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Role of Apolipoproteins in Neurodegenerative Diseases

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Abstract

Since lipids are insoluble in water, they are carried in the blood as particles called lipoproteins. Lipoproteins consisting of lipids and proteins are multicomponent complexes. The classification of lipoproteins, which are divided into several main groups such as low density lipoprotein (LDL), high density lipoprotein (HDL), very low density lipoprotein (VLDL) and chylomicrons, is based on their density, size, lipid and apolipoprotein content. Apolipoproteins are the protein component of lipoproteins that carry lipids from the blood to various tissues of the body for metabolism and utilisation. Apolipoproteins play an important role in lipid metabolism. They regulate many metabolic enzymes and interact with lipoprotein receptors. Numerous studies have shown that apolipoprotein phenotype, different allelic polymorphism and apolipoprotein gene mutation can affect metabolism and utilisation of blood lipids and consequently trigger the onset and development of atherosclerosis, hyperlipidaemia, cerebrovascular and cardiovascular diseases. Furthermore, apolipoproteins have been associated with neurodegenerative diseases and different apolipoprotein polymorphisms have been evaluated as risk factors or protective agents in different neurodegenerative diseases. This review presents evidence from some studies linking apolipoproteins with Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS) and frontotemporal degeneration disease.

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1. Introduction

Water-insoluble lipids are carried in the blood in the form of particles known as lipoproteins. Lipoproteins consist of a hydrophobic triglyceride/cholesterol ester core surrounded by a single amphiphilic phospholipid layer with embedded apolipoproteins (Dai et al., 2023). Lipoproteins consisting of lipids and proteins are involved in transporting triglycerides and cholesterol in the blood (Ross & Pawlina, 2011). It is divided into several main groups, including low density lipoprotein (LDL), high density lipoprotein (HDL), very low density lipoprotein (VLDL) and chylomicrons (Ross & Pawlina, 2011). Classification is based on the density, size, lipid and apolipoprotein content of lipoproteins (Tóth et al., 2020). Apolipoproteins are synthesised in various organs, especially in the liver and intestine (Table 1). Changes in the expression levels, function and spatial structure of apolipoproteins have been closely associated with various diseases (Liu et al., 2021). Numerous studies have shown that apolipoprotein phenotype, different allelic polymorphism and apolipoprotein gene mutation can affect metabolism and utilisation of blood lipids and consequently trigger the onset and development of atherosclerosis, hyperlipidaemia, cerebrovascular and cardiovascular diseases (Liu et al., 2021; Richardson et al., 2020). Some apolipoproteins have been reported to be related to neurodegenerative diseases (Reichert et al., 2020b) (Table 1). The aetiology of various neurodegenerative diseases is not clear because there are different neurodegenerative diseases and the central nervous system is made up of different cell populations with unique functions (Mathieu et al., 2020; Reichert et al., 2020a; Reichert et al., 2020b).

Here, we present evidence from some studies linking apolipoproteins to neurodegenerative diseases with a high prevalence in the general population. These studies are predominantly human studies and were selected by searching PubMed and Google Scholar databases using various combinations of the name of the apolipoprotein type and the name of a common neurodegenerative disease.

2. Apolipoproteins and neurodegenerative diseases

This Apolipoproteins include subfamilies A, B, C, D, E, L, F, H, M, N and R, each with different functions (Liu et al., 2021). Beyond their basic functions such as regulation of lipid transport and structural stabilisation of lipoproteins, apolipoproteins play important roles in lipid metabolism through the organisation of a number of metabolic enzymes and molecular interactions with lipoprotein receptors (Liu et al., 2021; Ramasamy, 2014; Tóth et al., 2020). Apolipoproteins are both amphipathic molecules and regulators of the lipoprotein system and are metabolised via receptors, enzymes and transporters (Bahrami et al., 2019). The low-density lipoprotein receptor (LDLR), a cell surface receptor, mediates the uptake and catabolism of plasma lipoproteins containing apolipoprotein B (apoB) or apolipoprotein E (apoE) (Brown & Goldstein, 1986). The main task of this receptor is to remove LDL from the bloodstream (Brown & Goldstein, 1986). The blood-brain barrier effectively blocks the uptake of lipoprotein-bound cholesterol from the bloodstream, so that cholesterol levels in the brain are independent of those in peripheral tissues (Björkhem & Meaney, 2004). It has been reported that some cholesterol in

