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Hereditary spastic paraplegias: Identification of a novel SPG57 variant affecting TFG oligomerization and description of HSP subtypes in Sudan

Ashraf Yahia Osman Mohamed
National University-Sudan, Sudan

Hereditary spastic paraplegias (HSP) are the second most common type of motor neuron disease recognized worldwide. HSP can be pure or complex according to the absence or presence of additional neurological and non-neurological manifestations. There are more than 67 known HSP genes with different patterns of inheritance. Autosomal dominant HSP forms are the most frequent in western populations while recessive HSP predominates in highly consanguineous communities. Our goals were to estimate the relative frequencies of known HSP genes in Sudanese families with the disease and perform genotype-phenotype correlation to extend the clinical spectrum associated with HSP genes. We have used next generation sequencing to screen 74 HSP-related genes in 23 consanguineous families from Sudan and candidate gene sequencing in two other families (total of 25 families). We established a genetic diagnosis in six families with autosomal recessive *HSP (SPG11* in three families and *TFG/SPG57*, *SACS*, and *ALS2* in one family each). An autosomal dominant HSP (ATL1/SPG3A) was also identified in one additional family. Six out of seven identified variants were novel. The *TFG/SPG57* variant (*p.(Arg22Trp)* in the PB1 domain) is the second SPG57 HSP variant to be identified worldwide, and we demonstrated its impact on TFG oligomerization *in vitro*. There were no patients with visual impairment as observed in a previously reported SPG57 family (p. (Arg106Cys) in coiled coil domain), suggesting unique contributions of the PB1 and coiled coil domains in TFG complex formation/function and a possible phenotype correlation to variant location. Some families manifested marked phenotypic variations implying the possibility of modifier factors complicated by high inbreeding. In conclusion, we identified the first Sudanese families carrying novel variants in 6 HSP genes. The difficulty to reach a genetic diagnosis in the majority of studied families suggests the possibility of new genes, unusual models of inheritance or noncoding variations underlying spinocerebellar degeneration.

kambalawy@hotmail.com

In vitro interaction of soluble and amyloid form of serum amyloid protein with amyloid P component to hepta 1-6 cells

Asokan Chinnasamy and **Shagari A B**
Sokoto State University, Nigeria

Hepta 1-6 cell binding study is important in relation to the activity of membrane proteins, because losing the activity of such systems will ultimately lead to malfunction or death of the cell. The interactions of Serum Amyloid A (SAA) and Serum Amyloid A protofibrils with Serum Amyloid P component [SAP ($CaCl_2$)] to hepta 1-6 cells of the mouse are dealt with in detail to study the binding of SAA protofibrils in various conditions. The induced fluorescence, circular dichroism, FACScan and MTT assay results have shown the SAA and SAA fibrils binding with SAP ($CaCl_2$) 0.12-1.2 nM and cell toxicity with the hepta 1-6 cells. Specifically, interaction of serum amyloid A fibrils with a cell surface binding site/receptor might alter the local environment to cause cellular dysfunction and to be more favorable for amyloid formation. Already RAGE (receptor for advanced glycation endproducts) a polyvalent receptor in the immunoglobulin super family has been implicated in binding with the isoform of SAA (SAA1.1) which has the highest fibirillogenic property. In the present study, SAA fibrils have more binding and cell cytotoxicity than SAA protein and has protective role with SAP ($CaCl_2$).

asokan_74@hotmail.com