Scientific Research Publishing

Case Reports in Clinical Medicine, 2024, 13, 25-36
https://www.scirp.org/journal/crcm
ISSN Online: 2325-7083
ISSN Print: 2325-7075

Quantifying Kinematic Tremor in an NGLY1-Deficient Individual: A Case Study

Brock Futrell[1,2*], Christopher Alexander Malaya[1,2], Dacia Martinez Diaz[1,2], Christian Alfaro[1,2], Hannah Elizabeth Gustafson[1,2], Subhalakshmi Chandrasekaran[1,2], Rhea Mohan Phatak[3], Bernhard Suter[4,5], Charles Shannon Layne[1,2,6]

[1]Department of Health and Human Performance, University of Houston, Houston, USA
[2]Center for Neuromotor and Biomechanics Research, University of Houston, Houston, USA
[3]Department of Computer Science and Engineering, Texas A&M University, College Station, USA
[4]Blue Bird Circle Rett Center, Texas Children's Hospital, Houston, USA
[5]Baylor College of Medicine Houston, USA
[6]Center for NeuroEngineering and Cognitive Science, University of Houston, Houston, USA
Email: *bfutrell@cougarnet.uh.edu

How to cite this paper: Futrell, B., Malaya, C.A., Diaz, D.M., Alfaro, C., Gustafson, H.E., Chandrasekaran, S., Phatak, R.M., Suter, B. and Layne, C.S. (2024) Quantifying Kinematic Tremor in an NGLY1-Deficient Individual: A Case Study. *Case Reports in Clinical Medicine*, **13**, 25-36.
https://doi.org/10.4236/crcm.2024.131003

Received: December 19, 2023
Accepted: January 19, 2024
Published: January 22, 2024

Abstract

NGLY1 Deficiency is an autosomal recessive congenital disorder that has been identified in less than 100 individuals. Most individuals with NGLY1 Deficiency display hyperkinetic movement disorders, including choreiform, athetoid, dystonic myoclonic, dyskinetic, and dysmetric movements. Developing a consistent and concise consensus on the classification and evaluation of tremors is essential to forward the research and treatment of tremors. It has also been reported that some individuals with NGLY1 Deficiency demonstrate tremor, but such tremor has never been formally investigated. The primary objective of this study is to determine if an individual with NGLY1 Deficiency demonstrates an identifiable tremor during a series of arm movements and, if so, describe the frequency and power characteristics of that tremor. Arm movement kinematics were obtained using a 16-camera Vicon system, and time series trajectory waveforms for three planes of a marker placed on the hand were developed. Custom MATLAB scripts were utilized to compute Fast Fourier Transformations of the data within the identified waveform segments. A mean frequency of 2.30 Hz (SD = 1.05) with a mean power of 5.02 |P1(f)| (SD = 4.63) suggests that our participant's kinematic data did display a persistent tremor in both hands across all tasks and movement planes. Analyses of the reaching hand and the non-reaching hand suggest the participant displayed an action tremor in both postural and intention (kinetic) tremors. Future directions should include assessing additional individuals with NGLY1 Deficiency to determine if the tremor is a distinguishable disorder behavior. Ad-

ditionally, evaluating other anatomical sites, such as the elbow, head, and lower limbs, would provide further insights into the characteristics of this tremor.

Keywords

Tremor, NGLY, Fast Fourier Transformation, Reaching, Hyperkinetic Movement

1. Introduction

NGLY1 Deficiency is an autosomal recessive congenital disorder identified in less than 100 individuals by 2022 [1]. One instance of NGLY1 Deficiency was described in 2012, with several variants of this condition being described since [2]. However, there are similar characteristics among the variants. These characteristics include neuromuscular dysfunction such as axonal or demyelinating peripheral neuropathy, alacrimia, cognitive developmental delay, small fiber neuropathy and scoliosis. Other characteristics are more orthopedic in nature and include joint contractures, fractures, and hip dysplasia [3]. Although to date, there have been no laboratory-based evaluations of the movement difficulties of individuals with NGLY1 Deficiency, a variety of movement disorders have been identified through visual inspection. Most commonly reported are hyperkinetic movement disorders, including choreiform, athetoid, dystonic myoclonic, dyskinetic, and dysmetric movements [4]. A review by [3] also mentioned a case study where the participant experienced developmental disabilities, axial hypotonia and hyperkinetic movement disorder by 12 months of age. While this participant displayed a normal brain MRI scan, other case studies mention brain MRIs showing delayed myelination, which can lead to nervous system detriments mentioned previously [5]. As a majority of individuals with NGLY1 Deficiency are reported to have hyperkinetic movements [6], there is a clear benefit to quantify these movements. In addition to the above-mentioned movement difficulties, action tremor has been identified as a characteristic sometimes associated with NGLY1 Deficiency [7]. However, the characteristics of this tremor have not yet been formally assessed using laboratory-based techniques.