Table 1. Some apolipoproteins related to neurodegenerative diseases

Apolipoprotein	Synthesis	Lipoprotein	Neurodegenerative Disease
ApoA-I	Intestine, liver (Dominiczak & Caslake, 2011)	HDl, chylomicrons, VLDL (Dominiczak & Caslake, 2011)	Alzheimer's disease (Bergt et al., 2006; Johansson et al., 2017; Kawano et al., 1995; Kuriyama et al., 1994; Liu et al., 2006; Merched et al., 2000; Saczynski et al., 2007; Paula-Lima et al., 2009; Wisniewski et al., 1995) Multiple sclerosis (Murali et al., 2020; McComb et al., 2020) Amyotrophic lateral sclerosis (Thompson et al., 2022) Frontotemporal degeneration disease (Kim et al., 2018)
ApoA-II	Intestine, liver (Dominiczak & Caslake, 2011)	HDl, chylomicrons, VLDL (Dominiczak & Caslake, 2011)	Alzheimer's disease (Kuriyama et al., 1994) Frontotemporal degeneration disease (Kim et al., 2018)
ApoA-IV	Intestine, liver (Dominiczak & Caslake, 2011)	HDl, chylomicrons (Dominiczak & Caslake, 2011)	Huntington's disease (Huang et al., 2011)
ApoB (ApoB-48, ApoB-100)	Intestine (ApoB-48), liver (ApoB-100) (Dominiczak & Caslake, 2011)	Chylomicrons (ApoB-48), chylomicron remnants (ApoB-48), VLDL (ApoB-100), IDL (ApoB-100), LDL (ApoB-100) (Dominiczak & Caslake, 2011)	Alzheimer's disease (Choi et al., 2016; Namba et al., 1992; Tóth et al., 2020) Parkinson's disease (Fang et al., 2019; Lehnert et al., 2012; Wei et al., 2013) Huntington's disease (Chang et al., 2023) Amyotrophic lateral sclerosis (Thompson et al., 2022) Frontotemporal degeneration disease (Kim et al., 2018)
ApoC-I	Intestine, liver (Dominiczak & Caslake, 2011)	Chylomicrons, VLDL, HDL (Dominiczak & Caslake, 2011)	Frontotemporal degeneration disease (Kim et al., 2018)
ApoC-III	Intestine, liver (Dominiczak & Caslake, 2011)	Chylomicrons, VLDL, HDL (Dominiczak & Caslake, 2011)	Alzheimer's disease (Adunsky et al., 2002; Muenchhoff et al., 2017; Shih et al., 2014; Zhang & Alzheimer's Disease Neuroimaging Initiative, 2020)
ApoD	Astrocytes, oligoastrocytes, Schwann cells, pericytes (Rassart et al., 2000)	HDL (Fyfe-Desmarais et al., 2023)	Parkinson's disease (Waldner et al., 2018) Multiple sclerosis (Reindl et al., 2001; Navarro et al., 2018)
ApoE(ApoE-IV)	Intestine, liver, brain, spleen, kidney, adrenals and other (Dominiczak & Caslake, 2011)	Chylomicron remnants, mature VLDL, VLDL remnants, LDL and HDL (Dominiczak & Caslake, 2011)	Alzheimer's disease (Farrer et al., 1997; Hong et al., 2020; Koizumi et al., 2018) Parkinson's disease (Mata et al., 2014; Real et al., 2023; Tsuang et al., 2013) Multiple sclerosis (McComb et al., 2020) Amyotrophic lateral sclerosis (Leoni et al., 2019) Frontotemporal degeneration disease (Su et al., 2017)
ApoH	Liver (Leduc et al., 2008)	Chylomicron, VLDL (Nakaya et al., 1980)	Alzheimer's disease (Misra et al., 2021; Öhrfelt et al., 2011)
ApoJ (Clusterin/CLU)	Testis, prostate, brain (Vitali et al., 2014)	HDL (Vitali et al., 2014)	Alzheimer's disease (Calero et al., 2000; Foster et al., 2019; Zlokovic et al., 1996) Parkinson's disease (Lenzi et al., 2020; Lin et al., 2021; Maarouf et al., 2012; Přikrylová Vranová et al., 2010; Zhang et al., 2012) Multiple sclerosis (van Luijn et al., 2016)

the brain is absorbed by the blood-brain barrier as lipoprotein-bound cholesterol (Balazs et al., 2004; Vitali et al., 2014). Atherosclerotic changes can occur in the entire vascular system, including the blood vessels associated with the brain (Tóth et al., 2020). The structure of the brain capillaries is favourable for the maintenance of proper neural function (Tóth et al., 2020). Endothelial cells, which are the basic cellular components of the blood brain barrier, are characterised by the lack of fenestrae, low transcytosis rate, tight junctions and the presence of selective transporters (Fanning & Anderson, 2009; Tóth et al., 2020). Blood brain barrier dysfunction is usually accompanied by morphological changes such as impaired tight junctions, basement membrane changes and pericyte loss (Tóth et al., 2020). Dyslipidaemia is a known risk factor for intracranial atherosclerosis (Park et al., 2011; Turan et al., 2010). Brain endothelial cell function may be affected by the increased production of arachidonic acid metabolites that occur under hyperlipidaemia (Tóth et al., 2020). Lipolysis products of triglyceride-rich lipoproteins can also increase blood brain barrier permeability through disruption of intercellular connections, which in turn induces apoptosis and affects lipid bulk morphology and composition (Eiselein et al., 2007; Wang et al., 2008). Reactive oxygen species may also be involved in endothelial cell damage caused by triglyceride-rich lipoproteins (Antonios et al., 2008; Wang et al., 2008) Most signs suggestive of a blood brain barrier with a deconstructed and altered structure and permeability are observed in neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), chronic traumatic encephalopathy and HIV-1-associated dementia (Sweeney et al., 2018).

Deposits of apolipoprotein A-I (apoA-I) and amyloid beta (Aβ) have been found in the human brain and it has been described that these deposits can be detected in the cerebrospinal fluid (CSF) of Alzheimer's patients (Paula-Lima et al., 2009; Wisniewski et al., 1995). In a study, it was reported that CSF apoA-I level decreased in Alzheimer's patients and this was associated with cognitive function and AD (Johansson et al., 2017). In another study, a high level of apoA-I in the serum was associated with a decreased risk of dementia (Saczynski et al., 2007). It has been reported that decreased apoA-I levels are associated with cognitive decline in AD patients (Kawano et al., 1995; Merched et al., 2000). In a study involving a group of patients with sporadic late-onset Alzheimer's dementia, a group of patients with vascular dementia and a control group, it was reported that HDL-cholesterol levels were lower in both groups of patients compared with the control group, and that apoA-I and apolipoprotein A-II (apoA-II) levels decreased in both groups of patients, especially in the vascular dementia group, and that the apoA-I/A-II ratio increased in both groups of patients (Kuriyama et al., 1994). Many studies have reported decreased serum and plasma apoA-I concentrations in AD patients, while some have reported unchanged apoA-I levels (Bergt et al., 2006; Liu et al., 2006; Merched et al., 2000). Serum apolipoprotein B-100 (apoB-100) is normally unable to cross the blood-brain barrier, but the pathological changes in the blood-brain barrier seen in AD may allow various serum-derived proteins to enter the brain (Tóth et al., 2020). In a study, it was observed that apoB-100 protein

