Increased maternal compared to paternal transmission of Alzheimer's Disease may be due to increased incidence of depression in women

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Keywords: neurodegeneration, genetics, mitochondria, comorbidity

Data sources described in article publicly available or available after approved application to UK Biobank.

Conflicts of interest: none

Dr. Lehrer and Dr. Rheinstein contributed equally to the conception, writing, and data analysis of this study.

This work was supported in part through the computational resources and staff expertise provided by Scientific Computing at the Icahn School of Medicine at Mount Sinai. Research reported in this paper was also supported by the Office of Research Infrastructure of the National Institutes of Health under award numbers S10OD018522 and S10OD026880. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Abstract

Mothers transmit Alzheimer's disease (AD) more frequently than fathers. We examined parental transmission of AD in UK Biobank data. Of 953 AD cases 493 were male (51.7%) and 460 were female (48.3%). Yet mothers were twice as likely to transmit AD, compared to fathers. Other factors than female longevity may be at work to promote maternal transmission of AD. Among these are the X chromosome, mitochondria, and AD comorbidities, especially depression. Epidemiological and molecular investigations have shown evidence that several illnesses, in particular type 2 diabetes, cardiovascular disease, depression, and gastrointestinal disorders, may raise the risk of AD. Of these four, type 2 diabetes, cardiovascular disease, and gastrointestinal disorders are approximately equally distributed between older men and women. Only depression, especially major depression, predominates in women. Major depression is genetic and quite heritable, more so in women than in men. People with AD frequently experience depression, especially in the early and middle stages. And depression may be a risk factor for cognitive impairment and AD. The same genetic risk factors that cause depression may also be responsible for some occurrences of AD. The fact that AD is polygenic like depression means that several different variants could work together to increase disease vulnerability. We conclude that depression in the mother, a multigenic illness, is most likely the basis for the fact that mothers transmit AD twice as often as fathers.

Mothers transmit Alzheimer's disease (AD) more frequently than fathers (Heggeli *et al.*, 2012). Heggeli et al reported that mothers of both AD cases and controls were more often affected than fathers, even after adjusting for age. But cases' mothers were no more often demented than controls' mothers, which does not support the maternal AD transmission. Rather, the increased number of affected mothers could relate, at least in part, to female longevity.

While female longevity is a portion of the cause of increased AD in women, it is not solely responsible (Lehrer & Rheinstein, 2015). Another cause may be stronger female immune systems (Klein & Flanagan, 2016). Women are twice as likely as men to have autoimmune disease (Angum *et al.*, 2020). The amyloid plaques characteristic of AD may be the output of part of the brain's immune system (Eimer *et al.*, 2018). Due to their stronger immune systems, women may end up having more amyloid plaques than men. As a result, women may have a greater risk of developing AD.

Mosconi et al linked maternal AD transmission to a relationship between reduced cerebral metabolic rate of glucose in AD-vulnerable brain regions and a maternal family history of AD in cognitively normal individuals (Mosconi *et al.*, 2007).

We examined parental transmission of AD in UK Biobank data. Of 953 AD cases 493 were male (51.7%) and 460 were female (48.3%). Yet mothers were twice as likely to transmit AD, compared to fathers (Lehrer & Rheinstein, 2023) Figure 1. Therefore, factors other than female longevity and autoimmunity may be at work to promote maternal transmission of AD. Among these are the X chromosome, mitochondria, and AD comorbidities, especially depression.

X chromosome

867 known genes reside on the X chromosome, which comes from the mother, and many of these genes are involved in the growth of tissues like bone, neural, blood, hepatic, renal, retina, ears, cardiac, skin, and teeth. The involvement of genes on the X chromosome results in at least 533 diseases. A defective (mutated) gene is located on the X chromosome when there is an X-linked recessive inheritance pattern. X-linked recessive diseases include Duchenne muscular dystrophy, several forms of colorblindness, and hemophilia A (Basta & Pandya, 2020).

