Identification of Novel Mutations in HEXA Gene in Children Affected with Tay Sachs Disease from India

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Tay Sachs disease (TSD) is a neurodegenerative disorder due to b-hexosaminidase A deficiency caused by mutations in the HEXA gene. The mutations leading to Tay Sachs disease in India are yet unknown. We aimed to determine mutations leading to TSD in India by complete sequencing of the HEXA gene. The clinical inclusion criteria included neuroregression, seizures, exaggerated startle reflex, macrocephaly, cherry red spot on fundus examination and spasticity. Neuroimaging criteria included thalamic hyperdensities on CT scan/T1W images of MRI of the brain. Biochemical criteria included deficiency of hexosaminidase A (less than 2% of total hexosaminidase activity for infantile patients). Total leukocyte hexosaminidase activity was assayed by 4-methylumbelliferyl-N-acetyl-b-D-glucosamine lysis and hexosaminidase A activity was assayed by heat inactivation method and 4-methylumbelliferyl-N-acetyl-b-D-glucosamine-6-sulphate lysis method. The exons and exon-intron boundaries of the HEXA gene were bidirectionally sequenced using an automated sequencer. Mutations were confirmed in parents and looked up in public databases. In silico analysis for mutations was carried out using SIFT, Polyphen2, MutationT@ster and Accelrys Discovery Studio softwares. Fifteen families were included in the study. We identified six novel missense mutations, c.340 G.A (p.E114K), c.964 G.A (p.D322N), c.964 G.T (p.D322Y), c.1178C.G(p.R393P) and c.1385A.T (p.R462V), c.1432 G.A (p.G478R) and two previously reported mutations. c.1277_1278insTATC and c.508C.T (p.R170W). The mutation p.E462V was found in six unrelated families from Gujarat indicating a founder effect.

A previously known splice site mutation c.805+1 G.C and another intronic mutation c.672+30 T.G of unknown significance were also identified. Mutations could not be identified in one family. We conclude that TSD patients from Gujarat should be screened for the common mutation p.E462V.