**THE JANUS FACE OF THE KINESIN LIGHT CHAIN 1 56836 CC GENETIC VARIANT**

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Leukoaraiosis (LA), a neuroimaging term, can be defined as hypointense areas on certain CT scans or hyperintensity signals on T2-weighted MRI scans of the white matter of the brain. LA can cause a cognitive decline and frequently occurs in the elderly population, resulting in an impaired quality of life. Various genetic factors have been postulated to be able to contribute to a greater susceptibility to the development of LA.

Although there are several clinical and basic scientific data on LA, very little is known of the molecular events that occur in the glia cells during the evolution or propagation of LA. A new metabolic approach to these biochemical processes recently hypothesized that the chronic hypoxia caused by endothelial dysfunctions or other small-vessel pathologies may give rise to functional damage of the cytoskeleton of the glia cells. Functionally damaged kinesin (cytoskeleton motor protein) can lead to malfunctions in the molecular cross-talk between the nucleus and the mitochondria (resulting in a slowly developing energetic crisis) and in the trafficking of the molecular apparatus governing the assembly of the myelin sheaths (resulting in damaged myelin synthesis).

In this context, the aim of the present study was to examine how the susceptibility to LA is affected by the presence of the G56836C variant of KLC1, a genetic variation reported to be associated with neurodegeneration. In our case-control study (LA: N=229; controls: N=264), the KLC1 G56836C variant of kinesin alone did not prove to be a risk factor for LA, with or without ischemic stroke, in either heterozygous or homozygous form. The 56836CC homozygous variant, however, had a marked modifying effect on the development of LA in subjects with unfavourable clinical factors: it enhanced the unfavourable effect of hypertension on LA (a 3.88-fold higher of risk of LA), and yielded a risk of LA in smokers (a 10.23-fold higher risk of LA) (this latter clinical factor alone, without the 56836CC variant not posing a risk of LA). The presence of the 56836CC variant in hypertensive smokers proved to be an additional risk enhancer (a 7.76-fold higher risk of LA).On the basis of our results, trafficking of the mitochondria has been hypostatized in the pathomechanism of ischemic demyelinization.

Although the clinical and biochemical features of LA are quite different from the ones in multiple sclerosis (MS) (another frequent demyelinization disorder), we extended our observation as to whether the kinesin light-chain 1 (KLC1) G56836C single nucleotide polymorphism (SNP) can have an effect on the development of MS too? Albeit well-defined autoimmune activity of different types against the central nervous system plays of a great importance in the course of MS disease, the pathomechanism and the direct causative factors have not yet been elucidated.

In our secondary case-control study (relapsing-remitting MS: N=102; controls: N=207), we analyzed the roles of the above genetic variant of the kinesin protein in the relapsing-remitting MS. The KLC1 56836CC genetic variant was calculated to be significant preventive factor for the occurrence of MS (1.0% vs. 8.33%, $p<0.011$; OR: 0.1, 95% CI: 0.11-0.85, $p<0.05$). Accordingly, the following hypotheses might be conducted: 1, Reduced myelin synthesis resulting from the presence of the KLC1 56836CC genetic variant may be favourable in MS (because of a reduced autoimmune process). 2, Reduced trafficking of mitochondria (resulting from the presence of the KLC1 56836CC genetic variant) might also reduce the apoptosis-like process in glia cells (chemicals from mitochondria can be trigger factors of apoptosis). 3, If MS is affected by mitochondrial disorders, the reduced trafficking of mitochondria in the glia cells might also be favourable.

The KLC1 56836CC kinesin genetic variant shows a Janus face in the two demyelinization disorders. This Janus feature may draw attention to new intracellular pathomechanisms behind some white matter disorders.

References:

Szolnoki Z. Pathomechanism of leukoaraiosis: molecular bridge between the genetic, biochemical, and clinical processes (a mitochondrial hypothesis)
Neuromolecular Med. 2007;9:21-33.

Szolnoki, Z., Kondacs, A., Mandi, Y., Somogyvari, F. A genetic variant in cytoskeleton motors amplifies susceptibility to leukoaraiosis in hypertensive smokers: gene-environmental interactions behind vascular white matter demyelinization. J. Mol. Neurosci. 2007;33:173-9.

Szolnoki Z, Kondacs A, Mandi Y, Somogyvari F. A cytoskeleton motor protein genetic variant may exert a protetective effect on the occurrence of multiple sclerosis:
the Janus face of the kinesin light chain 1 56836CC variant.- 2007, Neuromolecular Med. 2007; 9(4):335-9.

Szolnoki Z.Reduced noncovalent connections in leukoaraiosis. Expert Rev Neurother. 2008;8:205-13.