accumulated in neurofibrillary tangles and senile plaques in the brains of Alzheimer's patients (Namba et al., 1992). In a study of cognitively normal elderly individuals, it was reported that serum triglycerides and apoB were associated with cerebral Aβ deposition, but total cholesterol, LDL-cholesterol, HDL-cholesterol and apoA-I levels were not associated with cerebral Aβ deposition (Choi et al., 2016). The role of apolipoprotein C-III (apoC-III) in the pathogenesis of AD is not clear, although some studies suggest that it may play a role (Zhang & Alzheimer's Disease Neuroimaging Initiative, 2020). In a study, it was stated that apoC-III may be the main pathogenic factor of AD after Aβ and tau (Zhang & Alzheimer's Disease Neuroimaging Initiative, 2020). Some studies have shown a positive correlation between decreased apoC-III levels and cognitive performance in AD patients (Muenchhoff et al., 2017; Shih et al., 2014). It has been suggested that apoC-III can bind circulating Aβ and that plasma apoC-III levels are decreased in patients with AD (Adunsky et al., 2002; Shih et al., 2014). ApoE is an apolipoprotein expressed in central nervous system and apolipoprotein E-IV (apoE-IV) protein encoded by the e4 allele is genetically associated with AD (Farrer et al., 1997). In a genome-wide association study of AD, apoE was reported to have profound effects on Aβ42-related phenotypes (Hong et al., 2020). In one study, it was shown that APOE-ε4 may negatively affect the microvascular functions in brain, thus contribute to impairing white matter and cognitive function (Koizumi et al., 2018). Apolipoprotein H (apoH, beta-2-glycoprotein 1), which prevents the activation of blood coagulation, is a lipid-binding protein (Misra et al., 2021). In one study, it was stated that the amount of apoH was significantly increased in CSF samples of those with moderate to severe AD (Öhrfelt et al., 2011). However, in a proteomic study using CSF samples from Alzheimer's patients and controls, it was reported that a significant decrease in the amount of apoH was detected in the CSF of Alzheimer's patients compared to controls (Misra et al., 2021). Apolipoprotein J (apoJ, clusterin, CLU), a ubiquitous glycoprotein that can interact with many different molecules, has been reported to be associated with amyloid (Calero et al., 2000). Studies have shown that CLU binds Aβ peptides, prevents their aggregation and provides their clearance by various means (Foster et al., 2019; Zlokovic et al., 1996).

About 30% of people with PD are reported to develop PD dementia during the course of the disease (Lehnert et al., 2012). In a study, it was reported that apoB-100 was significantly decreased in Parkinson's patients compared to non-demented controls (Lehnert et al., 2012). In a retrospective study, serum lipid and lipoprotein levels of Parkinson's patients were investigated and it was shown that significantly lower serum triglyceride, VLDL-cholesterol and apoB values were found in Parkinson's patients (Wei et al., 2013). It has also been reported that higher apoB, total cholesterol, LDL-cholesterol and triglyceride levels are associated with a lower risk of PD (Fang et al., 2019). In a study of healthy controls and PD patients with mild to moderate neurological impairment, a correlation between apolipoprotein D (apoD) and PD stage was reported (Waldner et al., 2018). The link between AD and the APOE-ε4 allele has led to studies investigating the links between PD and apoE polymorphisms (Huang et al., 2004). It has been reported that apoE is not a PD susceptibility gene, but although PD is clinically defined by motor

symptoms, many patients develop dementia within years after diagnosis (Aarsland et al., 2003; Hely et al. 2008; Hughes et al., 2000; Tsuang et al., 2013). As a result of a study, it was reported that the APOE-ε4 allele is an important determinant for cognitive function in PD (Mata et al., 2014). However, it has been reported that apoE genotype is not correlated with brain amyloid burden in autopsy patients with PD (Gomperts et al., 2013). In a recent study, APOE-ε4 allele was identified as an important risk factor in the development of PD dementia (Real et al., 2023). PD is a progressive neurodegenerative disorder characterised by the loss of dopamine-secreting dopaminergic neurons and the accumulation of α-synuclein (α-syn) (Lenzi et al., 2020). Clusterin (CLU) is a molecular chaperone and has been described to prevent Aβ accumulation in AD, but its role in the pathogenesis of PD is not yet known (Lenzi et al., 2020; Zlokovic et al., 1996). The study of CLU showed that CLU co-localised with α-syn in biopsies from patients with α-synucleinopathies and was an α-syn-related protein (Sasaki et al., 2002). Studies have shown that CLU expression is upregulated in CSF and serum samples from Parkinson's patients (Maarouf et al., 2012; Přikrylová Vranová et al., 2010; Zhang et al., 2012). In a recent study, it has been reported that CLU gene polymorphism is associated with PD and high levels of CLU are expressed in the plasma of PD patients (Lin et al., 2021).

Cholesterol biomarkers have been reported to be important for monitoring brain damage and disease progression in MS (Browne et al., 2014; Murali et al., 2020; Weinstock-Guttman et al., 2011). In a prospective longitudinal study of healthy controls, patients with progressive MS and patients with relapsing-remitting MS, increases in apoA-I and HDL-cholesterol were reported to be protective in MS (Murali et al., 2020). ApoD, which is involved in the removal of lipids in neurodegeneration, has been reported to be found at high levels in MS patients (Reindl et al., 2001). However, in a different study, a clear decrease in apoD expression was found in human multiple sclerosis plaques (Navarro et al., 2018). In a prospective longitudinal study of patients with relapsing-remitting MS and patients with progressive multiple sclerosis, it was reported that apoA-I and apoE may be associated with grey matter damage in multiple sclerosis (McComb et al., 2020). It has been reported that chromogranin A (CgA) and CLU expression is increased in reactive astrocytes in MS white matter lesions, which indicates that CgA and CLU, as neuroinflammatory mediators, may be CSF markers in MS patients (van Luijn et al., 2016).

HD has been reported to be associated with changes in lipid composition and impaired lipoprotein metabolism (Chang et al., 2023). In the study in which control and Huntington's patient groups were included, it was reported that prothrombin, apolipoprotein A-IV (apoA-IV), haptoglobin levels were higher in the CSF of Huntington's patient group compared to the control group (Huang et al., 2011). It has been reported that weight loss occurs in both the early and advanced stages of HD and that high levels of apoA-IV in the CNS inhibit food intake and stabilise body weight in the long term (Huang et al., 2011). In a study, it was reported that plasma levels of total cholesterol, apoB, apoB-particle number and LDL components were lower in people with presymptomatic HD and symptomatic HD (Chang et al., 2023).

In a study on ALS, it was reported that changes in neurofilaments and apoE were observed in bulbar-onset fast progressing ALS compared to limb-onset fast progressing ALS (Leoni et al., 2019). In another study, high HDL and apoA-I levels were associated with a decreased risk of ALS, whereas high total cholesterol:HDL ratio, LDL and apoB levels were associated with an increased risk of ALS (Thompson et al., 2022).

