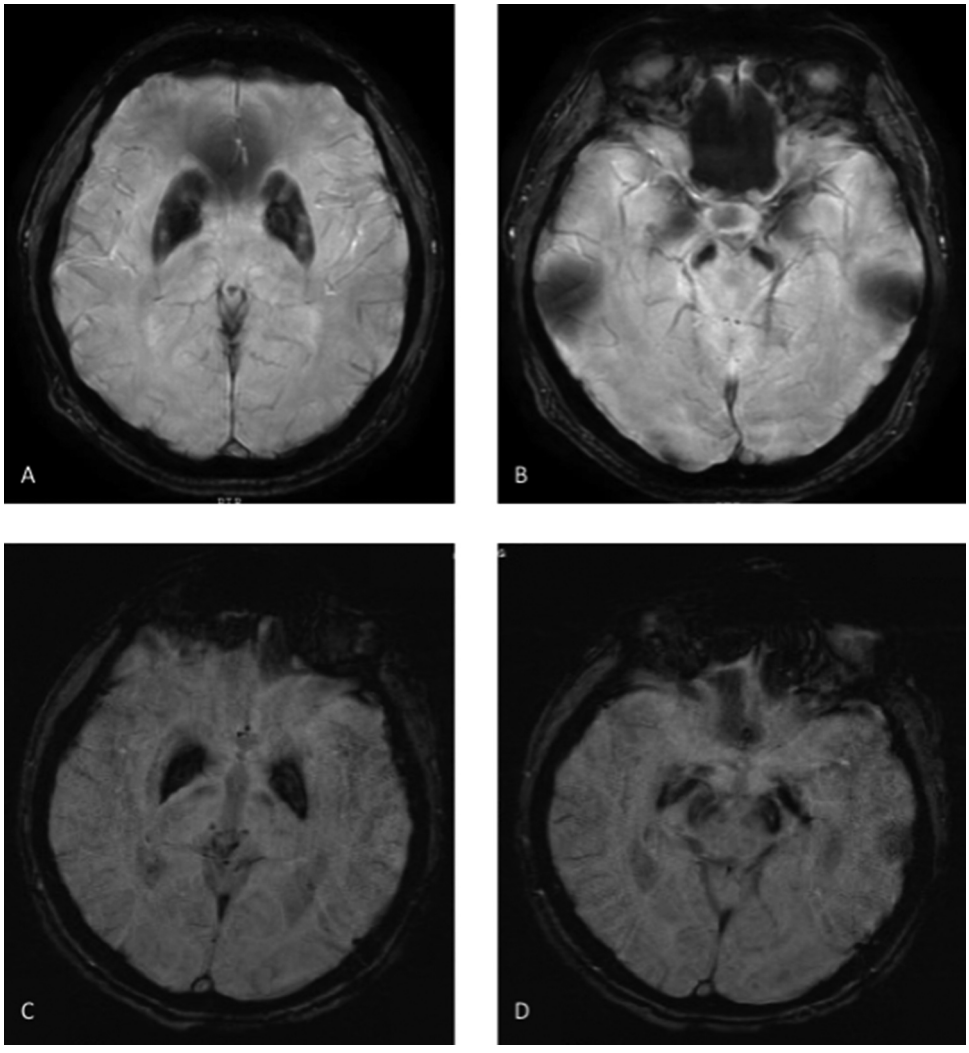

Figure 1. Brain MR images of the case 1 and 2. The axial susceptibility-weighted angiography (SWAN) MR images demonstrating hypointensity of the globus pallidus (A) and substantia nigra (B) that indicate iron accumulation in case 1. The susceptibility weighted imaging (SWI) axial images demonstrating hypointensity of the globus pallidus (C) and substantia nigra (D) that indicate iron accumulation in case 2.

presented oromandibular motor involvement with dysarthria, which deteriorated gradually into chewing problem and incomprehensible dysarthria even his relatives were unable to understand his words at the age of 24.

During his latest neurological examination, he had an evident cognitive involvement. Due to his cognitive decline, both general knowledge, language skills, and memory abilities were decreased, and he was disoriented with respect to time and place. His speech was hypophonic, nasal, and echolalic. Fundus examination revealed pale optic discs. Risus sardonicus and bradymimi were observed. He could not chew but swallow. It may be that no paresis was detected on motor examination; however, even independent sitting balance was not maintained. Dystonic contractions were prominent in the lower extremities during action, and dystonic posture could be observed in the left arm at rest. There was bilateral rigidity. Bradykinesia and postural instability were remarkable. Brain MRI revealed iron depositions at globus pallidus and substantial nigra, suggesting MPAN disease (Figure 1(C), 1(D)).

Genetic analyses

DNA was extracted from peripheral blood samples of both cases using QIAamp DNA Blood Maxi Kit (Qiagen GmbH, Hilden, Germany). Informed consents were obtained from all family members and control individuals in accordance with Istanbul University, Istanbul Faculty of Medicine, Clinical Ethics Committee.