A recent report from a committee composed of clinicians and scientists defined tremor as: "an involuntary, rhythmic, oscillatory movement of a body part" [8]. Many authors suggest conducting laboratory-based investigations would be necessary to quantify tremor characteristics of different hyperkinetic movement conditions [3] [5] [9] [10].

Several types of tremors exist, including subtypes with differing underlying etiologies. Developing a consistent and concise consensus on the classification and evaluation of tremors is essential to forward the research and treatment of tremors. Action tremor is a common type of tremor, identified as a hyperkinetic movement that hinders the execution of voluntary movement (kinetic move-

ment) or a hyperkinetic movement that occurs while maintaining a position against gravity (postural tremor) [8]. Examples of action tremors include intention tremors, typically manifesting during goal-directed movements and postural tremor, which manifests when a muscular contraction occurs against an object or gravity.

Many tremor conditions can be characterized by frequency, such as Parkinsonian resting tremors that range from 3 - 6 Hz and are associated with particular areas of brain dysfunction. For example, Parkinsonian tremor is related to basal ganglia dysfunction, while intention tremor is associated with cerebellar dysfunction [11]. While assessing tremor frequency alone can provide helpful information, frequency information in isolation is not enough for a confident diagnosis due to the potential crossover between conditions. Therefore, a comprehensive tremor assessment benefits from including information about both frequency and the power of the dominant frequency. The combination of these two measures provides essential information that promotes opportunities to efficiently and effectively research and ultimately treat tremors regardless of etiology. Several instances of documenting tremors in NGLY patients exist in the literature [2] [3] [4], but to our knowledge, none mentions quantitative reports on the frequency and power characteristics of the proposed NGLY1 tremor. Therefore, the primary objective of this study is to determine if an individual with NGLY1 Deficiency demonstrates an identifiable tremor during a series of arm movements and, if so, describe the characteristics of that tremor using frequency and power.

2. Methods

2.1. Study Participant

The NGLY1 participant in this study carries both a heterozygous frameshift variant c.1242 delT and a splice site affecting c.858 + 1G > A variant in the NGLY1 gene. Her developmental trajectory was delayed from infancy and was first noted as abnormal around 8 months. She achieved sitting only at 14 months, crawling at 19 months, and walking with a walker at 3 years of age at 36 months, she lost the ability to stand or walk independently. At the time of our assessment, she had a Gross Motor Function Classification System—Expanded & Revised (GMFCFS E&R) score of 4 and her highest level of gross motor skill was standing with support. Along with developing a generalized increase in muscle tone she started developing movement disorders that are typical for NGLY1 Deficiency which included tremor, choreo-athetoid movements, dysmetria during intentional reaches, and orofacial dyskinesias. The movement disorder became more pronounced over time. The parents provided written informed consent for the participant.

2.2. Tasks

A series of arm-reaching tasks were performed from the seated position. Each

reach began with the participant's hands resting comfortably in her lap (Table 1). Movements were categorized based on the goal of the task. One category was labeled open-ended, during which the participant moved her hand to a point in space and then returned it to her lap. For example, a shoulder flexion with elbows extended. The second category of tasks involved reaching for small objects, such as a tennis ball or a pen, to be removed from the hand of a research assistant who held the objects in front of the participant at the participant's arm length. The participant grasped the object, moved it to her lap, and returned it to the research assistant's hand. These movements were labeled as "goal-directed" movements. A total of 12 different movements were performed; each movement was repeated twice, with each arm. An exception was the open-ended movements in which, after performing the left and right-hand movements independently, the same movements were performed by both hands simultaneously. For example, both hands were simultaneously raised above the head. A total of 54 arm movement trials were performed.

Table 1. Description of tasks.