In a study, it was reported that APOE-ε4 was associated with an increased risk of frontotemporal lobar degeneration (FTLD) in all genetic models, whereas there was no significant association between APOE-ε2 allele and FTLD in most genetic models and subgroup analyses (Su et al., 2017). At the end of a study, it was reported that apoA-I and apoA-II levels decreased, apoB levels did not change, but apolipoprotein C-I (apoC-I) level decreased in behavioral variant frontotemporal dementia (bvFTD) patients compared to controls. In addition, it was reported that apoB:apoA-I ratio and standard lipid ratios were significantly increased in bvFTD patients compared with AD patients and controls (Kim et al., 2018.

3. Conclusion

Mothers The functions of apolipoproteins involved in lipid metabolism have been associated with neurodegenerative diseases. However, there are inconsistent findings in studies and different apolipoprotein polymorphisms have been evaluated as risk factors or protective agents in different neurodegenerative diseases. This points to specificities in the mechanisms that cause neurodegenerative diseases. Therefore, further and comprehensive studies on apolipoproteins are required both to elucidate the mechanisms of the development of neurodegenerative diseases that seriously worsen the quality of life of people and to slow down and reduce the neurodegeneration process. Studies in this direction will contribute to the development of new clinical and pharmacological treatments.

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Conflicts of Interest

The authors declare that there is no conflict of interest between them.

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Author Contributions

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References

Aarsland, D., Andersen, K., Larsen, J. P., & Lolk, A. (2003). Prevalence and characteristics of dementia in Parkinson disease: an 8-year prospective study. *Archives of neurology*, 60(3), 387-392. https://doi.org/10.1001/archneur.60.3.387

Adunsky, A., Chesnin, V., Davidson, M., Gerber, Y., Alexander, K., & Haratz, D. (2002). A cross-sectional study of lipids and ApoC levels in Alzheimer's patients with and without cardiovascular disease. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, 57(11), M757-M761. https://doi.org/10.1093/gerona/57.11.m757

Antonios, N., Angiolillo, D. J., & Silliman, S. (2008). Hypertriglyceridemia and ischemic stroke. *European neurology*, 60(6), 269-278. https://doi.org/10.1159/000157880

Bahrami, A., Barreto, G. E., Lombardi, G., Pirro, M., & Sahebkar, A. (2019). Emerging roles for high-density

lipoproteins in neurodegenerative disorders. *BioFactors*, 45(5), 725-739. https://doi.org/10.1002/biof.1541

Balazs, Z., Panzenboeck, U., Hammer, A., Sovic, A., Quehenberger, O., Malle, E., & Sattler, W. (2004). Uptake and transport of high ‐ density lipoprotein (HDL) and HDL ‐ associated α ‐ tocopherol by an in vitro blood – brain barrier model. *Journal of neurochemistry*, 89(4), 939-950. https://doi.org/10.1111/j.1471-4159.2004.02373.x

Bergt, C., Nakano, T., Ditterich, J., DeCarli, C., & Eiserich, J. P. (2006). Oxidized plasma high-density lipoprotein is decreased in Alzheimer's disease. *Free Radical Biology and Medicine*, 41(10), 1542-1547. https://doi.org/10.1016/j.freeradbiomed.2006.08.019

Björkhem, I., & Meaney, S. (2004). Brain cholesterol: long secret life behind a barrier. *Arteriosclerosis, thrombosis, and vascular biology*, 24(5), 806-815. https://doi.org/10.1161/01.ATV.0000120374.59826.1b .

Brown, M. S., & Goldstein, J. L. (1986). A receptor-mediated pathway for cholesterol homeostasis. *Science*, 232(4746), 34-47. https://doi.org/10.1126/science.3513311

Browne, R. W., Weinstock-Guttman, B., Horakova, D., Zivadinov, R., Bodziak, M. L., Tamaño-Blanco, M., Badgett, D., Tyblova, M., Vaneckova, M., Seidl, Z., Krasensky, J., Bergsland, N., Ramasamy, D. P., Hagemeier, J., Havrdova, E., & Ramanathan, M. (2014). Apolipoproteins are associated with new MRI lesions and deep grey matter atrophy in clinically isolated syndromes. *Journal of Neurology, Neurosurgery & Psychiatry*, 85(8), 859-864. https://doi.org/10.1136/jnnp-2013-307106

Calero, M., Rostagno, A., Matsubara, E., Zlokovic, B., Frangione, B., & Ghiso, J. (2000). Apolipoprotein J (clusterin) and Alzheimer's disease. *Microscopy research and technique*, 50(4), 305-315. https://doi.org/10.1002/1097-0029(20000815)50:4<305::AID-JEMT10>3.0.CO;2-L

Chang, K. H., Cheng, M. L., Lo, C. J., Fan, C. M., Wu, Y. R., & Chen, C. M. (2023). Alternations of Lipoprotein Profiles in the Plasma as Biomarkers of Huntington's Disease. *Cells*, 12(3), 385. https://doi.org/10.3390/cells12030385

Choi, H. J., Byun, M. S., Yi, D., Choe, Y. M., Sohn, B. K., Baek, H. W., Lee, J. H., Kim, H. J., Han, J. Y., Yoon, E. J., Kim, Y. K., Woo, J. I., & Lee, D. Y. (2016). Association between serum triglycerides and cerebral amyloidosis in cognitively normal elderly. *The American Journal of Geriatric Psychiatry*, 24(8), 604-612. https://doi.org/10.1016/j.jagp.2016.03.001

Dai, L., Li, S., Hao, Q., Zhou, R., Zhou, H., Lei, W., Kang, H., Wu, H., Li, Y., & Ma, X. (2023). Low-density lipoprotein: a versatile nanoscale platform for targeted delivery. *Nanoscale Advances*, 5, 1011-1022. https://doi.org/10.1039/d2na00883a

Dominiczak, M. H., & Caslake, M. J. (2011). Apolipoproteins: metabolic role and clinical biochemistry applications. *Annals of clinical biochemistry*, 48(6), 498-515. https://doi.org/10.1258/acb.2011.011111

Eiselein, L., Wilson, D. W., Lamé, M. W., & Rutledge, J. C. (2007). Lipolysis products from triglyceride-rich lipoproteins increase endothelial permeability, perturb zonula occludens-1 and F-actin, and induce apoptosis. *American Journal of Physiology-Heart and Circulatory Physiology*, 292(6), H2745-H2753. https://doi.org/10.1152/ajpheart.00686.2006

