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Supplementary Data 1. Results of sex-stratified autosomal and X-linked analyses (Excel)

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Supplementary Methods:
Summary of models used in regression analyses

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Summary of models used in analyses:

Model A1: Aβ OR tau tangles ~ Participant Age of Death + Sex + Post-mortem Interval + Gene

Model A2: Aβ OR tau tangles ~ Participant Age of Death + Post-mortem Interval + Gene*Sex

Model A3: Aβ OR tau tangles ~ Participant Age of Death + Post-mortem Interval + Gene
- Male- or female-stratified

Model A4: Aβ OR tau tangles ~ Participant Age of Death + Post-mortem Interval + Gene + *APOE*ε4 status

Model A5: Aβ OR tau tangles ~ Participant Age of Death + Post-mortem Interval + Gene + Diagnosis

Model B1: Longitudinal Cognition ~ Participant Age of Death + Sex + Post-mortem Interval + Latency to Death + Education + Gene

Model B2: Longitudinal Cognition ~ Participant Age of Death + Post-mortem Interval + Latency to Death + Education + Gene*Sex

Model B3: Longitudinal Cognition ~ Participant Age of Death + Post-mortem Interval + Latency to Death + Education + Gene
- Male- or female-stratified

Model B4: Longitudinal Cognition ~ Participant Age of Death + Post-mortem Interval + Latency to Death + Education + Gene + Amyloid + Tau Tangles

Model B5: Longitudinal Cognition ~ Participant Age of Death + Post-mortem Interval + Latency to Death + Education + Gene + *APOE*ε4 status

Model B6: Longitudinal Cognition ~ Participant Age of Death + Post-mortem Interval + Latency to Death + Education + Gene + Amyloid + Tau Tangles + Diagnosis

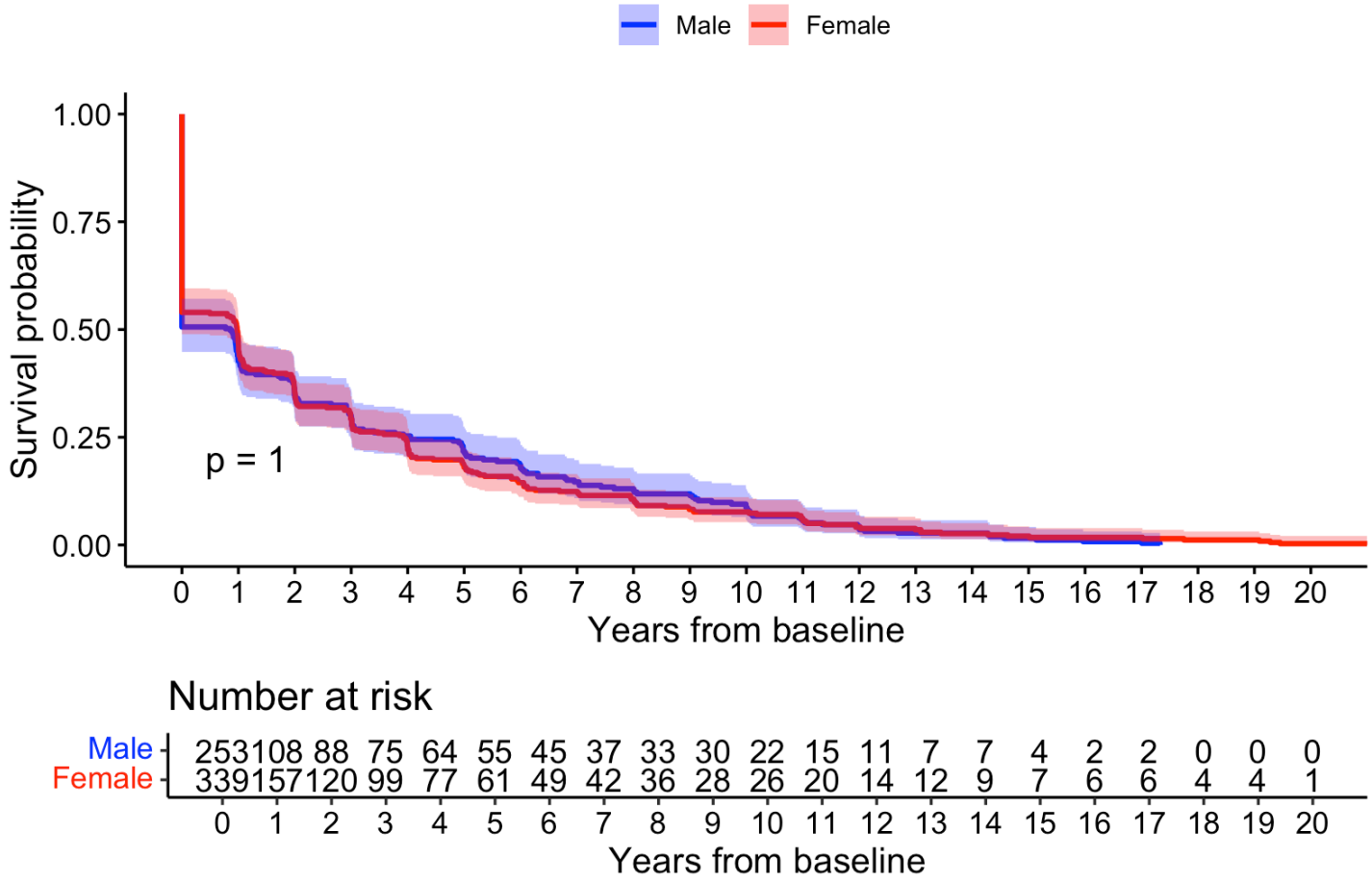
For *HDAC8, MCF2*, *FTX*, and *SLC10A3*:

