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FASTKD2 and human memory: functional pathways and prospects for novel therapeutic target development for Alzheimer's disease and age-associated memory decline

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Impairment in episodic memory is typically the earliest clinical deficit to appear in Alzheimer's disease (AD), the most common cause of dementia and a source of immense personal and societal burden. Unfortunately, the mechanisms underlying AD and other age-related conditions causing cognitive deficits are only partially understood, limiting the development of disease-modifying therapies and novel early diagnostic biomarkers.

Recently, we reported the discovery of a SNP in the *FASTKD2* gene associated with better memory performance in a large sample of older Americans [1]. We also demonstrated that this new memory-protective SNP was associated with increased volume and gray matter density in the hippocampus, a key brain structure for encoding and retrieving memories that

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is among the earliest regions affected by AD. Shortly thereafter, a separate report from an independent group identified perturbations in *FASTKD2* expression in brain astrocytes derived from postmortem tissue samples from AD patients [2].

Prior to these studies, *FASTKD2* had not been linked to cognition or AD. This new evidence obtained through diverse methodologies and analytical strategies suggests that *FASTKD2* may have potential as a novel target for biomarker and drug development against AD and age-associated cognitive decline. As a result, this is an opportune moment to critically appraise extant knowledge about *FASTKD2* and its functional pathways in order to guide next steps aimed at translating mechanistic knowledge into potential clinical strategies.

FASTKD protein family

FASTKD2 encodes one of a family of proteins (including FASTK and FASTKD1–5) that share a common structure including a mitochondrial targeting domain, multiple serine/threonine kinase domains and an RNA-binding domain [3]. Much of the early literature on this protein family focuses on FASTK, which constitutively inhibits apoptosis when tethered to the outer mitochondrial membrane but promotes apoptosis when released to the cell cytoplasm following activation of the Fas/CD95 'death receptor' [3,4]. The proapoptotic function of FASTK is mediated by its binding and modulating the function of TIA1, an mRNA-binding protein that normally silences the production of apoptotic and inflammatory mediators including TNF-α [5].

As discussed below, initial studies of the other FASTKD protein family members indicate broadly shared functions with FASTK. This evidence is not surprising given the common structure and mitochondrial localization of these proteins. However, a closer examination of these putative functional pathways can provide mechanistic clues to characterize the particular impact of *FASTKD2* on brain structure and function (Supplementary Figure 1; see online at: www.future-medicine.com/doi/suppl/10.2217/pgs.15.8).

FASTKD2 & apoptosis

The first functional study of *FASTKD2* ensued following the discovery of gene mutations causing a rare mitochondrial encephalomyopathy [6]. Due to its FASTK domain, the authors hypothesized a role for the FASTKD2 protein in apoptosis and found that on treatment with staurosporine (a well-described inducer of apoptosis), cells with loss-of-function *FASTKD2* mutations exhibited less apoptosis while cells with *FASTKD2* overexpression exhibited more apoptosis [6].

Subsequent studies identified FASTKD2 as a vital part – along with NRIF3 and DIF1 – of a 'death switch' modulating apoptosis in cancer cells [7,8]. Further insight can also be found in the broader interaction network for the FASTKD2 protein, which includes numerous proapoptotic factors including TRAF6, TSC22D1 and c-Myc [9].

In our report, we demonstrated that the novel *FASTKD2* SNP associated with better memory performance was also associated with lower levels in cerebrospinal fluid of four proteins involved in fas-mediated apoptosis [1]. Although it was beyond the scope of our manuscript

to directly assess the impact of this SNP on activation of apoptosis at the cellular level, this additional finding suggests that modulation of cell death pathways may account for the neuroprotective effect of *FASTKD2* on memory.