Fang, F., Zhan, Y., Hammar, N., Shen, X., Wirdefeldt, K., Walldius, G., & Mariosa, D. (2019). Lipids, Apolipoproteins, and the risk of Parkinson disease: a prospective cohort study and a Mendelian randomization analysis. *Circulation research*, 125(6), 643-652. https://doi.org/10.1161/CIRCRESAHA.119.314929

Fanning, A. S., & Anderson, J. M. (2009). Zonula occludens ‐ 1 and ‐ 2 are cytosolic scaffolds that regulate the assembly of cellular junctions. *Annals of the new York Academy of Sciences*, 1165(1), 113-120. https://doi.org/10.1111/j.1749-6632.2009.04440.x

Farrer, L. A., Cupples, L. A., Haines, J. L., Hyman, B., Kukull, W. A., Mayeux, R., Myers, R. H., Pericak-Vance, M. A., Risch, N., & Van Duijn, C. M. (1997). Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease: a meta-analysis. *Jama*, 278(16), 1349-1356. https://doi.org/10.1001/jama.1997.03550160069041

Foster, E. M., Dangla-Valls, A., Lovestone, S., Ribe, E. M., & Buckley, N. J. (2019). Clusterin in Alzheimer's disease: mechanisms, genetics, and lessons from other pathologies. *Frontiers in neuroscience*, 13, 164. https://doi.org/10.3389/fnins.2019.00164

Fyfe-Desmarais, G., Desmarais, F., Rassart, É., & Mounier, C. (2023). Apolipoprotein D in Oxidative Stress and Inflammation. *Antioxidants*, 12(5), 1027. https://doi.org/10.3390/antiox12051027

Gomperts, S. N., Locascio, J. J., Rentz, D., Santarlasci, A., Marquie, M., Johnson, K. A., & Growdon, J. H. (2013). Amyloid is linked to cognitive decline in patients with Parkinson disease without dementia. *Neurology*, 80(1), 85-91. https://doi.org/10.1212/WNL.0b013e31827b1a07

Hely, M. A., Reid, W. G., Adena, M. A., Halliday, G. M., & Morris, J. G. (2008). The Sydney multicenter study of Parkinson's disease: the inevitability of dementia at 20 years. *Movement disorders*, 23(6), 837-844. https://doi.org/10.1002/mds.21956

Hong, S., Prokopenko, D., Dobricic, V., Kilpert, F., Bos, I., Vos, S. J., Tijms, B. M., Andreasson, U., Blennow, K., Vandenberghe, R., Cleynen, I., Gabel, S., Schaeverbeke, J., Scheltens, P., Teunissen, C. E., Niemantsverdriet, E., Engelborghs, S., Frisoni, G., Blin, O., … & Bertram, L. (2020). Genome-wide association study of Alzheimer's disease CSF biomarkers in the EMIF-AD Multimodal Biomarker Discovery dataset. *Translational psychiatry*, 10(1),

403. https://doi.org/10.1038/s41398-020-01074-z

Huang, X., Chen, P. C., & Poole, C. (2004). APOE-ε2 allele associated with higher prevalence of sporadic Parkinson disease. *Neurology*, 62(12), 2198-2202. https://doi.org/10.1212/01.WNL.0000130159.28215.6A

Huang, Y. C., Wu, Y. R., Tseng, M. Y., Chen, Y. C., Hsieh, S. Y., & Chen, C. M. (2011). Increased prothrombin, apolipoprotein A-IV, and haptoglobin in the cerebrospinal fluid of patients with Huntington's disease. *PloS one*, 6(1), e15809. https://doi.org/10.1371/journal.pone.0015809

Hughes, T. A., Ross, H. F., Musa, S., Bhattacherjee, S., Nathan, R. N., Mindham, R. H. S., & Spokes, E. G. S. (2000). A 10-year study of the incidence of and factors predicting dementia in Parkinson's disease. *Neurology*, 54(8), 1596-1603. https://doi.org/10.1212/wnl.54.8.1596

Johansson, P., Almqvist, E. G., Bjerke, M., Wallin, A., Johansson, J. O., Andreasson, U., Blennow, K., Zetterberg, H., & Svensson, J. (2017). Reduced cerebrospinal fluid concentration of apolipoprotein AI in patients with Alzheimer's disease. *Journal of Alzheimer's Disease*, 59(3), 1017-1026. https://doi.org/10.3233/JAD-170226

Kawano, M., Kawakami, M., Otsuka, M., Yashima, H., Yaginuma, T., & Ueki, A. (1995). Marked decrease of plasma apolipoprotein AI and AII in Japanese patients with late-onset non-familial Alzheimer's disease. *Clinica chimica acta; international journal of clinical chemistry*, 239(2), 209-211. https://doi.org/10.1016/0009-8981(95)06115-t

Kim, W. S., He, Y., Phan, K., Ahmed, R. M., Rye, K. A., Piguet, O., Hodges, J. R., & Halliday, G. M. (2018). Altered high density lipoprotein composition in behavioral variant frontotemporal dementia. *Frontiers in neuroscience*, 12, 847. https://doi.org/10.3389/fnins.2018.00847

Koizumi, K., Hattori, Y., Ahn, S. J., Buendia, I., Ciacciarelli, A., Uekawa, K., Wang, G., Hiller, A., Zhao, L., Voss, H. U., Paul, S. M., Schaffer, C., Park, L., & Iadecola, C. (2018). Apoε4 disrupts neurovascular regulation and undermines white matter integrity and cognitive function. *Nature communications*, 9(1), 3816. https://doi.org/10.1038/s41467-018-06301-2

Kuriyama, M., Takahashi, K., Yamano, T., Hokezu, Y., Togo, S., Osame, M., & Igakura, T. (1994). Low levels of serum apolipoprotein AI and AII in senile dementia. *Psychiatry and Clinical Neurosciences*, 48(3), 589-593. https://doi.org/10.1111/j.1440-1819.1994.tb03019.x