Model C1: Longitudinal Cognition OR tau tangles ~ Participant Age of Death + Post-mortem Interval + Latency to Death + Education + Gene*Sex**APOE*ε4 status

Model C2: Longitudinal Cognition OR tau tangles ~ Participant Age of Death + Post-mortem Interval + Latency to Death + Education + Gene*Sex*Pathology (Amyloid+ OR Tau+)

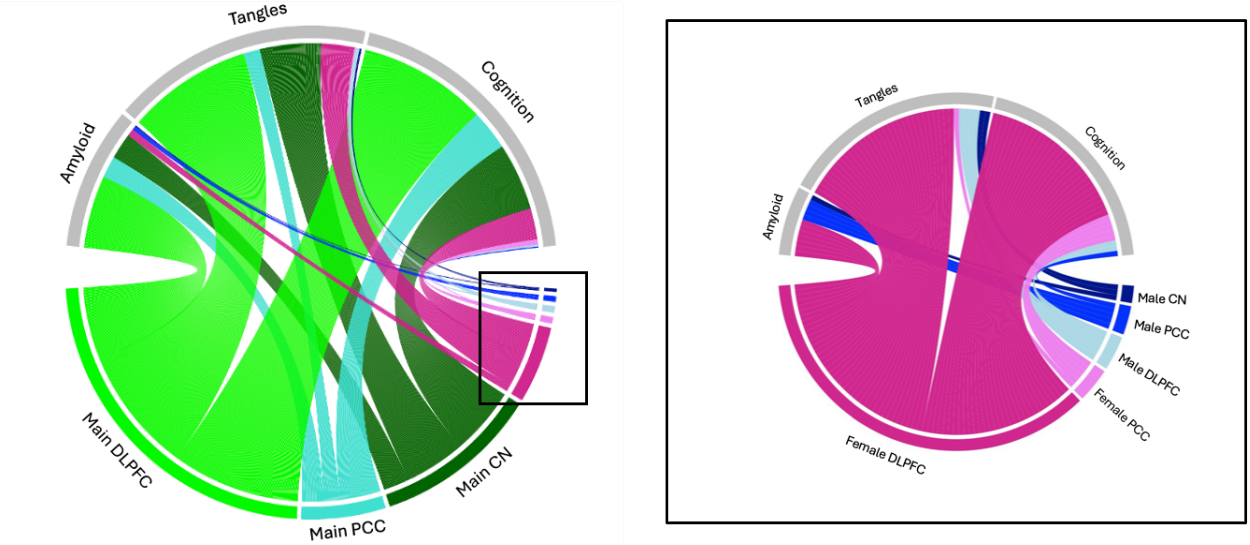
Model C3: Longitudinal Cognition OR tau tangles ~ Participant Age of Death + Post-mortem Interval + Latency to Death + Education + Gene*Sex*Diagnosis
- Further stratified by sex and diagnosis