A link between the X chromosome and AD has recently been identified in mice. In comparison to male brains, female brains have higher production of the X-linked ubiquitin-specific peptidase 11 (USP11), which leads to larger accumulation of tau protein (Yan *et al.*, 2022). Tauopathies, a group of neurodegenerative disorders that include Alzheimer's disease, are characterized by tau accumulation in the central nervous system. But a relationship between the X chromosome and AD has not turned up in numerous genome wide association studies (GWAS) of AD, even when family history was included (Bellenguez *et al.*, 2022; Marioni *et al.*, 2018).

Mitochondria

Nuclear genomes on chromosomes 1-22 are equally inherited from both parents, whereas the mitochondrial mode of transmission is entirely maternal. As a result, mutations linked to diseases affecting the mitochondria are always inherited from the mother, who transmits a circular single

stranded mitochondrial chromosome to her offspring (Chial & Craig, 2008). Among the most common mitochondrial diseases are Mitochondrial encephalopathy, Lactic acidosis and stroke-like episodes (MELAS) syndrome, Leber hereditary optic neuropathy (LHON), Leigh syndrome, Myoclonic epilepsy and ragged-red fiber disease (MERRF), and Kearns-Sayre syndrome (KSS). Mitochondrial diseases occur about once in 5,000 people.

The hallmark of AD is increasing neuronal dysfunction, and mitochondria play a crucial part in maintaining healthy neuronal function and longevity. Mitochondrial dysfunction, which develops upstream and could cause many downstream signs such as Aß and tau pathology, might be an underlying factor in AD. Abundant data suggest that oxidative damage and metabolic abnormalities are both present in AD (Ashleigh *et al.*, 2023).

Mitochondrial DNA variants have been inconsistently associated with AD (Zhang *et al.*, 2022). The most recent is mitochondrial SNP rs2853499 that was mapped to a novel mitochondrial small open reading frame called SHMOOSE with microprotein encoding potential. Cerebrospinal fluid (CSF) SHMOOSE levels in humans correlated with age, CSF tau, and brain white matter volume (Miller *et al.*, 2023).

SNP rs2853499 is in position chrMT:12372 (GRCh38.p14), alleles G>A, a single nucleotide variant (SNV), minor allele (A) frequency 0.417 in UK Biobank. We found that in subjects with AD 0.2% (401) carried the A allele, 0.2% (500) carried the G allele. This difference was not significant ($p = 0.091$, 2 tailed Fisher exact test, table 1).

Despite their role in neuronal function, mitochondria have yet to be demonstrated as a significant factor in AD.

Alzheimer's Disease Comorbidities

Epidemiological and molecular investigations have shown evidence that several illnesses, in particular type 2 diabetes, cardiovascular disease, depression, and gastrointestinal disorders, may raise the risk of AD (Santiago & Potashkin, 2021; Wang *et al.*, 2018). Of these four, type 2 diabetes, cardiovascular disease, and gastrointestinal disorders are approximately equally distributed between men and women. Cardiovascular disease is more common in younger men, but after menopause women are heavily affected as well. Only depression, especially major depression, predominates in women.

Major depressive illness will affect at least 10% of Americans at some point in their lives. Major depression affects twice as many women as it does men.

Major depression is quite heritable, more so in women than in men (Kendler *et al.*, 2018). Unrelated twins (also known as "fraternal" or "dizygotic") share 50% of their DNA, whereas identical (monozygotic) twins share 100% of their genes. If genes have a role in the causation, the identical twin of a patient should be at significantly higher risk for the disease than the non-identical twin, which applies to severe depression. The inheritability of depression is 19% in dizygotic twins, 76% percent in monozygotic twins, and it may be higher in cases of severe depression. Like hypertension and type 2

diabetes, depression and risk of depression are polygenic, many genes having been implicated (Mitchell *et al.*, 2021; Nelemans *et al.*, 2021).