Leduc, M. S., Shimmin, L. C., Klos, K. L., Hanis, C., Boerwinkle, E., & Hixson, J. E. (2008). Comprehensive evaluation of apolipoprotein H gene (APOH) variation identifies novel associations with measures of lipid metabolism in GENOA* s. *Journal of lipid research*, 49(12), 2648-2656. https://doi.org/10.1194/jlr.M800155-JLR200

Lehnert, S., Jesse, S., Rist, W., Steinacker, P., Soininen, H., Herukka, S. K., Tumani, H., Lenter, M., Oeckl, P., Ferger, B., Hengerer, B., & Otto, M. (2012). iTRAQ and multiple reaction monitoring as proteomic tools for biomarker search in cerebrospinal fluid of patients with Parkinson's disease dementia. *Experimental neurology*, 234(2), 499-505. https://doi.org/10.1016/j.expneurol.2012.01.024

Lenzi, C., Ramazzina, I., Russo, I., Filippini, A., Bettuzzi, S., & Rizzi, F. (2020). The down-regulation of clusterin expression enhances the αsynuclein aggregation process. *International Journal of Molecular Sciences*, 21(19), 7181. https://doi.org/10.3390/ijms21197181

Leoni, E., Bremang, M., Mitra, V., Zubiri, I., Jung, S., Lu, C. H., Adiutori, R., Lombardi, V., Russell, C., Koncarevic, S., Ward, M., Pike, I., & Malaspina, A. (2019). Combined tissue-fluid proteomics to unravel phenotypic variability in amyotrophic lateral sclerosis. *Scientific Reports*, 9(1), 4478. https://doi.org/10.1038/s41598-019-40632-4

Lin, Y., Lu, L., Zhou, M., Liu, H., Ye, P., Zhang, W., Qiu, J., Zhang, Z., Yang, X., Ding, L., Guo, W., Mo, M., Zhu, X., Zhang, X., Chen, X., & Xu, P. (2021). Association of CLU gene polymorphism with Parkinson's disease in the Chinese Han population. *The Journal of Gene Medicine*, 23(2), e3302. https://doi.org/10.1002/jgm.3302

Liu, H. C., Hu, C. J., Chang, J. G., Sung, S. M., Lee, L. S., Yuan, R. Y., & Leu, S. J. (2006). Proteomic identification of lower apolipoprotein AI in Alzheimer's disease. *Dementia and geriatric cognitive disorders*, 21(3), 155-161. https://doi.org/10.1159/000090676

Liu, T., Chen, J. M., Zhang, D., Zhang, Q., Peng, B., Xu, L., & Tang, H. (2021). ApoPred: identification of apolipoproteins and their subfamilies with multifarious features. *Frontiers in Cell and Developmental Biology*, 8, 621144. https://doi.org/10.3389/fcell.2020.621144

Maarouf, C. L., Beach, T. G., Adler, C. H., Shill, H. A., Sabbagh, M. N., Wu, T., Walker, D. G., Kokjohn, T. A., Roher, A. E., & Consortium, A. P. (2012). Cerebrospinal fluid biomarkers of neuropathologically diagnosed Parkinson's disease subjects. *Neurological research*, 34(7), 669-676. https://doi.org/10.1179/1743132812Y.0000000063

Mata , I. F., Leverenz, J. B., Weintraub, D., Trojanowski, J. Q., Hurtig, H. I., Van Deerlin, V. M., Ritz, B., Rausch, R., Rhodes, S. L., Factor, S. A., Wood-Siverio, C., Quinn, J. F., Chung, K. A., Peterson, A. L., Espay, A. J., Revilla, F. J., Devoto, J., Hu, S., Cholerton, B. A., Wan, J. Y., Montine, T. J., Edwards, K. L., & Zabetian, C. P. (2014). APOE, MAPT, and SNCA genes and cognitive performance in Parkinson disease. *JAMA neurology*, 71(11), 1405-1412. https://doi.org/10.1001/jamaneurol.2014.1455

Mathieu, C., Pappu, R. V., & Taylor, J. P. (2020). Beyond aggregation: Pathological phase transitions in neurodegenerative disease. *Science*, 370(6512), 56-60. https://doi.org/10.1126/science.abb8032

Merched , A., Xia, Y., Visvikis, S., Serot, J. M., & Siest,

G. (2000). Decreased high-density lipoprotein cholesterol and serum apolipoprotein AI concentrations are highly correlated with the severity of Alzheimer's disease☆. *Neurobiology of aging*, 21(1), 27-30. https://doi.org/10.1016/s0197-4580(99)00103-7

McComb, M., Parambi, R., Browne, R. W., Bodziak, M. L., Jakimovski, D., Bergsland, N., Maceski, A., Weinstock-Guttman, B., Jens Kuhle, J., Zivadinov, R., & Ramanathan, M. (2020). Apolipoproteins AI and E are associated with neuroaxonal injury to gray matter in multiple sclerosis. *Multiple sclerosis and related disorders*, 45, 102389. https://doi.org/10.1016/j.msard.2020.102389

Misra, A., Chakrabarti, S. S., Gambhir, I. S., Baghel, M. S., & Patil, Y. R. (2021). *Tandem mass spectrometry-based identification of protein profiles in the cerebrospinal fluid of Alzheimer's dementia patients*. https://doi.org/10.21203/rs.3.rs-574644/v1

Muenchhoff, J., Song, F., Poljak, A., Crawford, J. D., Mather, K. A., Kochan, N. A., Yang, Z., Trollor, J. N., Reppermund, S., Maston, K., Theobald, A., Kirchner-Adelhardt, S., Kwok, J. B., Richmond, R. L., McEvoy, M., Attia, J., Schofield, P. W., Brodaty, H., & Sachdev, P. S. (2017). Plasma apolipoproteins and physical and cognitive health in very old individuals. *Neurobiology of Aging*, 55, 49-60. https://doi.org/10.1016/j.neurobiolaging.2017.02.017

Murali, N., Browne, R. W., Fellows Maxwell, K., Bodziak, M. L., Jakimovski, D., Hagemeier, J., Bergsland, N., Weinstock-Guttman, B., Zivadinov, R., & Ramanathan, M. (2020). Cholesterol and neurodegeneration: longitudinal changes in serum cholesterol biomarkers are associated with new lesions and gray matter atrophy in multiple sclerosis over 5 years of follow-up. *European Journal of Neurology*, 27(1), 188-e4. https://doi.org/10.1111/ene.14055

