OPEN ACCESS Freely available online

ISSN: 2471-2663
Clinical & Medical Biochemistry

Short Communication

Klotho: An Anti-Aging Gene is Associated with Type 2 Diabetes Mellitus

Dongju Jung[1,2*]

[1]*Department of Biomedical Laboratory Science, Hoseo University, Asan, Republic of Korea;* [2]*Klotho Sciences Incorporation, Healthcare Innovation Park, Seongnam, Republic of Korea*

DESCRIPTION

Type 2 Diabetes Mellitus (T2DM) is a widespread chronic condition with a significant global impact. While lifestyle factors such as overeating and physical inactivity are established contributors to T2DM development, considerable scientific effort has also been directed toward identifying genetic risk factors. Numerous genetic mutations associated with T2DM pathogenesis involve genes integral to glucose metabolism and insulin signaling [1]. Among the genes extensively investigated for its role in T2DM is the anti-aging gene *Klotho* (*KL*). Despite the precise mechanisms remaining unclear, accumulating evidence underscores a strong association between *Klotho* and T2DM development. The *KL* encodes a type I transmembrane protein that functions as co-receptor for Fibroblast Growth Factor 23 (FGF23) and serves as a glycoprotein with β-glucuronidase activity. The anti-aging function of *Klotho* is evident in *Klotho*-deficient (kl-/kl-) mice, which exhibit premature aging phenotypes such as osteoporosis and arteriosclerosis, similar to those observed in humans [2]. *Klotho* plays an important role in regulating calcium and phosphate homeostasis by acting as a co-receptor with FGF23 receptor. Animal models demonstrate that depletion of *Klotho* leads to vascular calcification, which can be reversed with *Klotho* supplementation [3]. This deficiency in *Klotho* induces hypertension in mice, an age-related disease closely associated with vascular calcification [2].

The extracellular domain of *Klotho* can be shed and circulate throughout the body as a hormone-like factor. This secreted *Klotho*, consisting of the KL1 and KL2 domains, is generated by either proteolytic cleavage or alternative splicing of the *Klotho* mRNA. ADAM10 (A Disintegrin and Metalloproteinase 10) and ADAM17 (A Disintegrin and Metalloproteinase 17) metalloproteinases mediate the proteolytic process. ADAM10 produces the full-length 130 kDa soluble protein, while ADAM17 generates 70 kDa and 55 kDa fragments by cleaving between the KL1 and KL2 domains [4]. Unlike membrane-bound *Klotho*, secreted *Klotho* is believed to contribute to a broader range of anti-aging effects [5]. While sialic acids in α2-3- siallylactose and α2-6-siallylactose have been proposed as potential receptors for secreted *Klotho* [6], their weak binding affinity suggests the existence of as-yet-unidentified receptors.

The higher incidence of T2DM in the elderly population compared to younger individuals [7], suggests that therapeutically elevating levels of anti-aging proteins may offer a potential strategy for reducing its incidence in older adults. Indeed, studies have shown that increasing *Klotho* levels in T2DM patients and animal models ameliorates disease progression [8]. Although the precise mechanism through which *Klotho* suppresses T2DM is not yet elucidated, ongoing research and reporting continue to concentrate on unraveling its advantageous effects on the disease. To elucidate the association between genes and diseases, researchers frequently employ the case-control study methodology to assess the presence of differences between control and case groups. This is achieved by examining the statistical significance of genetic polymorphisms. Recent data published in the "Indian Journal of Clinical Biochemistry" indicates a significant relationship between Klotho and T2DM [9]. This study analyzed Single Nucleotide Polymorphisms (SNPs) of *KL* in a large dataset. Genetic data from the Korean Association Resource (KARE) cohort was obtained using the Affymetrix chip, which included 20 SNPs within the *Klotho* gene. Of these 20 SNPs, twelve showed significant associations with T2DM under various genetic models, including additive, dominant, and recessive. Notably, eight of these twelve SNPs displayed a significant correlation with T2DM in both the additive and dominant models. The odds ratios of seven of these eight SNPs consistently indicated susceptibility to T2DM, while one SNP was associated with resistance to the disease. Importantly, all eight SNPs were located in non-coding regions of the genome. Specifically, five SNPs (four and the T2DM-protective SNP) were located in intergenic regions, while three SNPs were positioned within introns. Consistent with the findings, Genome-Wide Association Studies (GWAS) conducted on various cohorts, including those of European and South Asian ancestry, have identified T2DM-associated KL SNPs [10].

