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NDUFA1 p.Gly32Arg variant in early-onset dementia

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ABSTRACT

Early-onset dementia (EOD) is highly heritable. However, in many EOD cases the genetic etiology remains unknown. Mitochondrial dysfunction is associated with neurodegeneration and the complex I (CI) deficiency is the most common enzyme deficiency in diseases related to oxidative phosphorylation. The X-chromosomal *NDUFA1* gene is essential for the activity of CI. Mutations in *NDUFA1* are associated with mitochondrial diseases especially with Leigh syndrome. CI deficiency is also associated with neurodegenerative diseases, such as Alzheimer's disease (AD). The aim of this study was to evaluate the role of *NDUFA1* variants in EOD patients. Next-generation sequencing panel was used to screen *NDUFA1* variants in a cohort of 37 EOD patients with a family history of dementia or an atypical or rapidly progressive course of disease. We identified a hemizygous p.Gly32Arg variant in two brothers with AD. Subsequent screening of the variant in a larger cohort of EOD patients (n = 279) revealed three additional variant carriers (one male and two heterozygote females), suggesting that *NDUFA1* variant p.Gly32Arg may play a role in neurodegenerative dementia.

1. Introduction

Mitochondrial diseases due to defects in oxidative phosphorylation system (OXPHOS) usually affect tissues with high energy demand, such as neurons, and are associated with a wide range of clinical phenotypes (Dimauro and Schon, 2003). Complex I (NADH: ubiquinone oxidoreductase, CI) deficiency is the most common single enzyme deficiency in OXPHOS disorders (Rodenburg, 2011). CI deficiency can lead to various mitochondrial diseases with heterogeneous phenotypes, for example fatal neonatal acidosis, Leigh syndrome and encephalomyopathy. Most patients develop symptoms before 12 months of age and commonly, the disease progresses rapidly leading to death in childhood (Fassone and Rahman, 2012). Mitochondrial dysfunction has also been reported to associate with neurodegenerative diseases, such as Alzheimer's disease (AD) and Parkinson's disease (Hroudová et al., 2014).

The *NDUFA1* gene locates in the X-chromosome and it encodes an evolutionarily highly conserved protein, which is an essential part of CI (Au et al., 1999). Previously four *NDUFA1* missense variants p.Gly8Arg, p.Arg37Ser, p.Gly32Arg and p.Pro19Ser have been reported to associate with neurological disease phenotypes, mainly Leigh syndrome, in hemizygous male patients (Fernandez-Moreira et al., 2007; Miyauchi et al., 2018; Potluri et al., 2009; Uehara et al., 2014). In addition, heterozygous p.Gly32Arg variant has been reported in a 15-month-old girl with OXPHOS deficiency and mild symptoms of somnolence and vomiting (Mayr et al., 2011). Male maternal cousins carrying the *NDUFA1* p.Gly32Arg variant represented with cognitive deterioration, seizures, aphasia, myoclonic jerks and hypotonia from the ages of four and five years onward (Potluri et al., 2009).

About half of the patients with early-onset dementia (EOD) have a family history of dementia with at least one affected first degree relative and the inheritance pattern is autosomal dominant in 10 %–15 % of these familial cases. However, the inflicting genetic factors are mostly unknown (Cacace el al., 2016.) Regarding the previously reported mitochondrial dysfunction and CI deficiency identified in patients with dementia (Giachin et al., 2016),

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Table 1
Demographics of the study cohorts

Cohort	I	II
Patients (n)	37	279
Male / Female	21/16	159/120
Mean age at onset, years (range)	55,3 (41–65)	57,2 (36–65)
Family history[a]:		
First degree relative with dementia (%)	16 (43)	
Second degree relative with dementia (%)	19 (51)	
Diagnoses:		
AD	27	160
FTLD	9	85
PSP	1	2
AD-VD		16
FTLD+MND		7
DLB		5
PDD		3
MSA		1

Key: AD, Alzheimer's disease; AD-VD, Mixed Alzheimer's disease and vascular dementia; DLB, Dementia with Lewy bodies; FTLD, Frontotemporal lobar degeneration; FTLD+MND, Frontotemporal lobar degeneration with motor neuron disease; MSA, Multiple System Atrophy; PDD, Parkinson's disease dementia; PSP, Progressive supranuclear palsy.

