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LECTURE

Mutational origins of Machado-Joseph disease

Sandra Martins[1]

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Abstract

Machado-Joseph disease (MJD) is the most frequent dominant ataxia worldwide, but *de novo* mutational events (i.e. expansions from normal or intermediate to the pathological range of (CAG)n alleles) do not seem to explain disease relative high frequency and diffusion into many populations. Previously, we have identified two SNP lineages, each underlying an independent MJD origin: the most ancient and worldwide spread Joseph (TTACAC) lineage, originated probably in Asia more than 6000 years ago; and the more recent Machado (GTGGCA) lineage, predominant in families of Portuguese extraction. Interestingly, these two lineages display different repeat instability biases upon paternal transmission of expanded alleles. Taking into account that the CAG repeat size is the parameter that better explains age-of-onset and disease severity, the identification of MJD lineages becomes even more important at the clinical level. More recently, we have been studying families from more remote and isolated communities in order to discern whether the presence of MJD in these populations is due to new mutational events or to the introduction of expanded alleles from other populations. A total of 20 SNPs flanking the expanded repeat was analysed in Australian aborigines and African families. No new mutational origins have been identified, but a "Joseph-derived" lineage shared by Australian aborigines and 9 Asian families suggested an introduction of the mutation in this community via Asia. By inferring a phylogenetic tree from genetic distances, we estimated that the Australasian Joseph-derived lineage dates back to more than 100 generations.

[1]i3S/IPATIMUP - Instituto de Investigação e Inovação em Saúde, Universidade do Porto

Correspondence: smartins@ipatimup.pt

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