Supplementary Figure 1. Kaplan-Meier plot assessing incidence of MCI/AD in females vs. males



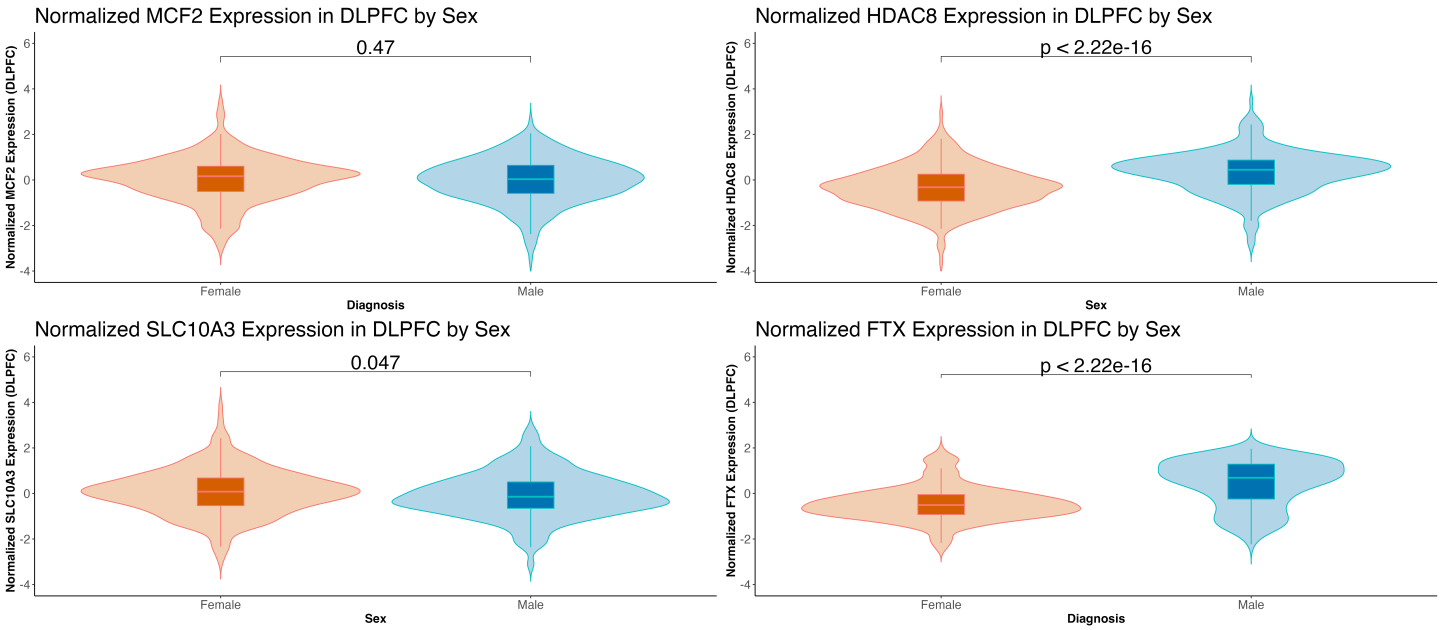
Kaplan-Meier curves generated from the pooled ROS/MAP sample (all brain regions, n=767) depicting time to first AD/MCI diagnosis. Blue line represents male samples; females are depicted in red. Bold lines represent cumulative probability over time. Shaded areas represent the 95% confidence interval.