[a] At least one first- or second-degree relative with dementia or cognitive decline.

we aimed to investigate the role of *NDUFA1* variants in a Finnish EOD cohort.

2. Patients and methods

EOD patients were diagnosed by experienced neurologists at the memory outpatient clinics in Oulu and Kuopio University Hospitals in Finland (Gorno-Tempini et al., 2011; Litvan et al., 1996; McKeith et al., 2017; McKhann et al., 2011; Rascovsky et al., 2011). The study protocol was approved by local ethic committees and the Declaration of Helsinki was complied. Patients or their caregivers provided a written informed consent. Our first cohort included 37 EOD patients with age at onset (AAO) before 65 years and family history of dementia or rapidly progressive or atypical course of disease. The second cohort included 279 EOD patients with AAO before 65 years (Table 1).

DNA was extracted using QiAmp DNA Blood Mini Kit (Qiagen, Hilden, Germany). Targeted gene exon libraries were prepared using NimbleGen SeqCap EZ Library kit (Roche, Basel, Switzerland) with customized SeqCap EZ Neurology Panel Design (Roche, Basel Switzerland) covering all exons and exon-intron boundaries of 255 genes associated with 87 neurological diseases and disorders and the panel included also 9 additional genes (Supplementary Table 1). Samples were sequenced with Illumina MiSeq sequencer (Illumina, San Diego, CA, USA). The average mean reading coverage was 160,1 (min 113,9, max 291,6) and on average 98,3 % of the target areas were sequenced at least 15 times (min 97,3 %, max 99,0 %). Pathogenic exonic and exon-intron boundary variants in the genes associated with AD, FTLD and PD (*APP, PSEN1, PSEN2, MAPT, GRN, VCP, CHMP2B, FUS, TARDBP, TREM2, TMEM106B, UBQLN2, SOD1, UBQLN1, PRNP, BIN1, SNCA, LRRK2, PINK1, PARK2, PARK7, SNCAIP, GBA, ATP13A2, UCHL1*, and *HTRA2*) as well as the *C9orf72* repeat expansion were excluded from our first cohort of 37 patients. The data of this cohort was manually screened to find rare (MAF < 0,01), exonic non-synonymous and other variants in nuclear genes associated with mitochondrial function. The identified p.Gly32Arg (NP_004532.1, NM_004541.4:c.94G>C) variant in *NDUFA1* was covered 63 times on average (min 57, max 69) in the Illumina MiSeq sequencer (Illumina, San Diego, USA, CA). This variant was subsequently screened from the second cohort of 279 EOD patients. All the identified variants were confirmed by Sanger sequencing with ABI3500xL Genetic Analyzer (Thermo Fisher Scientific, Waltham, MA, USA).