Arm used to complete reaching task	Task
	Open-ended reach*
Left and Right	Adduct hand across the midline to touch shoulder
Right	Abduct hand across the midline to touch shoulder
Both	90˚ shoulder abduction with full elbow extension
Left and Right	90˚ shoulder abduction with full elbow extension
Both	180˚ shoulder flexion with full elbow extension
Left and Right	180˚ shoulder flexion with full elbow extension
Both	90˚ shoulder flexion with full elbow extension
Left and Right	90˚ shoulder flexion with full elbow extension
	Goal-directed reaches
Left and Right	Grasp a 14 cm diameter ring (Horizontally presented)
Left and Right	Grasp pen (Vertically presented)
Left and Right	Grasp pen (Horizontally presented)
Left and Right	Grasp toy car
Left and Right	Grasp golf ball
Left and Right	Grasp tennis ball
Left and Right	Reach through a 14 cm diameter ring (Vertically presented)

*Each hand individually, first right, then left, and then both hands simultaneously.

Several unique features of our participant's hand movement control should be pointed out. When she was asked to produce a voluntary hand movement, for example, a right-hand reach, both hands would initially begin to move randomly, often, across all three joints, *i.e.*, shoulder, elbow, and wrist, with motion in all three planes of the shoulder and wrist*. These actions can loosely be described as arm "flapping" motions and are labeled segmental dystonia. However, these actions appeared to be free of muscle spasms, per se, which are often associated with dystonic movement. Eventually, the limb designated to complete the task would move more purposefully to complete the open-ended movements or grasp the object during the goal-directed tasks. We labeled this purposeful action as the "acceleration" phase of the movement. Prior to the hand beginning to return to the participant's lap, the hand would often "wander" at the endpoint of the open-ended movement or spend time trying to grasp the presented objects. We labeled this period as the "maintenance" phase. Using a camera-based motion capture system creates the possibility that high frequency motion may not be adequately captured if a low sample rate is used, for example 33 frames per second. However, given the present data was captured at 100 Hz and the identified tremor was well below 5 Hz, we are confident the tremor is accurately represented.

*The elbow joint motion is restricted to the sagittal plane when measured by the Vicon Nexus motion capture system, see below.

2.3. Data Collection and Processing

A 16-camera Vicon Nexus motion capture system (The MathWorks, Natick, MA) was utilized to obtain arm movement kinematics. Twenty-four reflective markers were placed on landmarks on the participant's upper body per the Nexus upper body model. Data was collected at ca 100 Hz, and the trajectories of the reflective markers placed on the hand were filtered using a 2nd order Butterworth filter. The participant's sagittal plane was defined as the X plane, the frontal plane as the Y plane, and the transverse plane as the Z plane.

After data collection, the marker trajectory data associated with the right and left markers placed on the first metacarpophalangeal joints, (*i.e.*, index finger knuckle) were downloaded. Time series waveforms of both index finger trajectories were developed for each plane as rotational and translation motions can differ across the planes of motion [12] [13]. The trajectory waveforms were visually inspected to identify segments that reflected oscillatory motion, *i.e.*, tremor (see **Figure 1(a)**). These waveform segments were then evaluated to quantify the characteristics of the tremor within a given waveform segment. As we were primarily interested in identifying tremor characteristics independent of active hand motion, waveform segments that represented the acceleration phase of the movements were excluded from the analyses (**Figure 1(a)**) with the following labels: 1) Pre-Movement, 2) Acceleration Phase, 3) Maintenance Phase , 4) Deceleration Phase, & 5) Post-Movement. **Figure 1(b)** and **Figure 1(c)** depict a "zoomed" view of sections 1 and 5 of **Figure 1(a)** showing visually incepted