Supplemental Figure 2: Chord diagram summarizing X-transcriptome wide analyses



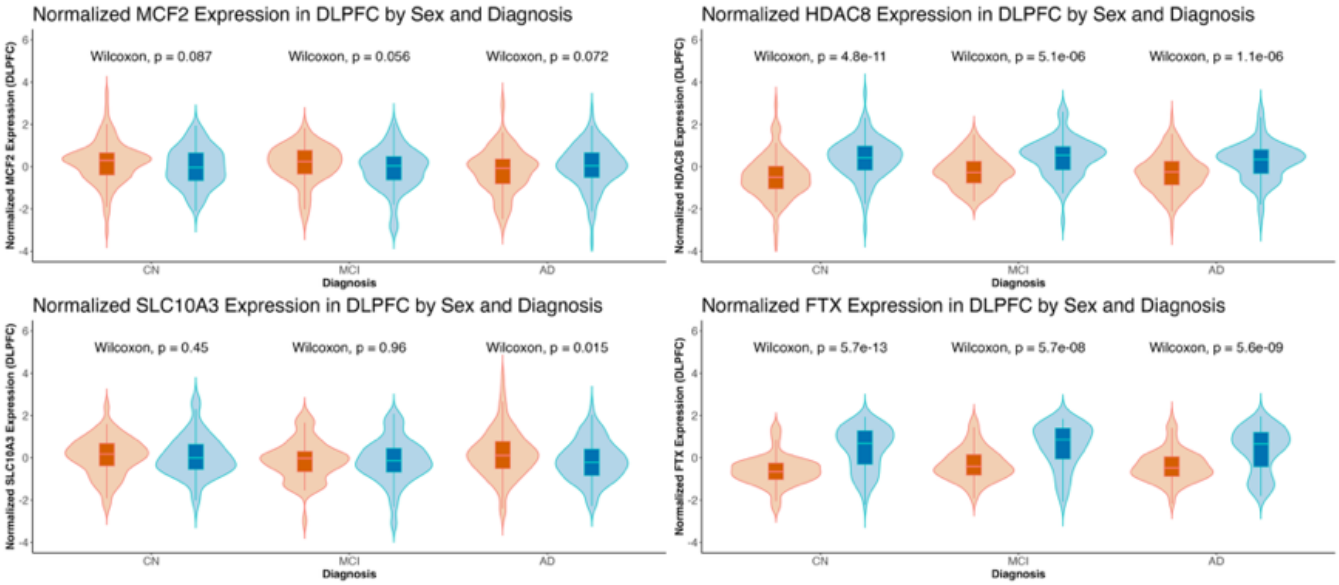
Chord diagrams summarizing the relative number of X-linked genes associated with Aβ, tau tangles, or longitudinal cognition in the Dorsolateral prefrontal cortex (DLPFC) or Posterior Cingulate Cortex (PCC) or Caudate Nucleus (CN) with chord size corresponding to number of significant genes. The right panel further highlights the significant male- and female-specific gene associations in sex-stratified analyses. Green chords represent the number of main effect associations (not sex-specific) we observe in the data. Pink chords represent female-specific gene associations and blue chords represent male-specific associations.

Supplementary Figure 3: Expression of *MCF2*, *HDAC8*, *FTX*, and *SLC10A3* in males and females.



