Poster ID – P.G-03

BIALLELIC VARIANTS IN *GLB1* CAUSES GM1 GANGLIOSIDOSIS DISEASE IN A FAMILY WITH TWO SIBLINGS

Shankar Aissvarya[1], Chong-Teik Lim[1], Meow-Keong Thong[2], Noraishah Mydin Abdul-Aziz[3], King-Hwa Ling[1,4], Karuppiah Thilakavathy[1,4]*

[1]Department of Biomedical Science, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, 43400 UPM Serdang, Malaysia, [2]Department of Population Medicine, M. Kandiah Faculty of Medicine and Health Science, Universiti Tunku Abdul Rahman, 43000 Kajang, Malaysia, [3]Associate Research Fellow, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, 43400 UPM Serdang, Malaysia, [4]Genetics and Regenerative Research Group, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, 43400 UPM Serdang, Malaysia
*Corresponding author: thilathy@upm.edu.my

Abstract

Introduction

GM1 gangliosidosis, is a lysosomal disease characterised by a build-up of GM1 ganglioside due to deficiencies in the β-galactosidase class of enzymes[1]. It is caused by variants within the *GLB1* gene, resulting in production of a defective form of the β-galactosidase enzyme[2]. This subsequently impairs cell physiology causing progressive destruction of the nerve cells in the central nervous system[3]. Hence, this study aims to identify the genetic variants responsible for GMI gangliosidosis in a family with two affected children. The proband, a 27-year-old man (age at diagnosis: 16-years-old), presented with learning difficulties and dystonic movement with severely reduced β-galactosidase activity. His 37-years-old brother, affected by the same condition, presented with a more severe phenotype. Both affected brothers showed progressive deterioration while both parents, older sister and older brother are unaffected.

Materials and Methods

Buccal swabs were collected from the proband, affected brother and parents. The proband's DNA was sent for whole-exome sequencing (WES) followed by variant identification through bioinformatics analyses. The identified variants were validated through Sanger sequencing, performed on proband and family members.

Results and Discussion

WES genetic analysis revealed the proband has a heterozygous pathogenic variant, (NM_000404.4:c.1325G>A, p.Arg442Gln), and a heterozygous variant of uncertain significance (VUS) (NM_000404.4:c.1022G>T, p.Gly341Val), in the *GLB1* gene. Sanger sequencing validated the variant found via WES. The affected brother carried the biallelic variants as the proband. The mother is heterozygous for the pathogenic variant while the father is heterozygous for the VUS. Interestingly, a previous study[4], found the same compound heterozygous variants in two GM1 gangliosidosis patients within the same family.

Conclusions

These findings not only confirmed the variants involved in GM1 gangliosidosis within this family but also emphasise the importance of comprehensive genetic analyses, particularly in unravelling inherited variants to facilitate appropriate genetic counselling and treatment options, including gene therapy.

Keywords
GMI gangliosidosis, *GLB1,* biallelic variant, whole exome sequencing, β-galactosidase

References

1. Rha, A. K., Maguire, A. S., & Martin, D. R. (2021). GM1 Gangliosidosis: Mechanisms and Management. Application of Clinical Genetics, Volume 14, 209–233. https://doi.org/10.2147/tacg.s206076
2. Regier, D. S., Tifft, C. J., & Rothermel, C. E. (2021, April 22). *GLB1-Related Disorders*. Nih.gov; University of Washington, Seattle. https://www.ncbi.nlm.nih.gov/books/NBK164500/
3. Nicoli, E.-R., Annunziata, I., d'Azzo, A., Platt, F. M., Tifft, C. J., & Stepien, K. M. (2021). GM1 Gangliosidosis—A Mini-Review. *Frontiers in Genetics*, *12*. https://doi.org/10.3389/fgene.2021.734878
4. Vikram Venkappayya Holla, Koti Neeraja, Stezin, A., Prasad, S., Bharat Kumar Surisetti, Manjunath Netravathi, Kamble, N., Yadav, R., & Pramod Kumar Pal. (2022). Utility of Clinical Exome Sequencing in Dystonia: A Single-Center Study From India. *Journal of Movement Disorders*, *15*(2), 156–161. https://doi.org/10.14802/jmd.21146