Genetic analysis of Case 1 was performed by means of whole exome sequencing (WES). Exonic DNA was captured with the SureSelect Human All Exon without UTR V6 kit (Agilent Technologies, Santa Clara, CA, USA) and sequenced on an Illumina Novaseq platform by Macrogen (Seoul, South Korea). Exome data analysis was carried out by using the pipeline of Sophia DDM (Sophia Genetics SA, Switzerland) and variant lists were browsed using the proprietary software of Sophia DDM. WES data of case 1 was first filtered for variants in NBIA associated genes and was then analyzed for all rare variants with a carrier frequency expected for an ultra-rare recessive disorder (alternative allele frequency; AAF < 0.14%; Hennekam, 2011).

Case 2 was analyzed only for *C19orf12 via* Sanger sequencing. Accordingly, all exons and exon-intron boundaries of the *C19orf12* transcript NM_001031726.3 was sequenced for case 2. Primer sequences of *C19orf12* are given in Table 1. PCR conditions are available upon request. Sanger sequencing data was analyzed using the CLC Main Workbench (Qiagen) software.

Results

WES analysis in case 1 and direct Sanger sequencing of *C19orf12* in case 2 have collectively led us to detect two distinct homozygous variants in *C19orf12* associated with MPAN.

Case 1 was homozygous for *C19orf12* (rs397514477; ENST00000392278.2:c.32C>T; p.(Thr11Met)), which is the leading cause of late-onset MPAN in patients from Turkey (Akcakaya et al., 2019; Olgiati et al., 2017). Sequence validation was performed for this variant in exon 2 *via* Sanger sequencing using standard procedures (Figure 2).

Table 1. Primer pairs used for PCR amplification and Sanger sequencing of *C19orf12*.

C19orf12 exonsexons	Forward primer	Reverse primer
Exon 1	CGCTCCCCCAGGTAAAGG	GTGGTGGATGTGGTGGGAG
Exon 2	GAGTGGCATTGTGATGGAAA	TTCAACGGCCCTTTTATGAC
Exon 3_Amplicon1	CTGCTCATGGTGATGGTGGT	CTCCCAAGCCACCTCTTCAG
Exon 3_Amplicon2	GGATGTCACTGTGTTGCCCA	CGGAGAAGAGTCCTGGGAAC

In case 2, we have identified an essential splice acceptor site variant residing in the last intronic sequence (rs1237641581; ENST00000392278.2:c.194–2A>G) in the homozygous state (Figure 2). This variant has previously been reported to be associated with MPAN along with ENST00000392278.2:c.142G>C; p.(Ala48Pro) in a compound heterozygous state (Hogarth et al., 2013; Gregory et al.,2019). The variant is observed in the GnomAD v2.1.1 database once in the heterozygous state.

Discussion

MPAN generally follows an autosomal recessive inheritance pattern, yet it may also be dominantly inherited (Monfrini et al., 2018; Gregory et al., 2019). The disease-associated gene *C19orf12* codes for four distinct Consensus CDS (CCDS) project isoforms as presented in the Ensembl database (GRCh38.p13; Supplementary Table 1). Herein, we have annotated the identified variations using the transcript encoding the largest and the canonical protein isoform, namely, ENST00000392278.2 (NM_001031726.3). Interestingly, rs397514477, which causes a relatively milder phenotype with an older age of onset, is predicted to alter protein sequence only in the canonical transcript; i.e. ENST00000392278.2:c.32C>T; p.(Thr11Met). This exact genomic position refers to either 5′UTR or intronic sequences in the other three CCDS transcripts (Supplementary Table 2). On the other hand, rs1237641581 associated with a more severe phenotype and a younger age of onset is annotated as a splice acceptor variant for all CCDS transcripts (Supplementary Table 2). Hence, it may be

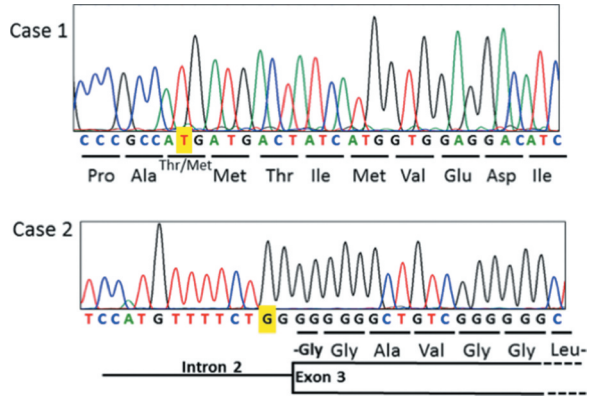

Figure 2. Sanger sequencing results of homozygous variations detected in *C19orf12* for case 1 and case 2.