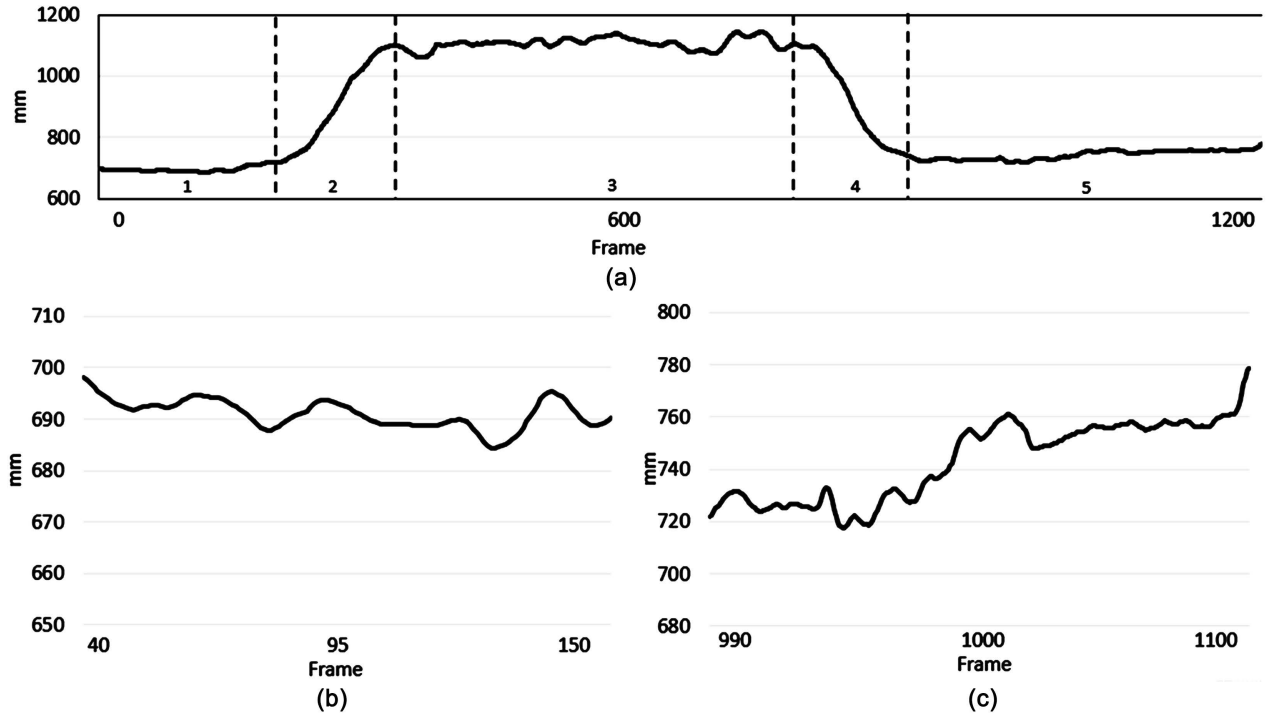

Figure 1. A representative time series kinematic profile was obtained during an active reach. (a) provides data representing an entire reach with different segments of the reach identified. (b) displayed the data from segment 1, while (c) represents data from segment 5.

tremor for further analysis. The hand the participant was instructed to use to complete the task was labeled the "reach" hand. The hand not completing the reach was labeled the "non-reaching" hand.

Custom MATLAB scripts (The MathWorks, Natick, MA) were utilized to compute Fast Fourier Transformations (FFT) of the data within the identified waveform segments. This process was repeated for the data of each plane for each movement, with peak frequency and the power at the peak frequency being recorded. Figure 2 provides a representative example of the output obtained from the customized FFT script displaying frequency and associated power. Means and standard deviations (SD) were calculated and used to assess potential differences in peak frequency and power between the active and inactive hands, right versus left hands, and plane.

In addition to determining if an identifiable tremor existed, we explored three secondary questions using the frequency and power variables: 1) are there differences between the reach and non-reaching hand, 2) are there differences between the left and right hand, 3) are there differences between the three planes of movement?

2.4. Statistical Analysis

To determine if the data provided evidence of tremor, we collapsed all the data over reach condition, hand, and movement plane. We calculated a mean and SD for both the frequency and power. After checking for normality using the