Correspondence to: Dongju Jung, Department of Biomedical Laboratory Science, Hoseo University, Asan, Republic of Korea, E-mail: djjungg@hoseo.edu

Received: 18-Dec-2023, Manuscript No. CMBO-23-24467; **Editor assigned:** 21-Dec-2023, PreQC No. CMBO-23-24467 (PQ); **Reviewed:** 04-Jan-2024, QC No. CMBO-23-24467; **Revised:** 11-Jan-2024, Manuscript No. CMBO-23-24467 (R); **Published:** 18-Jan-2024, DOI: 10.35841/2471-2663.24.10.202

Citation: Jung D (2024) *Klotho*: An Anti-Aging Gene is Associated with Type 2 Diabetes Mellitus. Clin Med Bio Chem. 10:202.

These findings suggest that genetic variants within the *Klotho* gene may contribute to T2DM across diverse population groups.

CONCLUSION

Investigations of *KL* SNPs within diverse cohorts have revealed a significant association between Klotho and T2DM. The observed *KL* variants emphasize the genetic complexity of T2DM. These studies have identified several *KL* variants exhibiting statistically significant associations with T2DM risk, suggesting that genetic mutations in the Klotho gene may represent a substantial contributing factor to T2DM pathogenesis.

REFERENCES

1. Matschinsky FM. Glucokinase, glucose homeostasis, and diabetes mellitus. Curr Diab Rep. 2005;5:171-176.
2. Kuro-o M, Matsumura Y, Aizawa H, Kawaguchi H, Suga T, Utsugi T, et al. Mutation of the mouse *klotho* gene leads to a syndrome resembling ageing. Nature. 1997;390(6655):45-51.
3. Hu MC, Shiizaki K, Kuro-o M, Moe OW. Fibroblast growth factor 23 and *Klotho*: Physiology and pathophysiology of an endocrine network of mineral metabolism. Annu Rev Physiol. 2013;75:503-533.
4. Xu Y, Sun Z. Molecular basis of *Klotho*: From gene to function in aging. Endocr Rev. 2015;36(2):174-193.
5. Kuro-o M. The *Klotho* proteins in health and disease. Nat Rev Nephrol. 2019;15(1):27-44.
6. Dalton G, An SW, Al-Juboori SI, Nischan N, Yoon J, Dobrinskikh E, et al. Soluble *klotho* binds monosialoganglioside to regulate membrane microdomains and growth factor signaling. Proc Natl Acad Sci U S A. 2017;114(4):752-757.
7. Chen L, Magliano DJ, Zimmet PZ. The worldwide epidemiology of type 2 diabetes mellitus—present and future perspectives. Nat Rev Endocrinol. 2012;8(4):228-236.
8. Lim SC, Liu JJ, Subramaniam T, Sum CF. Elevated circulating alpha-*klotho* by angiotensin II receptor blocker losartan is associated with reduction of albuminuria in type 2 diabetic patients. J Renin Angiotensin Aldosterone Syst. 2014;15(4):487-490.
9. Jin HS, Jung D. The KL genetic polymorphisms Associated with type 2 diabetes Mellitus. Indian J Clin Biochem. 2023;38(3): 385-392.
10. Mahajan A, Taliun D, Thurner M, Robertson NR, Torres JM, Rayner NW, et al. Fine-mapping type 2 diabetes loci to single-variant resolution using high-density imputation and islet-specific epigenome maps. Nat Genet. 2018;50(11):1505-1513.