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The genetic counseling in a patient affected by congenital polyneuropathy after a "diagnostic odyssey" recently solved with WES approach

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Abstract

Counseling after WES/WGS presents challenges for healthcare providers as the availability of consumer-driven is rapidly increasing. The present report uncovers an extremely rare homozygous nonsense mutation c. 1639C>T (p.Gln547Ter) in PRX gene of a patient with heterogeneous manifestation of Charcot-Marie-Tooth. Such studies can help to conduct genetic counseling and subsequently more accurate support to individual cases with neuro-genetic conditions and solved through whole genome/exome-wide screening.

Key Words: Charcot-Marie-Tooth, genetic counseling, stop-codon mutation, WES.

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Each person has many DNA variants in their genome: making the distinction between neutral and pathogenic mutations is a key challenge when interpreting the results of a targeted genetic testing approach such as Whole Exome Sequencing (WES). Establishing the genetic basis for complex neurological conditions using WES is challenging in the majority of cases, particularly in genetically heterogeneous conditions such as Charcot-Marie-Tooth (CMT). An additional challenge is to precisely define the clinical phenotype, e.g., distinguish congenital polyneuropathy from acquired chronic demyelinating neuropathies.[1] The following details a case illustrating the potential of genetic counseling in the WES process to define genetic etiology in a complex condition, directly leading to successful healthcare support.

Case report

An Italian 46-year-old man presented a neurologic condition with a progressive movement disorder (written informed consent was obtained). He is an only child with a negative family history. He was asymptomatic until the age of 2 years, when he finally started crawling and his "diagnostic odyssey" began. Following molecular and medical evaluations carried out by different neurological clinics in Lombardy, Computed Axial Tomography (CAT) and Electromyography (EMG) confirmed undetectable sensory nerve action potentials. At the age of 14 he was also subjected to two biopsies (ring finger and foot): cross section showed marked depletion of myelinated nerve fibers, replacement fibrosis and peripheral nerve segmental demyelination. He was described with a "short strides" walking and a gait disorder characterized by weakness of foot dorsiflexors, foot-drop, and excessive flexion of knees when walking; his toes barely cleared the ground, likely due to the paralysis of the anterior tibialis muscles. Electrophysiological analysis had confirmed undetectable sensory nerve action potentials and repeating clonic reflexes (hyperreflexia) and he received a clinical diagnosis of atypical "Hereditary Motor and Sensor Neuropathy, Type 1. His clinical picture didn't change until the age of 19 when he started to develop more functional impairments with lateral asymmetry: the right arm and the left leg are the most compromised. He was dependent on wheelchairs since the age of 27. The initial genetic testing analysis, which focused on variants in the PMP22 and MPZ genes, known to be associated with CMT, was negative. Recently, he performed a WES analysis with 3Billion Inc, a company focused on NGS applications for patients affected by rare diseases, which also confirmed the identified variants by paired-end Sanger sequencing. This analysis revealed a homozygous nonsense variant (NM_181882.2; c. 1639C>T, p.Gln547Ter) in the PRX gene (Periaxin). The Gln547Ter variant was previously reported as causal for CMT type 4F (MIM #128230), in another Italian case of compound heterozygosity.[2] We report here the first case of double homozygosity for the NM_181882.2 null mutation. The Gln547Ter variant, encoding for a stop codon, can be considered the probable cause of the consultand's condition, given its presentation, and was