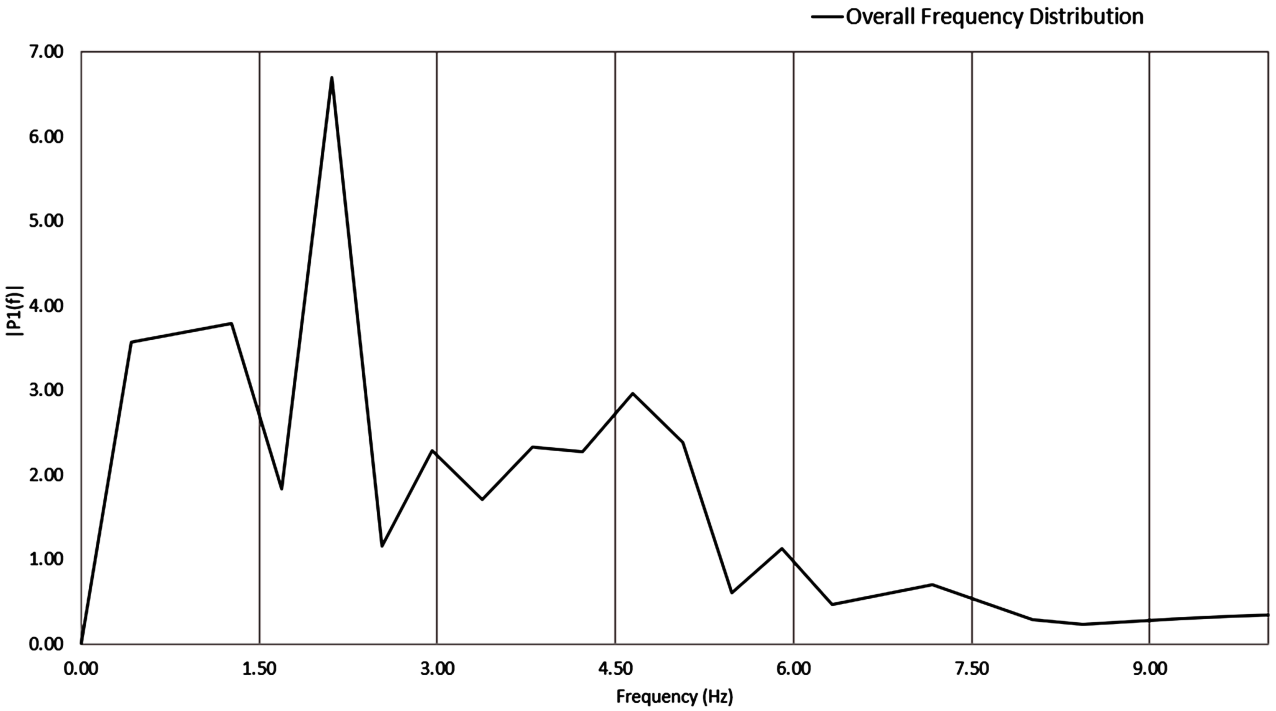

Figure 2. A representative output after performing the FFT analyses displaying frequency and associated power.

Kolmogorov-Smirnov test, the mean frequency was tested to determine if it differed from zero using a one-sample t-test with a hypothetical value of 0 frequency. After assessing the equality of variance using the Leven's test, Welch's t-test [14] was used to test for potential differences between reach conditions collapsed over hands and planes and left and right hands collapsed over reach conditions and plane. Finally, planes collapsed over reach conditions and hands were tested to determine differences in the tremor characteristics between the different planes of motion. An alpha level of $P < 0.05$ with Bonferroni corrections were applied when appropriate.

3. Results

When the data were collapsed over reach conditions, hand, and movement plane, a mean peak frequency of 2.30 Hz (SD = 1.05) with a mean power of 5.02 |P1(f)|, (SD = 4.63) was obtained. The one-sample t-test indicated the mean peak frequency was significantly different from the hypothetical value of 0 Hz ($P < 0.00001$, $t = 22.87$, $df = 108$). This suggests that our participant's kinematic data did display a persistent tremor in both hands across all tasks (reaching or non-reaching hand) and movement planes.

When collapsed over hand (left or right) and task role (reaching or non-reaching), there were no significant peak frequency differences between planes. The means and SDs of the X, Y and Z planes were 2.08 Hz (1.06), 2.40 Hz (1.04) and Z 2.17 Hz (1.06). For subsequent statistical testing, the means and SD for peak frequencies were collapsed over planes and arranged based on statistical comparisons with the results presented in **Table 2(a)** and **Table 2(b)**. Of note, higher

Table 2. (a) Reach and non-reach hand frequency (Hz); (b) Right vs. Left Hand Frequency (Hz).

(a)

		Mean	SD	P-Value
Reach Hand				
	Left Hand Task	2.12	0.99	0.38
	Right-Hand Task	2.15	1.04	
Non-Reach Hand				0.02*
	Left Hand Task	3.11	1.25	
	Right-Hand Task	2.33	0.79	

(b)

		Mean	SD	P-Value
Right Hand				0.76
	Reach Hand	2.15	1.04	
	Non-Reach Hand	2.23	0.79	
Left Hand				0.01*
	Reach Hand	2.12	0.99	
	Non-Reach Hand	3.11	1.25	

frequencies of >3 Hz (mean = 3.11; SD 1.25) were found in the non-reaching left hand both when compared to the frequency of the non-reaching right hand and to the left hand when it was the reaching hand. No other comparisons reached significance.

The means and SD for the power of peak frequencies are presented in Table 3(a) and Table 3(b) (Figure 3).