Depression and Alzheimer's Disease

People with AD frequently experience depression, especially in the early and middle stages. And according to a recent meta-analysis of clinical investigations, depression may be a risk factor for cognitive impairment and AD (Saiz-Vazquez *et al.*, 2021). Depression symptoms in cognitively healthy older individuals, together with brain amyloid, can incite changes in memory and thinking over time (Gatchel *et al.*, 2019).

The same genetic risk factors that might cause depression may also be responsible for some occurrences of AD (Ni *et al.*, 2018). In one study a correlation existed between the single nucleotide polymorphisms (SNPs) carried by people with AD and those in persons with depression. The SNPs linked to depression increase a person's likelihood of getting AD. The opposite, though, was not true. The chance of developing depression was not increased by the SNPs linked to AD (Harerimana *et al.*, 2022). This observation corroborates Heggeli et al's findings, noted above, that AD cases' mothers were no more often demented than controls' mothers.

The fact that AD is polygenic like depression means that several different variants could work together to increase disease vulnerability. Apolipoprotein E ε4 (APOE4) is the largest genetic risk factor for development of sporadic AD, but deep learning neural network models for polygenic risk may improve AD predictability (Zhou *et al.*, 2023).

We conclude that depression in the mother, a polygenic illness, is most likely the basis for the fact that mothers transmit AD twice as often as fathers.

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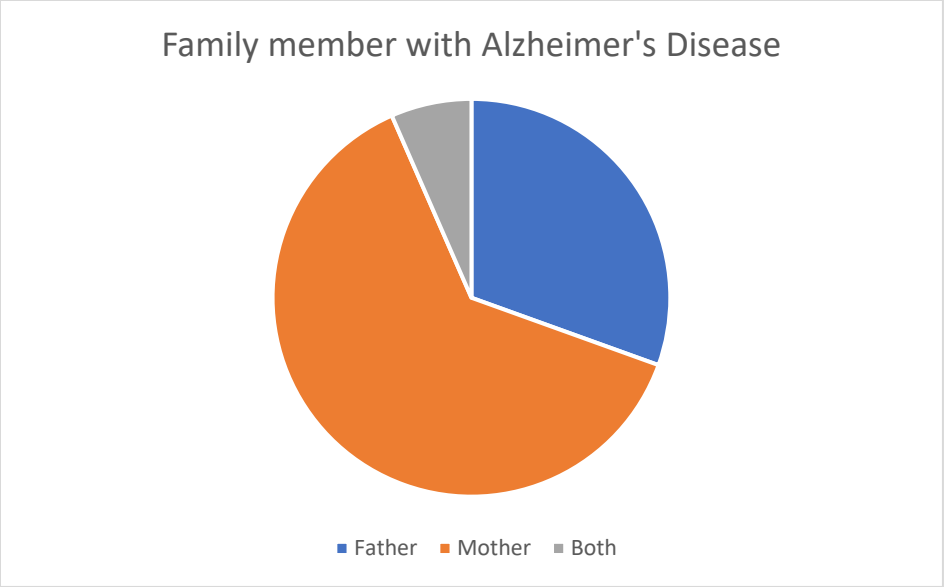

Figure 1. Alzheimer's Disease heritability in 259 subjects with AD in UK Biobank. Mothers were twice as likely as fathers to transmit AD.

		rs2853499 allele	rs2853499 allele	
Alzheimer's		A	G	Total
no	count	202750	283153	485903
	percent	99.80%	99.80%	99.80%
yes	count	401	500	901
	percent	0.20%	0.20%	0.20%
total	count	203151	283653	486804
	percent	100.00%	100.00%	100.00%

Table 1. Alzheimer's disease in 901 UK Biobank subjects versus incidence of rs2853499 allele (A,G). The result is insignificant ($p = 0.091$, 2 tail Fisher exact test).