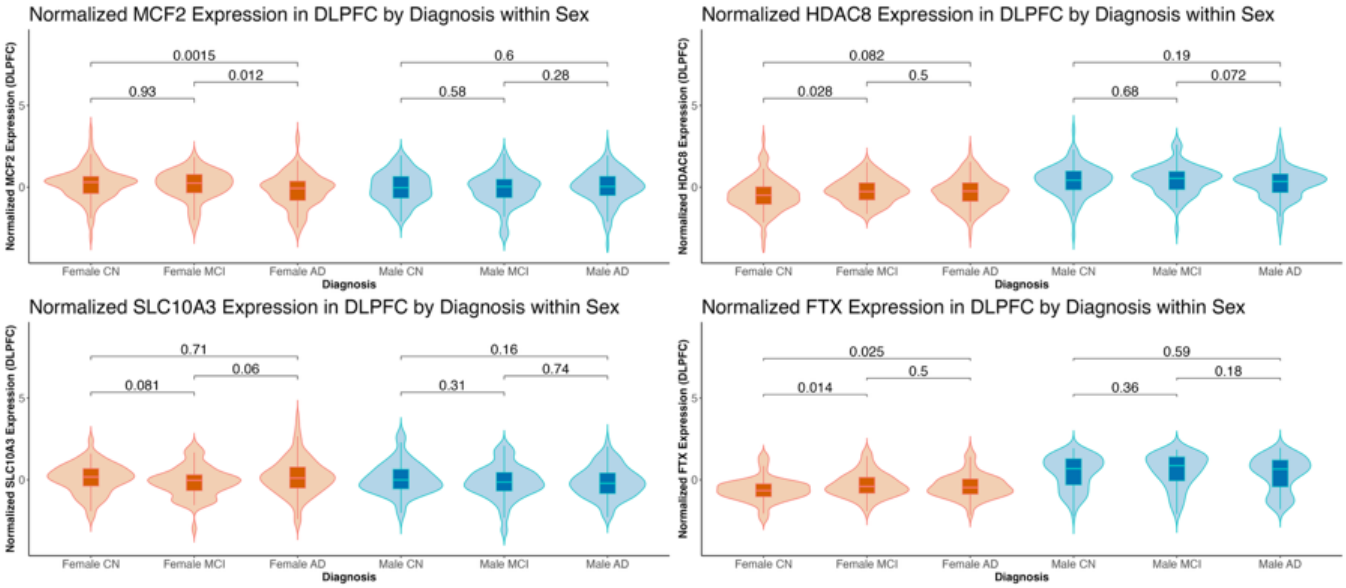
Violin plots summarizing the normalized expression of *MCF2*, *HDAC8*, *FTX*, and *SLC10A3* in the DLPFC. Females are in orange and males are in blue. Expression was compared between males and females. Wilcoxon p-values are provided for each gene. Box represents the 1st (25th percentile), 2nd (median), and 3rd (75th percentile) quartiles of data. Whiskers represent 1.5* interquartile range.

Supplementary Figure 4: Comparison of *MCF2*, *HDAC8*, *FTX*, and *SLC10A3* expression between males and females per each diagnosis.



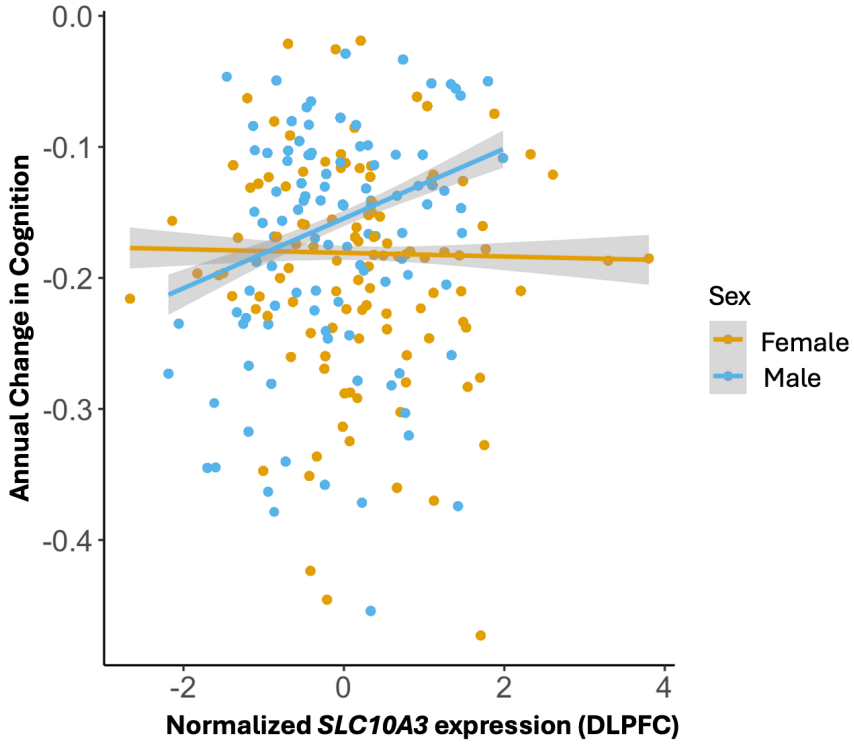
Violin plots summarizing the normalized expression of *MCF2*, *HDAC8*, *FTX*, and *SLC10A3* in the DLPFC. Females are in orange and males are in blue. Expression was compared between males and females within each diagnostic category. Wilcoxon p-values are provided for each comparison for each gene. Box represents the 1st (25th percentile), 2nd (median), and 3rd (75th percentile) quartiles of data. Whiskers represent 1.5* interquartile range.