FASTKD2 & mitochondrial function

The protein encoded by *FASTKD2* localizes to the inner mitochondrial membrane and is expressed at its highest levels in the richly energy-dependent tissues of the brain [6,10]. A nonsense mutation in *FASTKD2* is known to underlie respiratory chain complex IV (cytochrome c oxidase) deficiency, a rare and typically fatal disorder that presents in infancy with developmental delay, myopathy and encephalopathy including demyelinating brain lesions and epilepsy [6,11]. Recently, missense *FASTKD2* mutations were also identified in patients with inherited ataxias, a heterogeneous group of disorders with frequent mitochondrial origin [12].

It is not yet known how these *FASTKD2* mutations lead to their cellular and clinical phenotypes. For example, while *FASTKD2* may be directly involved in the synthesis, localization and/or function of cytochrome c oxidase, it is also possible that knocking out *FASTKD2* starts a chain of events yielding broader mitochondrial dysfunction negatively impacting the respiratory chain and its central role in cellular energetics. Indeed, the protein encoded by family member *FASTKD3* is known to interact with both respiratory chain components and mitochondrial DNA translation machinery [3], suggesting broad potential functionality of this protein class in the cellular powerhouse. Further study will be needed to better understand the pathogenic sequence initiated by rare mutations as well as more common genetic variants.

Beyond these findings in rare genetic conditions, mitochondrial dysfunction and closely related oxidative stress pathways are major candidate mechanisms proposed to underlie neurodegeneration in aging and disease [13,14]. The new identification of expression changes in *FASTKD2* and other mitochondrial genes in AD brain cells burnishes this hypothesis and enhances the foundation for additional functional genomics studies to clarify underlying mechanisms [2].

FASTKD2 & inflammation

Despite the mitochondrial localization of its encoded protein, there is an increasing body of work suggesting a proinflammatory role for *FASTKD2*. A likely mechanism for this effect may be related to the FASTK domain and its inhibition of TIA1, ultimately promoting production of the systemic inflammation mediator TNF-α [15,16]. The Fas/FasL axis is itself considered a strong regulator of inflammation and in some biological contexts may lead to tissue damage through inflammatory responses rather than through apoptosis [17]. This evidence may be particularly compelling in the setting of AD, where inflammation and immune system activation are increasingly viewed as playing central roles in mediating and/or compensating for cellular stress induced by amyloid-β deposition [18,19].

Future directions

Population genomics analyses of additional data sets, including other relevant AD endophenotypes, may provide further insight regarding the clinical impact of *FASTKD2*. Expression studies using microarray or RNA-seq data will also be useful to examine the relationship between specific genetic variants and canonical transcripts as well as splice variant and other alternative transcripts. Finally, deep sequencing of the *FASTKD2* locus in large samples will facilitate characterization of regional linkage disequilibrium structure (including functional 'tag' SNPs), other types of variants (including rare, copy number and structural variants) and epigenetic modification sites.

Functional genomic studies will also be crucial to elucidate the basic mechanisms connecting these genetic variants to expression and biological action. The overlap of two microRNA genes (*MIR 3130-1* and *2*) with the intron containing the memory-associated SNP raises the possibility that variants in this region may regulate microRNA-mediated silencing of gene expression [1]. However, other leading possibilities for further exploration include potential dysfunction in the *FASTKD2* RNA-binding domain [20] or at transcription factor or splicing machinery-binding sites. Although *FASTKD2* appears to lack homologs in yeast, worms and flies [6], the creation of mammalian models and/or cell lines will be vital for this effort and could be crossed with analogous AD model systems to directly assess the impact of knockout, knockdown and overexpression of *FASTKD2*.

Conclusion

Along with related new discoveries and prior functional studies of this gene, the novel association of *FASTKD2* with memory performance and hippocampal structure potentially opens new avenues for exploration of strategies to modulate neurodegeneration in AD and cognitive aging. Given that genes and proteins do not act in isolation [21], a better understanding of the range of biological activities for *FASTKD2* will help focus efforts to develop potential disease-modifying drugs targeting these functional pathways.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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