TARGETED SEQUENCING OF *HEXA* GENE SHOWS MISSENSE SUBSTITUTION (P.ARG499HIS) IN A LARGE PAKISTANI FAMILY WITH TAY-SACHS DISEASE

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Tay-Sachs disease or GM2 gangliosidosis, is caused by a deficiency of beta-hexosaminidase A (HEXA), resulting in lysosomal accumulation of GM2 ganglioside. However, deficiencies or reduced activities of HEXA and HEXB result in Sandhoff disease. The patients manifest with the macular cherry-red spots due to lipid-laden ganglion cells, hypotonia, low muscle tone, intractable seizures, developmental arrest, blindness, and neurological deterioration. The aim of this study was to identify the TSD-causing variant in a large Pakistani family showing typical symptoms of Tay-Sachs disease. Here, we studied a large Pakistani family with six TSD patients for the identification of the pathogenic variant by targeted DNA sequencing. As a result, we identified a missense substitution (p.Arg499His) in exon 13 of HEXA that was completely cosegregated among affected and normal individuals. In conclusion, we identified a missense substitution (p.Arg499His) in HEXA gene in a large consanguineous Pakistani family and further enriched the mutational spectrum of HEXA through Pakistani patients for the early diagnosis of the disease.

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Key words: *HEXA, HEXB, TSD, GM2 gangliosidosis, β-N-acetylhexosaminidase A.*

ЦІЛЬОВЕ СЕКВЕНУВАННЯ ГЕНУ *HEXA* ДЕМОНСТРУЄ МІСЕНС-ЗАМІНУ (P.ARG499HIS) У ВЕЛИКІЙ ПАКИСТАНСЬКІЙ РОДИНІ З ХВОРОБОЮ ТЕЯ-САКСА

Хвороба Тея-Сакса або GM2 гангліоліпідоз зумовлена дефіцитом бета-гексозамінідази А (*HEXA*), що призводить до лізосомного накопичення GM2 гангліозиду. Однак, недостатність або знижена активність *HEXA* і *HEXB* призводять до хвороби Сандхоффа. У пацієнтів з'являються такі симптоми, як вишнево-червоні плями на очних яблуках через накопичення ліпідів у гангліонарних клітинах, гіпотонія, слабкість м'язів, некеровані припадки, затримка розвитку, сліпота і погіршення неврологічних показників. Мета цього дослідження полягала в ідентифікації варіанту, який спричинив хворобу Тея-Сакса у великій пакистанській родині, яка демонструвала типові симптоми цієї хвороби і налічувала шість пацієнтів із хворобою Тея-Сакса. Ідентифікацію патогенного варіанту проводили за допомогою цільового секвенування ДНК. У результаті дослідження ми ідентифікували місенс заміну (p.Arg499His) в екзоні 13 *HEXA,* яка була повністю косегрегованою серед хворих та здорових осіб у великій єдинокровній пакистанській родині. Отже, ми ідентифікували місенс заміну (p.Arg499His) у гені *HEXA* і збагатили спектр мутацій *HEXA* серед пакистанських пацієнтів для ранньої діагностики захворювання.

Ключові слова: *HEXA, HEXB*, TSD, GM2 гангліоліпідоз, β-N-ацетилгексозамінідаза А.

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