Supplementary Figure 5: Comparison of *MCF2*, *HDAC8*, *FTX*, and *SLC10A3* expression between diagnosis categories in each sex.



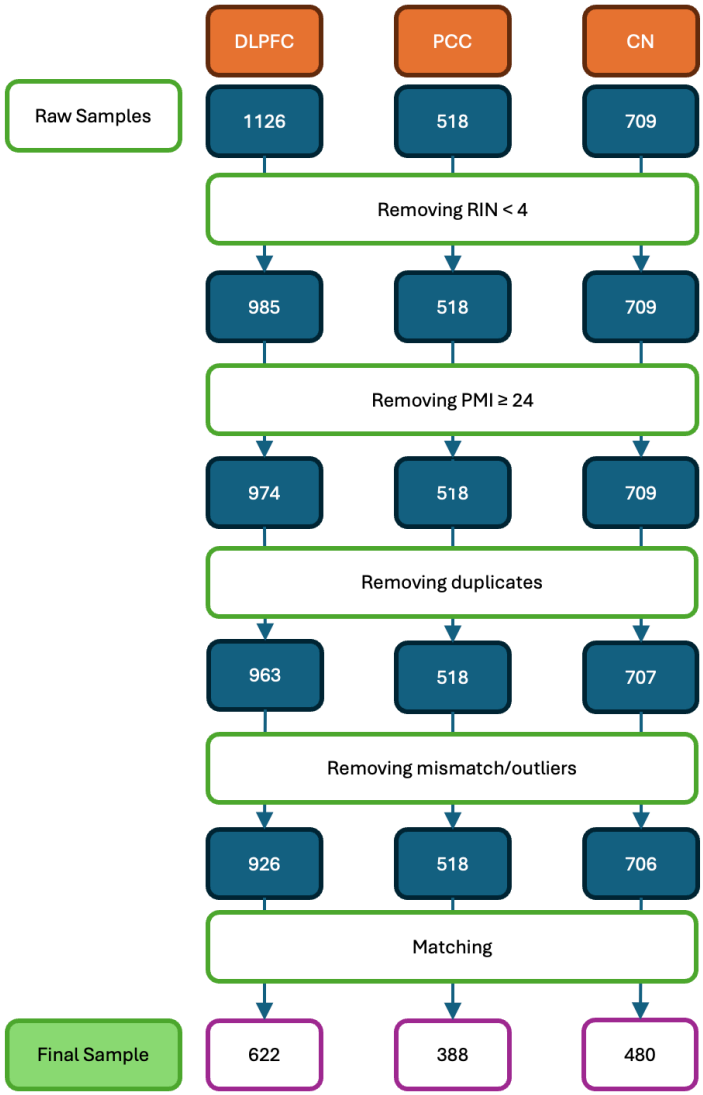
Violin plots summarizing the normalized expression of *MCF2*, *HDAC8*, *FTX*, and *SLC10A3* in the DLPFC. Females are in orange and males are in blue. Expression was compared between diagnosis categories within each sex. Wilcoxon p-values are provided for each comparison. Box represents the 1st (25th percentile), 2nd (median), and 3rd (75th percentile) quartiles of data. Whiskers represent 1.5* interquartile range.

Supplementary Figure 6: The association between *SLC10A3* and longitudinal cognition is moderated by sex and AD diagnosis.