4. Discussion

The current results indicate that our NGLY1 Deficient participant demonstrated quantifiable upper limb tremor in both arms and all three movement planes regardless of the limb's role in a given movement task (*i.e.*, reach or non-reach hand). Frequencies were relatively similar throughout each task regardless of hand or involvement, except when the left hand was the non-reaching hand during the tasks. Overall, the data provide compelling evidence that a tremor of approximately 2.30 Hz (SD = 1.05) was present in this individual.

The statistical comparisons of the power data indicate a significant distinction depending upon if the hand was reaching or non-reaching during a given task, regardless of whether it was the right or left hand (see Table 3(b)). The significant increase in power when the hand was involved in the reaching task reveals that the voluntary motion associated with the reach increases the power of the tremor despite the frequency remaining constant. It should be remembered that

data obtained during the acceleration period of the voluntary movement were not included in the tremor analysis. Thus, the increase in power was exhibited prior to the beginning of the acceleration phase of the movement or during the maintenance phase which occurred when the hand had either stopped accelerating, during open-ended movements or was grasping for an object once the hand had reached the distance that enabled grasping to occur, *i.e.*, movement endpoint, during the goal-directed movements. This endpoint control period occurred before the hand began to voluntarily return to the participant's lap.

Table 3. Power |P1(f)| Plane means collapsed over hand and movement task, left and right hand indicates collapsed over all planes and movement task. (a) Reach and Non-Reach Hand Power |P1(f)|; (b) Right vs. Left Hand Power |P1(f)|.

Plane	Mean	SD	P-Value
X	3.77	3.43	X vs Y = 0.29, X vs Z = 0.02*
Y	4.11	4.88	Y vs Z = 0.14
Z	5.15339	5.71	
Left Hand	5.17	5.25	Left vs Right = 0.17
Right Hand	5.01	4.16	
Reaching Hand	6.25	4.91	Reaching vs Non-reaching = 0.00*
Non-reaching Hand	2.91	3.29	
Open Ended	5.38	4.81	Open Ended vs Goal Directed = 0.84
Goal-directed	4.86	4.60	

(a)

		Mean	SD	P-Value
Reach Hand				
	Left Hand Task	6.45	4.13	0.07
	Right-Hand Task	6.04	5.66	
Non-Reach Hand				
	Left Hand Task	3.25	3.70	0.34
	Right-Hand Task	2.66	3.01	

(b)

		Mean	SD	P-Value
Right Hand				
	Reach Hand	6.45	4.13	0.00*
	Non-Reach Hand	2.66	3.01	
Left Hand				
	Reach Hand	6.04	5.66	0.00*