3. Results

We found two brothers carrying the hemizygous p.Gly32Arg *NDUFA1* variant in the first cohort of 37 EOD patients (patients A and B). Both patients had clinically diagnosed early-onset AD and the diagnosis of the patient A was neuropathologically confirmed. Pathogenic mutations in the genes associated with AD, FTLD and PD (*APP, PSEN1, PSEN2, MAPT, GRN, VCP, CHMP2B, FUS, TARDBP, TREM2, TMEM106B, UBQLN2, SOD1, UBQLN1, PRNP, BIN1, SNCA, LRRK2, PINK1, PARK2, PARK7, SNCAIP, GBA, ATP13A2, UCHL1*, and *HTRA2*) as well as the *C9orf72* repeat expansion were excluded from the patients. Three additional patients (one male and two females) carrying the same p.Gly32Arg variant were identified from the second EOD cohort. In our total EOD cohort of 316 patients, this gives a minor allele frequency of 0,011, which is 1,7 fold the allele frequency reported in the gnomAD (0.006551) and SISu (0.006448) databases (Karczewski et al., 2020; Lim et al., 2014). Two of the p.Gly32Arg *NDUFA1* variant carriers suffered from epilepsy, but not until in the severe stages of dementia. According to the patients' medical examinations and medical records, these patients or their relatives did not suffer from other typical major or minor symptoms associated with mitochondrial dysfunction prior to the onset of dementia. The clinical characteristics of the p.Gly32Arg *NDUFA1* variant carriers are further described in Table 2.

4. Discussion

Previously *NDUFA1* variants have been associated with childhood mitochondrial diseases in hemizygous males (Fernandez-Moreira et al., 2007; Miyauchi et al., 2018; Potluri et al., 2009; Uehara et al., 2014). This is the first report of X-chromosomal *NDUFA1* p.Gly32Arg variant identified in EOD patients. First we identified hemizygous p.Gly32Arg in two male patients in our strictly defined cohort, in which the known pathogenic mutations causing AD and FTLD were excluded. The same variant was identified in one more male patient and in two heterozygous female patients in the second EOD cohort. Neurodegenerative dementia has been described among second-degree relatives of previously described young patients carrying the *NDUFA1* p.Gly32Arg variant (Potluri et al., 2009).

Our male EOD patients with the p.Gly32Arg *NDUFA1* variant presented with seizures, myoclonia or extrapyramidal symptoms already at an early phase of the disease. These early symptoms and the rapid progression of AD raised suspicion of possible pathogenic *PSEN1* mutation, however, no pathogenic *PSEN1, PSEN2* or *APP* mutations were found from these EOD patients. Epileptic seizures, myoclonia and extrapyramidal symptoms are not common in early stages of AD. However, these symptoms are frequently present in advanced stages of neurodegenerative dementing diseases, as well as in adult-onset mitochondrial diseases and CI deficiency (Beagle et al., 2017; Ghaoui and Sue, 2018; Koene et al., 2012). In previous reports male patients carrying the p.Gly32Arg or p.Arg37Ser *NDUFA1* variant have also been reported to present with myoclonia and epileptic seizures (Fernandez-Moreira et al., 2007; Potluri et al., 2009). The early appearance of these symptoms and the rapid progression of dementia might be associated with mitochondrial dysfunction due to *NDUFA1* p.Gly32Arg variant.

The role of heterozygous *NDUFA1* variant in female patients is more complex. It is possible that this variant increases the risk for

Table 2
Characteristics of the p.Gly32Arg NDUFA1 variant carriers

Patient	A	B	C	D	E
Gender	Male	Male	Female	Male	Female
Age at onset (years)	48	51	61	64	58
Age at death	57	61		70	
Diagnosis	AD[a]	AD	AD	AD	AD
Family history of dementia	Mother and brother had EOAD	Mother and brother had EOAD	Cousin had EOAD	-	-
APOE status	$\varepsilon 3/\varepsilon 4$	$\varepsilon 4/\varepsilon 4$	$\varepsilon 3/\varepsilon 3$	$\varepsilon 3/\varepsilon 3$	$\varepsilon 3/\varepsilon 4$
Other symptoms	Myoclonia, Epileptic seizures	Epileptic seizures		Rigidity, Logopenic aphasia	

Key: AD, Alzheimer's disease; *APOE*, Apolipoprotein E; EOAD, Early onset Alzheimer's disease
[a] Confirmed neuropathologically