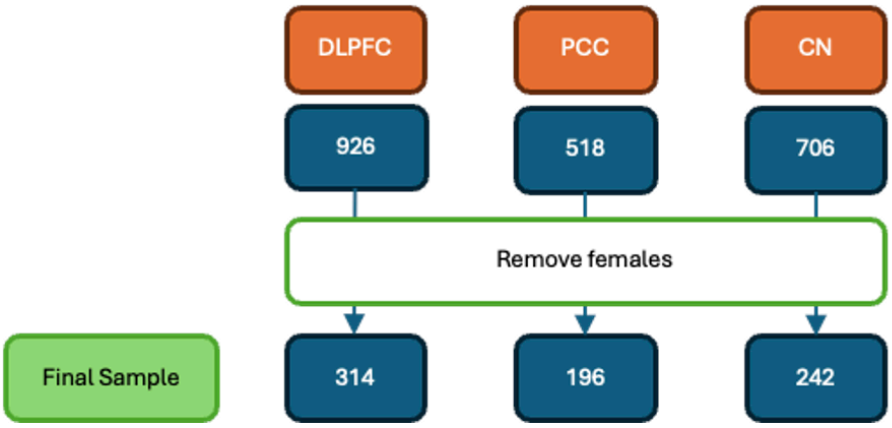
Scatterplot demonstrating the relationship between *SLC10A3* (x-axis) and annual change in cognition (y-axis). Bolded lines are lines of best fit as determined by linear models and shaded regions represent the 95% confidence interval. Females are colored in orange and males are colored in blue. Scatterplot only includes individuals who have been diagnosed with AD.

Supplementary Figure 7: Autosomal and X chromosome RNA sequencing quality control (QC) flow chart



A flow chart depicting the number of participants remaining after each step of RNA sequencing quality control. The final, matched sample used for analysis is depicted at the bottom.

Supplemental Figure 8: Y chromosome RNAseq QC flow chart



A flow chart depicting the number of participants remaining after each step of RNA sequencing quality control. Females were excluded as they do not have a Y chromosome. The final sample used for analysis is depicted at the bottom.

Supplementary Table 1: Demographics for all participants

	TOTAL
N	767
Age at Death (years)	88.26±6.54
Education (years)	16.76±3.49
Follow-up (years)	7.41±4.92
Latency to Death (years)	0.74±0.95
Post-mortem Interval (hours)	7.62±4.45
% Normal Cognition (n)	34 (261)
% MCI	25 (189)
% AD*	41 (317)
% *APOEε4* positive	26
% Non-Hispanic White	98
Amyloid (mm^2)	3.98±4.09
Tau Tangles (mm^2)	6.28±8.00
Cognition at Last Visit	-0.73±1.05
Annual Change in Cognition	-0.11±0.10

*14 decedents have non-AD dementia
Values shown as mean ± standard deviation unless otherwise noted.

Supplementary Table 2: Number of unique genes showing significant associations with AD endophenotypes.

			Sex-Specific			
	Main		**Male**		**Female**	
Outcome	**Autosomal**	**X**	**Autosomal**	**X**	**Autosomal**	**X**
Amyloid	3809	98	66	5	151	7
Tau Tangles	5774	169	318	6	543	33
Cognition	5696	168	219	3	918	35
Unique Genes Across All Regions and Outcomes	8850	257	578	13	1,454	62

Supplementary Table 3: Summary table of model estimates including sensitivity analyses including *APOE*ε4 and pathology for significant *sex x X-linked* gene interactions in the DLPFC

