



## Case Report

A Novel Pathogenic Variant of *COL4A1* Gene in a Patient with Neuropathy: A Case ReportSajad Rafiee Komachali<sup>1,2</sup>, Khalil Khashei Varnamkhasti<sup>1,2</sup>, Seyyed Reza Mousavi<sup>1,2</sup>, Farzaneh Salimi, Mansoor Salehi<sup>1,2\*</sup><sup>1</sup>Cellular, Molecular and Genetics Research Center, Isfahan University of Medical Sciences, Isfahan, Iran<sup>2</sup>Medical Genetics Research Center of Genome, Isfahan University of Medical Sciences, Isfahan, Iran

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## ABSTRACT

**Background:** Neuropathies a result of damage to the peripheral nerves are a heterogeneous group of diseases which may occur due to underlying genetic abnormalities. Exciting capabilities of the whole exome sequencing to detect disorders at the level of genome, especially in heterogeneous disorder groups, made it easy to determine which of the genetic variation disease causing in an individual patient. This paper reports a novel *COL4A1* gene variation that was found in a case with para-clinical diagnosis of neuropathy, following molecular analysis. **Case presentation:** We report a 54 year-old man from the Al-Zahra Hospital, Isfahan University of Medical Sciences admitted to genome genetic center with para-clinical diagnosis of neuropathy based on electromyography. Further molecular analysis of patient genomic DNA using whole exome sequencing, revealed a heterozygous *COL4A1* pathogenic variant NM\_001303110: c.A1G: p.M1V. The result verified by Sanger Sequencing.

## INTRODUCTION

A major cause of disability and reduced quality of life can resulted by an etiologically heterogeneous group of peripheral nervous system disorders such as peripheral neuropathies (1,2). The peripheral neuropathies (also called polyneuropathies) refers to a wide spectrum of neurologic conditions which according to anatomic region and distribution across the peripheral nervous system can be divided into two clinical disease groups: Charcot–Marie–Tooth disease; when the neuropathy is the primary part of the disorder and familial amyloid polyneuropathy, mitochondrial neuropathy, porphyrias; when the neuropathy is part of a more generalized neurologic disorder (3). Hundreds of causes can led to sensory and motor symptoms of peripheral neuropathy, including; muscle cramps, weakness, and wasting, that may take several clinic visits to find the etiology (4,5). Over the past decades, identify sequence variants that contribute to disease susceptibility as a rapid approach had led to much more success of neuropathies diagnosis through the use of whole exome sequencing, among a lot of research which has been performed to elucidate pathophysiology of peripheral neuropathy (1). It has molecular been found that, genetic alterations leading to disruption of the molecular networks linking the basement membranes and myofiber cytoskeleton are well-established

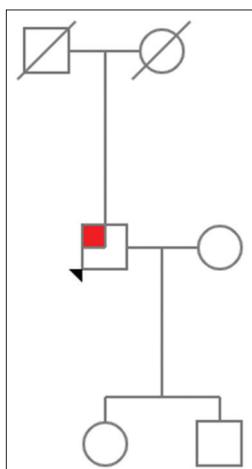
causes of muscular dystrophies that often involve peripheral neuropathy. Basement membranes by form an organized scaffold, provides structural support to cells, and influences and modifies cellular behavior. About 50% of all basement membranes makes up from six distinct chains of type IV collagen that known as  $\alpha$  -chains ( $\alpha 1 - \alpha 6$ ). Collagen type IV alpha 1 chain (*COL4A1*), is a fundamental protein of the basement membrane that its coding gene variations cause a spectrum of peripheral neuropathy disorders includes: muscle cramps and motor impairment (6,7). Here, for the first time, we report a case on the findings the NM\_001303110: c.A1G: p.M1V heterozygous variant of the *COL4A1* gene, that was identified by whole-exome sequencing. Our aim with this case report to propose that the novel pathogenic NM\_001303110: c.A1G: p.M1V variant can cause peripheral neuropathy.