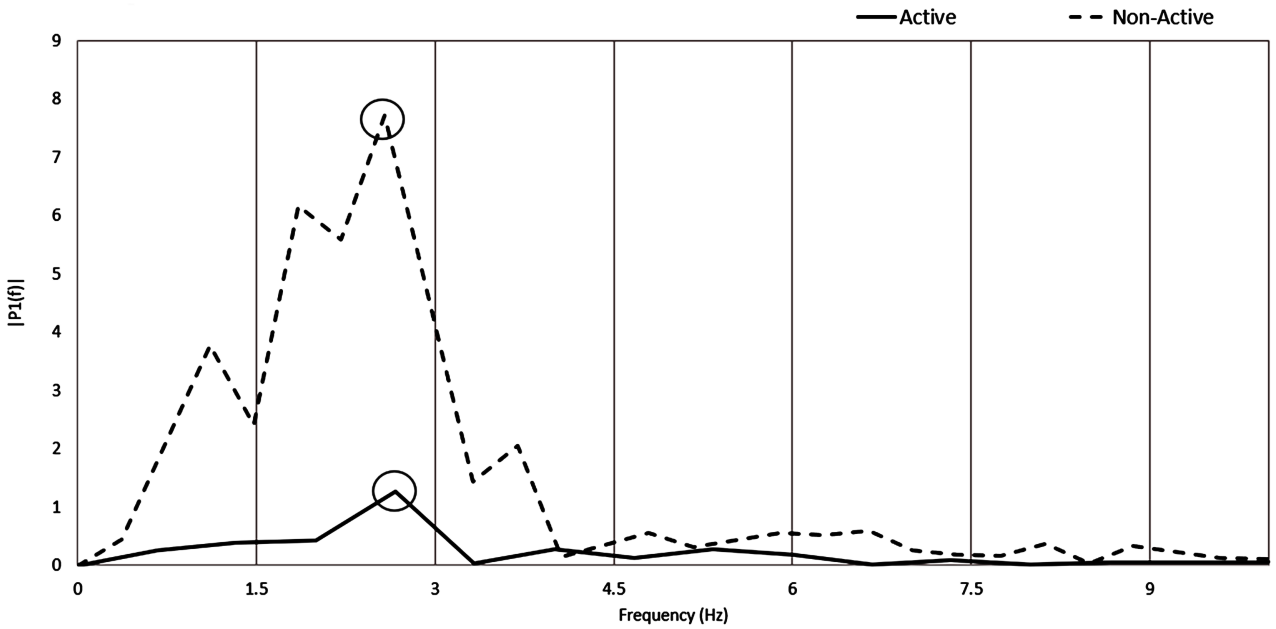

Figure 3. Exemplar data displaying similar mean frequencies but differences in associated power for an active and non-active right hand reach. The ovals identify peak frequency and the associated power for each movement.

Many attempts have been made to standardize the classification of tremors. The Consensus Statement on the Classification of Tremors by [8] proposed classification phraseology with the intent to standardize tremor classification to forward research and treatment of conditions that have tremor associations. The task force proposed two main (categories) aspects to identify tremor: clinical features and etiology. By incorporating this two-aspect approach, increased diagnosis efficiency assists where clinical features are used to define the syndrome.

The clinical features include multiple categories, age of onset, anatomical distribution, tremor frequency, and activation conditions. To provide some examples for each category, age of onset, has multiple grouping such as those aged from birth to 2 years as infancy, individuals aged 3 - 12 as childhood and 13 - 20 as adolescence. Another category, anatomical distribution, is used to identify if the tremor is localized to only one body region or prevalent across multiple body segments. As previously mentioned, activation conditions are separated into resting and action tremors, with the current report focusing on two aspects of action tremors: intention and postural tremors.

The second axis of classification is more directly related to the etiology of the disease. Classification is divided into nine categories: neurodegenerative, chromosomal aneuploidy, mitochondrial genetic disorders, infectious and other inflammatory diseases, endocrine and metabolic disorders, neuropathies and spinal muscular atrophies, toxins, drugs, and others.

We proposed that based on our findings, our participant with NGLY1 Deficiency displayed an action tremor that is present both during intentional and postural activities. Further utilizing the previously mentioned methods for classifying tremor, our participant would be classified as an adolescent with a first

axis < 4 Hz intention and postural action tremor that is dramatically presented unilaterally when maintaining elbow flexion against gravity with a second axis identifying the underlying etiology, in this case, the participant has been previously diagnosed with NGLY1 Deficiency. Interestingly, when either the right or left hand were the hands performing the reaches, they displayed no differences in either frequency or power. However, the increase in postural tremor in the left hand when the right hand was performing the reach may suggest an asymmetry in brain functioning, particularly during movement planning stages that manifested when our participant focused on the moving hand. Unlike action and intentions tremor, which is present during voluntary movement, the currently assessed tremor was exacerbated in both power and frequency in the arm that was not being used to complete a voluntary reach. If confirmed in future studies, this aspect of the tremor could potentially be used by clinicians as a distinguishing characteristic of individuals with NGLY1 Deficiency, possibly in a diagnostic fashion. Future work could then be devoted to using available brain scanning technology to attempt to identify if certain brain structure deficiencies are associated with the unique tremor pattern.

5. Limitations and Future Directions

The most important limitation is that data was obtained from a single participant, thereby limiting the generalizability of the findings. Thus, we cannot answer the question of whether movement tremor is a prevalent feature of NGLY Deficiency. However, the results are supportive of previous reports that tremor is an identified feature of NGLY1 [2] [3] [4].

Further, greater insights into the quantitative features of the identified tremor may have been obtained if additional body segment trajectories had been analyzed. Future directions should include increased participant numbers and upper and lower limb segment analyses as well as the head. Finally, obtaining brain imaging information would enable clinicians to identify specific brain regions most closely linked to the generation of the tremor. These additions would help to more fully characterize movement tremor within the population of individuals with NGLY1 Deficiency and possibly lead to therapeutic or pharmacological countermeasures designed to reduce the tremor.

Acknowledgements

We thank our participant and her family for her willingness to take part in this study.