speculated that the milder clinical outcome for rs397514477 may be due to its effect on the coding sequence only in a single transcript. Nevertheless, this dramatic clinical distinction may also be associated with the variant type. We have previously discussed that variants with potential truncating effects may be associated with a younger age of onset compared to missense variants (Akcakaya et al., 2019). However, in the case of rs1237641581, it is not possible to speculate on the potential loss of function effect due to nonsense mediated decay mechanism, as this variant resides either within the last or the penultimate exon in different transcripts. As expected for rare disorders, the genotype to phenotype correlations in MPAN can only be possible when cumulative data is available in the literature for retrospective studies. Additionally, potential utilization of RNA and protein based studies will help to elucidate the functional impact of variations in disease pathogenesis.

The type of pathogenic variants in *C19orf12* can be in the form of missense, nonsense, frameshift, or splice-site (Gregory et al., 2019). Nevertheless, the most common pathogenic variations among populations from Turkey and Eastern-Europe are c.32C>T; p.Thr11Met, and c.204_214del11; p.G69Rfs*10, respectively (Hartig et al., 2011; Hogarth et al., 2013; Olgiati et al., 2017). This is why it is considered that founder mutations in *C19orf12* exist in the aforementioned geographical territories. Case 1 was found to be homozygous for the rs397514477; ENST00000392278.2:c.32C>T; p.(Thr11Met) variant. This prominently adult onset variant was reported to be associated with a broad spectrum of phenotypes, including parkinsonism, pyramidal signs, psychiatric disturbances, cognitive decline, and motor axonal neuropathy (Olgiati et al., 2017). Case 1 fits in this spectrum especially due to his neuropsychological findings and adult onset of the disease. Nevertheless, this case presents with a different symptomatology such as executive dysfunction as an initial finding, which remained stable for almost 8 years. This is the most striking feature of case 1. Although non-motor symptomatology can be seen in late-onset MPANs, the absence of positive psychiatric findings such as hallucinations, psychotic symptoms or additional Parkinsonism-like extrapyramidal symptoms for a long time is not a common presentation (Dogu et al., 2013; Olgiati et al., 2017). Some general symptoms of MPAN, such as spastic paresis, extrapyramidal signs and optic nerve atrophy, were not observed in this case, either. During neurological examination, he had no noticeable difficulty in walking. After detection of iron deposition in the brain, WES was preferred as it is a more comprehensive approach that enables the detection of all the NBIA-associated variants. As a result, we have identified and further Sanger validated a *C19orf12* variant (rs397514477) in the homozygous state, which is already known to be associated with late-onset MPAN (Olgiati et al., 2017).

Case 2 had a healthy development until the age of 9. The typical clinical and radiological finding directly led us to sequence *C19orf12*, as the disease phenotype was highly consistent with MPAN. The result was the detection of a homozygous splice acceptor variant: ENST00000392278.2: c.194–2A>G (rs1237641581). The compound heterozygous state of this variant has previously been associated with MPAN, and it is considered to possibly affect splicing by altering a consensus splice signal. However, as it is located in the very last intron, it is not possible to state if the variant is translated into an abnormal protein or if it creates a null allele through nonsense-mediated RNA decay mechanism.

MPAN-associated c.194–2A>G variant has been detected in compound heterozygous state with c.142G>C; p.Ala48Pro (Hogarth et al., 2013; Gregory et al., 2019). A report indicates that of the two compound heterozygous and possibly related MPAN patients in whom age of disease onset was 10, one was clinically found to have progressive spasticity, parkinsonism, and cognitive decline, whereas the other had developmental delay, spasticity, and gait changes (Gregory et al., 2019). Case 2 may be considered significant in that he reflects the "pure" phenotypic effect of rs1237641581 in the homozygous state.

It should be noted that, in populations with a high rate of parental consanguinity, in which Turkey is included, ultra-rare variants may frequently be observed in the homozygous state and cause autosomal recessive disorders. With this in mind, two distinct MPAN patients both born to consanguineous and asymptomatic parents have been sequenced and not surprisingly, different homozygous causative mutations have been detected.

In conclusion, the two MPAN cases presented herein have homozygous pathogenic variations, which are consistent with the age of disease onset, clinical findings, and MRI features. Doubtless to say that detection of more cases with MPAN may enable us, researchers, to better understand the association between variation types and associated clinical findings. It is also important to refer families for genetic counseling.

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Availability of Data and Materials

All data, without identifiers, will be available per reasonable request. The contact person is, SA Ugur Iseri e-mail: sibel.ugur@istanbul.edu.tr

Disclosure statement

No potential conflict of interest was reported by the author(s).

Ethics approval and consent to participate

The study protocol has been approved by the Clinical Research Ethics Committee, Istanbul Faculty of Medicine at Istanbul University and written informed consents were obtained.

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