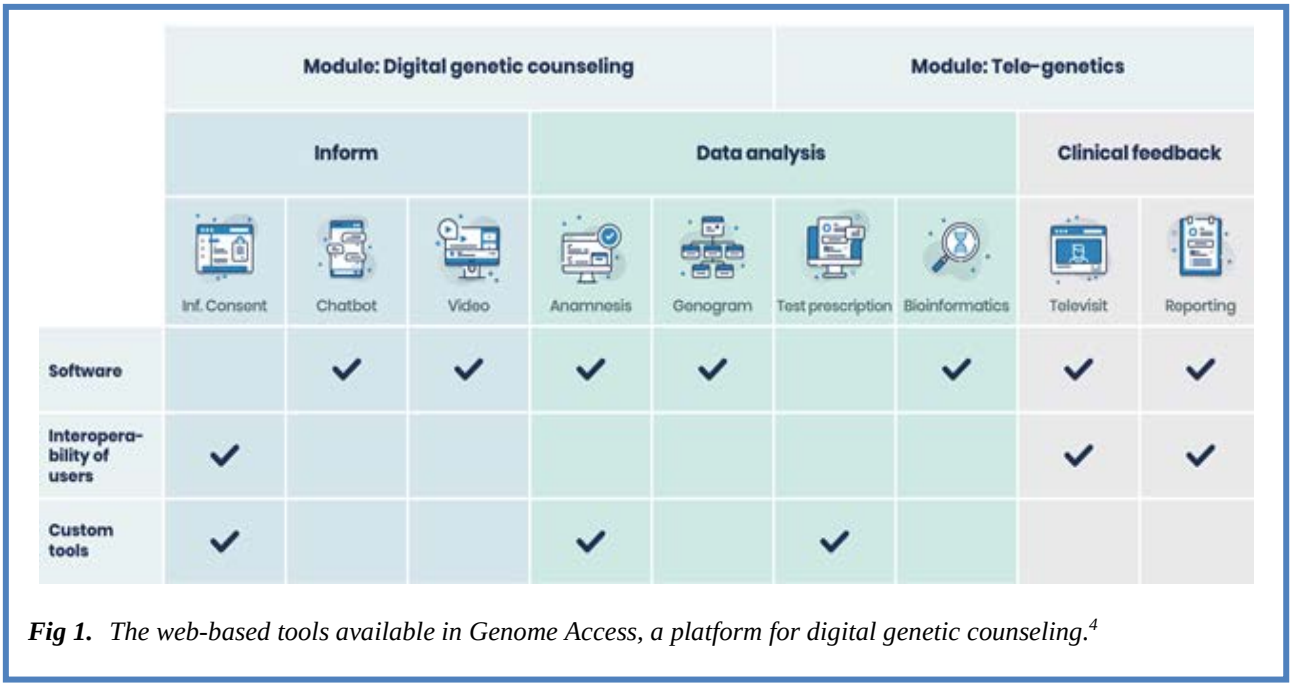

Fig 1. *The web-based tools available in Genome Access, a platform for digital genetic counseling.*[4]

reported as a positive diagnostic result. During the counseling we've explained to the consultand the inheritance patterns of the Gln547Ter variant and the risk of recurrence within his family. At the wrap-up of the counseling session, we referred the consultand to an appropriate neurologist with long-term experience of CMT, and provided him with the details of the local patient advocacy organization (https://www.acmt-rete.it/).

Discussion

It is generally accepted that individuals with congenital polyneuropathy of unknown etiology should undergo WES and consult appropriately. Identifying the genetic etiology of a condition can guide management and provide valuable information about the risks of the condition for family members. The emerging availability of efficient DNA sequencing, coupled with the inherent difficulties in establishing a diagnosis for many complex neurological presentations, requires consideration of general strategies for targeted genetic testing. We recommend not limiting screening to a single family of genes (i.e., those involved in CMT) to avoid the risk of missing the diagnosis in heterogeneous conditions, such as CMT, and include the sequencing of PRX in cases of undiagnosed CMT, at least in the north of Italy where the frequency of the NM_181882.2 variant could be higher than expected. To provide an accurate diagnosis and correct healthcare support for persons with complex neurological conditions, it may be increasingly useful to consider extensive genetic testing through an extended clinical panel or WES and, therefore, post-test genetic counseling, in person or via a telegenetic platform as well,[3] is needed to help consultand to make informed selections about the type of additional outcomes he/she may receive, understand the options and implications of the results for medical management and the impact on his/her family members. In conclusion, we recommend that any genetic counseling service should engage a multidisciplinary team of trained bioinformaticians, molecular and clinical geneticists, and genetic counselors as well,[4] in order to guarantee the releasing of reports with a detailed interpretation of the pathogenicity (or lack thereof) of any rare identified variants and Variant of Uncertain Significance (VUS), if any. The outcome of the genetic counseling sessions should be also in compliance with the Genetic Counseling Outcome Scale (GCOS)-24 scale.[5.] Also genetic counseling services are now involved in the so-called digital transformation leveraging information technologies (Figure 1).

List of acronyms

CAT - Computed Axial Tomography
CMT - Charcot-Marie-Tooth
EMG - Electromyography
GCOS - Genetic Counseling Outcome Scale -24 scale
VUS - Variant of Uncertain Significance
WES - Whole Exome Sequencing

Contributions of Authors

MC: Conceptualization, Funding acquisition, Investigation, Project administration, Software, Writing-original draft. AD: Conceptualization, Writing-review and editing. Both contributors approved the manuscript and agreed with study publication.

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Conflict of Interest

The authors declare they do not have any conflict of interest. Kaleidos is a no-profit enterprise aimed at improving the knowledge on genomics.

Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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References

1. Bordini BJ, Monrad P. Differentiating Familial Neuropathies from Guillain-Barré Syndrome. Pediatr Clin North Am. 2017 Feb;64(1):231-252. doi: 10.1016/j.pcl.2016.08.015.
2. Marchesi C, Milani M, Morbin M, Cesani M, Lauria G, Scaioli V, Piccolo G, Fabrizi GM, Cavallaro T, Taroni F, Pareyson D. Four novel cases of periaxin-related neuropathy and review of the literature. Neurology. 2010 Nov 16;75(20):1830-8. doi: 10.1212/WNL.0b013e3181fd6314.
3. Du L, Becher SI. Genetic and Genomic Consultation: Are We Ready for Direct-to-Consumer Telegenetics? Front Genet. 2018 Dec 3;9:550. doi: 10.3389/fgene.2018.005504.
4. Crimi M, Mineri R, Godino L, Bertonazzi B, Bruzzone C, Pivetta B, Cordier C, Coviello DA, Feroce I. Building awareness on genetic counselling: the launch of Italian Association of Genetic Counsellors (AIGeCo). J Community Genet. 2020 Oct;11(4):495-496. doi: 10.1007/s12687-020-00483-3.
5. Thomas C, McAllister M. Establishing the minimum clinically important difference for the Genetic Counseling Outcome Scale (GCOS-24). J Genet Couns. 2019 Oct;28(5):1003-1010. doi: 10.1002/jgc4.1152. Epub 2019 Jul 30..

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