Funding

This study was funded by a grant from the Grace Science Foundation to CSL.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Pandey, A., Adams, J.M., Han, S.Y. and Jafar-Nejad, H. (2022) NGLY1 Deficiency, a Congenital Disorder of Deglycosylation: From Disease Gene Function to Pathophysiology. *Cells*, **11**, 1155. https://doi.org/10.3390/cells11071155

[2] Lipiński, P., Bogdańska, A., Różdżyńska-Świątkowska, A., Wierzbicka-Rucińska, A. and Tylki-Szymańska, A. (2020) NGLY1 Deficiency: Novel Patient, Review of the Literature and Diagnostic Algorithm. *JIMD Reports*, **51**, 82-88. https://doi.org/10.1002/jmd2.12086

[3] Dabaj, I., *et al.* (2021) NGLY1 Deficiency: A Rare Newly Described Condition with a Typical Presentation. *Life*, **11**, 187. https://doi.org/10.3390/life11030187

[4] Lipari Pinto, P., *et al.* (2020) NGLY1 Deficiency—A Rare Congenital Disorder of Deglycosylation. *JIMD Reports*, **53**, 2-9. https://doi.org/10.1002/jmd2.12108

[5] Lam, C., Wolfe, L., Need, A., Shashi, V. and Enns, G. (2023) NGLY1-Related Congenital Disorder of Deglycosylation. In: Adam, M.P., Mirzaa, G.M., Pagon, R.A., Wallace, S.E., Bean, L.J., Gripp, K.W. and Amemiya, A., Eds., *GeneReviews®*. University of Washington, Seattle. http://www.ncbi.nlm.nih.gov/books/NBK481554/

[6] Stanclift, C.R., *et al.* (2022) NGLY1 Deficiency: Estimated Incidence, Clinical Features, and Genotypic Spectrum from the NGLY1 Registry. *Orphanet Journal of Rare Diseases*, **17**, Article No. 440. https://doi.org/10.1186/s13023-022-02592-3

[7] Need, A.C., *et al.* (2012) Clinical Application of Exome Sequencing in Undiagnosed Genetic Conditions. *Journal of Medical Genetics*, **49**, 353-361. https://doi.org/10.1136/jmedgenet-2012-100819

[8] Bhatia, K.P., *et al.* (2018) Consensus Statement on the Classification of Tremors from the Task Force on Tremor of the International Parkinson and Movement Disorder Society: IPMDS Task Force on Tremor Consensus Statement. *Movement Disorders*, **33**, 75-87. https://doi.org/10.1002/mds.27121

[9] Chang, C.A., Wei, X., Martin, S.R., Sinasac, D.S. and Al-Hertani, W. (2019) Transiently Elevated Plasma Methionine, Sadenosylmethionine and Sadenosylhomocysteine: Unreported Laboratory Findings in a Patient with NGLY1 Deficiency, a Congenital Disorder of Deglycosylation. *JIMD Reports*, **49**, 21-29. https://doi.org/10.1002/jmd2.12064

[10] Hope, K.A., Berman, A.R., Peterson, R.T. and Chow, C.Y. (2022) An *in vivo* Drug Repurposing Screen and Transcriptional Analyses Reveals the Serotonin Pathway and GSK3 as Major Therapeutic Targets for NGLY1 Deficiency. *PLOS Genetics*, **18**, e1010228. https://doi.org/10.1371/journal.pgen.1010228

[11] Hess, C.W. and Pullman, S.L. (2012) Tremor: Clinical Phenomenology and Assessment Techniques. *Tremor and Other Hyperkinetic Movements*, **2**, Article No. 2. https://doi.org/10.5334/tohm.115

[12] Krishna, R., Pathirana, P.N., Horne, M., Power, L. and Szmulewicz, D.J. (2019) Quantitative Assessment of Cerebellar Ataxia, through Automated Limb Functional Tests. *Journal of NeuroEngineering and Rehabilitation*, **16**, Article No. 31. https://doi.org/10.1186/s12984-019-0490-3

[13] Morgan, K.D. and Noehren, B. (2018) Identification of Knee Gait Waveform Pattern Alterations in Individuals with Patellofemoral Pain Using Fast Fourier Transform. *PLOS ONE*, **13**, e0209015. https://doi.org/10.1371/journal.pone.0209015

[14] Delacre, M., Lakens, D. and Leys, C. (2022) Correction: Why Psychologists Should by Default Use Welch's t-Test Instead of Student's t-Test. *International Review of Social Psychology*, **35**, 21. https://doi.org/10.5334/irsp.661