EOD, not just in hemizygous males, but also in heterozygous females. Mayr et al. (2011) reported a female patient with a X-linked deficiency in the respiratory chain due to a heterozygous *NDUFA1* p.Gly32Arg variant. This patient presented with mild symptoms of muscular hypotonia and moderate lactic acidosis in her early years. Since the affected girl was only five years old at the time of the publication, her later disease progression is uncertain (Mayr et al., 2011). However, CI deficiency was found in the biochemical analysis of her muscle biopsy. Investigation of the X-inactivation pattern showed that 74 % of the paternally inherited allele was active in her muscle sample. Since the degree of X-inactivation may vary in different tissues, female heterozygous carriers of this variant can easily be missed, if they present with only mild muscular symptoms in childhood. Possibly the only clear manifestation of that variant appears later in life as EOD. Our two female patients were heterozygous for the *NDUFA1* p.Gly32Arg variant and the mother of the two brothers carrying the variant (patients A and B) had also been diagnosed with EOAD with AAO of 65 years. Unfortunately, no samples for genetic testing were available from their mother. In a previous report, the grandmother of the p.Gly32Arg variant carriers presenting with progressive neurodegenerative disorder also suffered from EOAD (Potluri et al., 2009).

The phenotypes of the previously reported patients and our patients carrying the *NDUFA1* p.Gly32Arg variant differ considerably. Therefore, also other genetical factors should be taken into account. However, all the known pathogenic mutations in the genes causing AD or FTLD were excluded from the EOD patients carrying the *NDUFA1* p.Gly32Arg variant. Three of our patients were carriers of the *APOE*ε4 allele (one homozygote), which is a known risk factor for both late- and early-onset AD (Cacace et al., 2016). Future research is required to confirm our results and to find out whether *APOE*ε4 allele together with *NDUFA1* p.Gly32Arg variant produce a synergistic risk for EOD or whether other genetical factors are needed. It is also possible that the EOD patients presented in this article possessed yet unknown genetical factors that have protected them from childhood onset diseases, such as Leigh syndrome. If protective genetic factors would be identified in the future, it would also give new opportunities for the development of treatments for the devastating childhood onset syndromes. Another important subject for future research is to identify the factors that caused the diseases to onset early in life in the previously reported patients.

There are some limitations in our study. Certain *SORL1* and *ABCA7* variants have previously been associated with EOAD (Campion et al., 2019; De Roeck et al., 2019). However, these variants have not been excluded from our patients and therefore we cannot rule out the possible effects of these variants.

In conclusion, we describe five EOD patients who carried the p.Gly32Arg variant in *NDUFA1*, suggesting that this variant may play a role in neurodegenerative dementia in addition to the previously reported mitochondrial diseases of childhood. However, due to the small number of patients, our study does not have enough power to give statistically significant results. Further studies with larger well-characterized cohorts, as well as functional studies are needed to investigate the role of *NDUFA1* p.Gly32Arg variant also in late-onset neurodegenerative diseases.

Verification

1 Authors have no conflicts of interest to report.
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4 The research protocols have been approved by the local ethics committees and the study has been done in accord with the Helsinki Declaration.
5 All the authors have contributed to the study, reviewed the final version of the submitted manuscript, and approved it for submission. The authors take full responsibility for the data, the analyses and interpretation, and the conduct of the research.

Disclosure Statement

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Author contributions

Samuli Huttula: Investigation, Formal analysis, Writing - original draft, Writing - review & editing, Henri Väyrynen: Investigation, Writing - review & editing, Seppo Helisalmi: Formal analysis, Writing - review & editing, Laura Kytövuori: Investigation, Formal analysis, Writing - review & editing, Laura Luukkainen: Investigation, Writing - review & editing, Mikko Hiltunen: Resources,

Data curation, Writing - review & editing, Anne M Remes: Writing - original draft, Writing - review & editing, Supervision, Resources, Data curation, Funding acquisition, Conceptualization, Johanna Krüger: Resources, Writing - original draft, Writing - review & editing, Supervision, Project administration, Conceptualization.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neurobiolaging.2021.09.026.

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