## CASE PRESENTATION

A 54-year-old male patient with a past 10 years medical history includes of legs muscle weakness and cramp, lack of co-ordination and falling, sharp pain of toe (multi times per hour), ataxia, urinary retention and more severe symptoms over the past 5 years, such as progressive muscle weakness and need to equipment/standing aids, with neuropathy diagnosed on electromyography criteria, presented to genome genetic

**Table 1.** Incidental variants identified by whole exome sequencing in patient

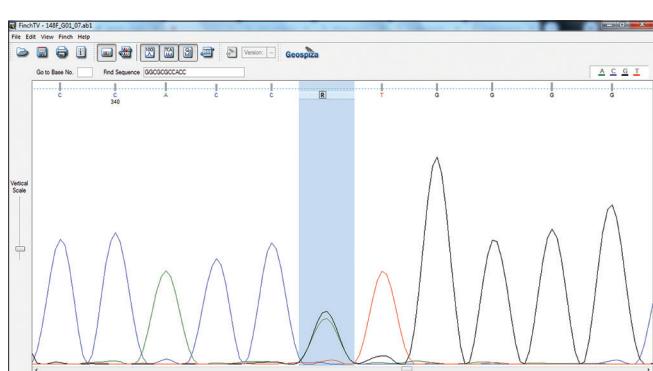
Gene	Variant	Genotype	Disease (OMIM)	Inheritance	Pathogenicity	
					ACMG	Clinvar
<i>ALG8</i>	NM_001007027:exon10: c.C1090T: p.R364X	Het	Congenital disorder of glycosylation, type Ih	AR	Pathogenic	Pathogenic
<i>FLG</i>	NM_002016: exon3: c. 2976_2977del: p.R992Sfs*31	Het	Ichthyosis vulgaris {Dermatitis, atopic, susceptibility to, 2}	AD, AR	Pathogenic	-
<i>ROBO3</i>	NM_022370:exon9: c.C1382T: p.T461M	Het	Gaze palsy, familial horizontal, with progressive scoliosis, 1	AR	Likely Pathogenic	-
<i>SLC38A8</i>	NM_001080442:exon7: c.C895T: p.R299W	Het	Foveal hypoplasia 2, with or without optic nerve misrouting and/or anterior segment dysgenesis	AR	Likely Pathogenic	-
<i>CYBA</i>	NM_000101:exon4: c.C272T: p.A91V	Het	Chronic granulomatous disease 4	AR	Likely Pathogenic	

**Figure 1.** Pedigree of the patient with segregation of the identified *COL4A1* pathogenic variant

ic DNA was extracted from the patient's specimen and whole exome sequencing was done on Illumina Hiseq4000 platform with 100X depth of coverage and 101 bp paired end reads. Raw sequence data analysis, including base calling, demultiplexing, alignment to the hg19 human reference genome (Genome Reference Consortium GRCh37) and variant calling was performed. Whole exome sequencing analysis revealed a heterozygous *COL4A1* pathogenic variant NM\_001303110: c.A1G: p.M1V, with autosomal dominant inheritance pattern. Some other incidental variant (s) that can be important because it may help prevent incidence of a disease or guide the management of signs and symptoms if the disease develops or is already present, had identified in patient as a secondary findings of whole exome sequencing (Table 1). The candidate variation from whole-exome sequencing, further confirmed using Sanger sequencing (Figure 2).

## DISCUSSION AND CONCLUDING REMARKS

Any given individual genome, contains millions different of sequence variants which will have no or normal effect in phenotype. However, a small percent of gene variants may harbor pathogenic mutations that cause or predispose to disease. In neurological disease, single base substitutions as the most DNA variation are substantially contribute to an individual's risk for developing disease. In recent years, improvements of sequencing-based studies, such as whole-genome sequencing, has facilitated the identification of genetic variants and a greater understanding of the etiology of many neurological diseases (8). Implementation of the whole-genome sequencing, determine the medical condition and the potential predispositions to unconsidered conditions in the future, which may have implications for other family members. Similarly, in the present case, based on the whole-genome sequencing data, we now know that the a not previously reported pathogenic *COL4A1* gene variation, contribute to development peripheral neuropathy. In this case because of died parents, assumed that *COL4A1* pathogenic variant NM\_001303110: c.A1G: p.M1V, is a de novo variation that may be originate

**Figure 2.** The variant point (c.A1G: p.M1V) in *COL4A1* gene in patient that was confirmed by Sanger sequencing

center (Isfahan, IRAN) to identify the presence of possible genetic variants. He had no cardiovascular disease, hematology and other laboratory abnormalities. Family history also reported no obvious similar condition in family members (Figure 1). To tested hypothesis of genetic predisposition, patient was drawn blood samples for whole exome analysis. Genom-

from errors in DNA replication during. Finally, in turn, this finding offers the possibility of targeted medical consultations and interventions, and, in some cases, treatment.

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