Nakaya, Y., Schaefer, E. J., & Brewer Jr, H. B. (1980). Activation of human post heparin lipoprotein lipase by apolipoprotein H (β2-glycoprotein I). *Biochemical and biophysical research communications*, 95(3), 1168-1172. https://doi.org/10.1016/0006-291X(80)91595-8

Namba, Y., Tsuchiya, H., & Ikeda, K. (1992). Apolipoprotein B immunoreactivity in senile plaque and vascular amyloids and neurofibrillary tangles in the brains of patients with Alzheimer's disease. *Neuroscience letters*, 134(2), 264-266. https://doi.org/10.1016/0304-3940(92)90531-b

Navarro, A., Rioseras, B., Del Valle, E., Martínez-Pinilla, E., Astudillo, A., & Tolivia, J. (2018). Expression pattern of myelin-related apolipoprotein D in human multiple sclerosis lesions. *Frontiers in Aging Neuroscience*, 10, 254. https://doi.org/10.3389/fnagi.2018.00254

Öhrfelt, A., Andreasson, U., Simon, A., Zetterberg, H., Edman, Å., Potter, W., Holder, D., Devanarayan, V., Seeburger, J., Smith, A. D., Blennow, K., & Wallin, A. (2011). Screening for new biomarkers for subcortical vascular dementia and Alzheimer's disease. *Dementia and geriatric cognitive disorders extra*, 1(1), 31-42. https://doi.org/10.1159/000323417

Park, J. H., Hong, K. S., Lee, E. J., Lee, J., & Kim, D. E. (2011). High levels of apolipoprotein B/AI ratio are associated with intracranial atherosclerotic stenosis. *Stroke*, 42(11), 3040-3046. https://doi.org/10.1161/STROKEAHA.111.620104

Paula-Lima, A. C., Tricerri, M. A., Brito-Moreira, J., Bomfim, T. R., Oliveira, F. F., Magdesian, M. H., Grinberg, L. T., Panizzutti, R., & Ferreira, S. T. (2009). Human apolipoprotein A–I binds amyloid-β and prevents Aβ-induced neurotoxicity. *The international journal of biochemistry & cell biology*, 41(6), 1361-1370. https://doi.org/10.1016/j.biocel.2008.12.003

Přikrylová Vranová, H., Mareš, J., Nevrlý, M., Stejskal, D., Zapletalová, J., Hluštík, P., & Kaňovský, P. (2010). CSF markers of neurodegeneration in Parkinson's disease. *Journal of neural transmission*, 117, 1177-1181. https://doi.org/10.1007/s00702-010-0462-z

Ramasamy, I. (2014). Recent advances in physiological lipoprotein metabolism. *Clinical Chemistry and Laboratory Medicine (CCLM)*, 52(12), 1695-1727. https://doi.org/10.1515/cclm-2013-0358

Rassart, E., Bedirian, A., Do Carmo, S., Guinard, O., Sirois, J., Terrisse, L., & Milne, R. (2000). Apolipoprotein d. *Biochimica et Biophysica Acta (BBA)-Protein Structure and Molecular Enzymology*, 1482(1-2), 185-198. https://doi.org/10.1016/S0167-4838(00)00162-X

Real, R., Martinez-Carrasco, A., Reynolds, R. H., Lawton, M. A., Tan, M. M., Shoai, M., Corvol, J. C., Ryten, M., Bresner, C., Hubbard, L., Brice, A., Lesage, S., Faouzi, J., Elbaz, A., Artaud, F., Williams, N., Hu, M. T. M., Ben-Shlomo, Y., Grosset, D. G., ... & Morris, H. R. (2023). Association between the LRP1B and APOE loci and the development of Parkinson's disease dementia. *Brain*, 146(5), 1873-1887. https://doi.org/10.1093/brain/awac414

Reichert, C. O., de Freitas, F. A., Sampaio-Silva, J., Rokita-Rosa, L., Barros, P. D. L., Levy, D., & Bydlowski, S. P. (2020a). Ferroptosis mechanisms involved in neurodegenerative diseases. *International journal of molecular sciences*, 21(22), 8765. https://doi.org/10.3390/ijms21228765

Reichert, C. O., Levy, D., & Bydlowski, S. P. (2020b). Paraoxonase role in human neurodegenerative diseases. *Antioxidants*, 10(1), 11. https://doi.org/10.3390/antiox10010011

Reindl, M., Knipping, G., Wicher, I., Dilitz, E., Egg, R., Deisenhammer, F., & Berger, T. (2001). Increased intrathecal production of apolipoprotein D in multiple sclerosis. *Journal of neuroimmunology*, 119(2), 327-332. https://doi.org/10.1016/s0165-5728(01)00378-2

Richardson, T. G., Sanderson, E., Palmer, T. M., Ala-Korpela, M., Ference, B. A., Davey Smith, G., & Holmes, M. V. (2020). Evaluating the relationship between circulating lipoprotein lipids and apolipoproteins with risk of coronary heart disease: A multivariable Mendelian randomisation analysis. *PLoS*

medicine, 17(3), e1003062. https://doi.org/10.1371/journal.pmed.1003062

Ross MH, & Pawlina W. (2011). *Histology: A text and atlas with correlated cell and molecular biology*. Baltimore, Philadelphia: Lippincott Williams & Wilkins.

Saczynski, J. S., White, L., Peila, R. L., Rodriguez, B. L., & Launer, L. J. (2007). The relation between apolipoprotein AI and dementia: the Honolulu-Asia aging study. *American journal of epidemiology*, 165(9), 985-992. https://doi.org/10.1093/aje/kwm027

Sasaki , K., Doh-ura, K., Wakisaka, Y., & Iwaki, T. (2002). Clusterin/apolipoprotein J is associated with cortical Lewy bodies: immunohistochemical study in cases with α-synucleinopathies. *Acta neuropathologica*, 104, 225-230. https://doi.org/10.1007/s00401-002-0546-4

Shih, Y. H., Tsai, K. J., Lee, C. W., Shiesh, S. C., Chen, W. T., Pai, M. C., & Kuo, Y. M. (2014). Apolipoprotein C-III is an amyloid-β-binding protein and an early marker for Alzheimer's disease. *Journal of Alzheimer's Disease*, 41(3), 855-865. https://doi.org/10.3233/JAD-140111

Su, W. H., Shi, Z. H., Liu, S. L., Wang, X. D., Liu, S., & Ji, Y. (2017). Updated meta-analysis of the role of APOE ε2/ε3/ε4 alleles in frontotemporal lobar degeneration. *Oncotarget*, 8(27), 43721. https://doi.org/10.18632/oncotarget.17341

Sweeney, M. D., Sagare, A. P., & Zlokovic, B. V. (2018). Blood–brain barrier breakdown in Alzheimer disease and other neurodegenerative disorders. *Nature Reviews Neurology*, 14(3), 133-150. https://doi.org/10.1038/nrneurol.2017.188

Thompson, A. G., Talbot, K., & Turner, M. R. (2022). Higher blood high density lipoprotein and apolipoprotein A1 levels are associated with reduced risk of developing amyotrophic lateral sclerosis. *Journal of Neurology, Neurosurgery & Psychiatry*, 93(1), 75-81. https://doi.org/10.1136/jnnp-2021-327133

Tóth, M. E., Dukay, B., Hoyk, Z., & Sántha, M. (2020). Cerebrovascular changes and neurodegeneration related to hyperlipidemia: characteristics of the human ApoB-100 transgenic mice. *Current Pharmaceutical Design*, 26(13), 1486-1494. https://doi.org/10.2174/1381612826666200218101818

Tsuang, D., Leverenz, J. B., Lopez, O. L., Hamilton, R. L., Bennett, D. A., Schneider, J. A., Buchman, A. S., Larson, E. B., Crane, P. K., Kaye, J. A., Kramer, P., Woltjer, R., Trojanowski, J. O., Weintraub, D., Chen-Plotkin, A. S., Irwin, D. J., Rick, J., Schellenberg, G. D., Watson, G. S., … & Zabetian, C. P. (2013). APOE ϵ4 increases risk for dementia in pure synucleinopathies. *JAMA neurology*, 70(2), 223-228. https://doi.org/10.1001/jamaneurol.2013.600

Turan, T. N., Makki, A. A., Tsappidi, S., Cotsonis, G., Lynn, M. J., Cloft, H. J., & Chimowitz, M. I. (2010). Risk factors associated with severity and location of intracranial arterial stenosis. *Stroke*, 41(8), 1636-1640. https://doi.org/10.1161/STROKEAHA.110.584672

van Luijn, M. M., van Meurs, M., Stoop, M. P., Verbraak, E., Wierenga-Wolf, A. F., Melief, M. J., Kreft, K. L., Verdijk, R. M., 't Hart, B. A., Luider, T. M., Laman, J. D., & Hintzen, R. Q. (2016). Elevated expression of the cerebrospinal fluid disease markers chromogranin a and clusterin in astrocytes of multiple sclerosis white matter lesions. *Journal of Neuropathology & Experimental Neurology*, 75(1), 86-98. https://doi.org/10.1093/jnen/nlv004

Vitali, C., Wellington, C. L., & Calabresi, L. (2014). HDL and cholesterol handling in the brain. *Cardiovascular research*, 103(3), 405-413. https://doi.org/10.1093/cvr/cvu148

Waldner, A., Dassati, S., Redl, B., Smania, N., & Gandolfi, M. (2018). Apolipoprotein D concentration in human plasma during aging and in Parkinson's disease: a cross-sectional study. *Parkinson's Disease*, 2018. https://doi.org/10.1155/2018/3751516

Wang, L., Sapuri-Butti, A. R., Aung, H. H., Parikh, A. N., & Rutledge, J. C. (2008). Triglyceride-rich lipoprotein lipolysis increases aggregation of endothelial cell membrane microdomains and produces reactive oxygen species. *American Journal of Physiology-Heart and Circulatory Physiology*, 295(1), H237-H244. https://doi.org/10.1152/ajpheart.01366.2007

Wei, Q., Wang, H., Tian, Y., Xu, F., Chen, X., & Wang, K. (2013). Reduced serum levels of triglyceride, very low density lipoprotein cholesterol and apolipoprotein B in Parkinson's disease patients. *PLoS One*, 8(9), e75743. https://doi.org/10.1371/journal.pone.0075743

Weinstock-Guttman, B., Zivadinov, R., Mahfooz, N., Carl, E., Drake, A., Schneider, J., Teter, B., Hussein, S., Mehta, B., Weiskopf, M., Durfee, J., Bergsland, N., & Ramanathan, M. (2011). Serum lipid profiles are associated with disability and MRI outcomes in multiple sclerosis. *Journal of neuroinflammation*, 8(1), 1-7. https://doi.org/10.1186/1742-2094-8-127

Wisniewski, T., Golabek, A. A., Kida, E., Wisniewski, K. E., & Frangione, B. (1995). Conformational mimicry in Alzheimer's disease. Role of apolipoproteins in amyloidogenesis. *The American journal of pathology*, 147(2), 238. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1869828/pdf/amjpathol00044-0015.pdf

Zhang, X., & Alzheimer's Disease Neuroimaging Initiative. (2020). Higher plasma APOC-III was associated with a slower reduction of β-amyloid levels in cerebrospinal fluid among older individuals without dementia. *Neuropsychiatric Disease and Treatment*, 1139-1144. https://doi.org/10.2147/NDT.S238985

Zhang, X., Yin, X., Yu, H., Liu, X., Yang, F., Yao, J., Jin, H., & Yang, P. (2012). Quantitative proteomic analysis of serum proteins in patients with Parkinson's disease using an isobaric tag for relative and absolute quantification labeling, two-dimensional liquid chromatography, and tandem mass spectrometry. *Analyst*, 137(2), 490-495. https://doi.org/10.1039/c1an15551b

Zlokovic, B. V., Martel, C. L., Matsubara, E., McComb, J. G., Zheng, G., McCluskey, R. T., Frangione, B., &

Ghiso, J. (1996). Glycoprotein 330/megalin: probable role in receptor-mediated transport of apolipoprotein J alone and in a complex with Alzheimer disease amyloid beta at the blood-brain and blood-cerebrospinal fluid barriers. *Proceedings of the National Academy of Sciences*, 93(9), 4229-4234. https://doi.org/10.1073/pnas.93.9.4229