Outcome	Gene	Analysis	β	SE	T	$P_{Uncorrected}$
Tau Tangles	*MCF2*	**Sex *x MCF2***	**0.28**	**0.07**	**3.74**	**0.0002**
		Sex *x MCF2* + *APOE*ε4	0.26	0.07	3.65	0.0003
		Sex *x MCF2* + Aβ	0.19	0.07	2.94	0.003
		Male-stratified	0.10	0.05	1.94	0.052
		Male-stratified + *APOE*ε4	0.08	0.05	1.74	0.08
		Male-stratified + Aβ	0.07	0.04	1.60	0.11
		Female-stratified	**-0.18**	**0.06**	**-3.33**	**0.001**
		Female-stratified + *APOE*ε4	-0.18	0.05	-3.29	0.001
		Female-stratified + Aβ	-0.12	0.05	-2.42	0.02
	HDAC8	***Sex x HDAC8***	**-0.30**	**0.08**	**-3.82**	**0.0001**
		Sex *x HDAC8* + *APOE*ε4	-0.29	0.088	-3.86	0.0001
		Sex *x HDAC8* + Aβ	-0.20	0.07	-2.87	0.004
		Male-stratified	-0.08	0.05	-1.60	0.11
		Male-stratified + *APOE*ε4	-0.08	0.05	-1.61	0.11
		Male-stratified + Aβ	-0.03	0.05	-0.65	0.51
		Female-stratified	**0.22**	**0.06**	**3.75**	**0.0002**
		Female-stratified + *APOE*ε4	0.21	0.05	3.74	0.0002
		Female-stratified + Aβ	0.17	0.05	3.39	0.001
Longitudinal Cognition	*SLC10A3*	***Sex x SLC10A3***	**0.04**	**0.01**	**3.69**	**0.0002**
		Sex *x SLC10A3* + *APOE*ε4	0.04	0.01	3.69	0.0002
		Sex *x SLC10A3* + Aβ + tau	0.04	0.01	3.62	0.0003
		Male-stratified	0.02	0.01	2.51	0.01[a]
		Male-stratified + *APOE*ε4	0.02	0.01	2.48	0.01
		Male-stratified + Aβ + tau	**0.02**	0.01	2.31	0.02
		Female-stratified	**-0.02**	**0.01**	**-2.7.**	**0.006**
		Female-stratified + *APOE*ε4	-0.02	0.01	-2.78	0.01
		Female-stratified + Aβ + tau	-0.02	0.01	-2.84	0.005
	FTX	***Sex x FTX***	**0.04**	**0.01**	**3.82**	**0.0001**
		Sex *x FTX* + *APOE*ε4	0.04	0.01	3.85	0.0001
		Sex *x FTX* + Aβ + tau	0.04	0.01	3.31	0.001
		Male-stratified	**0.02**	**0.01**	**3.58**	**0.0004**
		Male-stratified + *APOE*ε4	0.02	0.01	3.53	0.0004
		Male-stratified + Aβ + tau	0.03	0.01	3.70	0.0002
		Female-stratified	-0.02	0.01	-2.06	0.04
		Female-stratified + *APOE*ε4	-0.02	0.01	-2.22	0.03
		Female-stratified + Aβ + tau	-0.01	0.01	-1.31	0.19

All presented p-values are uncorrected. Bolded values represent those that survived FDR-correction ($p \leq 0.05$) in discovery analyses. P-values for sensitivity analyses are not corrected. Abbreviations: SE = standard error, T = t-value.

Supplementary Table 4: Linear model estimates for *sex x X-linked gene x APOE-ε4* interaction analyses

Outcome	Gene	Analysis	β	SE	T	$P_{uncorrected}$
Tau Tangles	*MCF2*	Sex x *MCF2* x *APOE*ε4	0.03	0.16	0.18	0.86
	HDAC8	Sex *x HDAC8 x APOE*ε4	-0.25	0.18	-1.40	0.16
Longitudinal Cognition	*SLC10A3*	Sex *x SLC10A3 x APOE*ε4	-0.04	0.02	-1.75	0.08
	FTX	**Sex *x FTX x APOE*ε4**	**0.05**	**0.02**	**2.20**	**0.03**
		*APOE*ε4-negative females	-0.01	0.01	-1.48	0.14
		*APOE*ε4-positive females	-0.04	0.02	-1.66	0.10
		***APOE*ε4-negative males**	**0.01**	**0.01**	**1.96**	**0.0498**
		***APOE*ε4-positive males**	**0.05**	**0.02**	**2.85**	**0.01**

All presented p-values are uncorrected. P-values for sensitivity analyses are not corrected. Bolded values represent significant values. Abbreviations: SE = standard error, T = t-value.

Supplementary Table 5: Linear model estimates for *sex x X-linked gene x* pathology interaction analyses

Outcome	Gene	Analysis	β	SE	T	$P_{uncorrected}$
Tau Tangles	*MCF2*	Sex x *MCF2* x Aβ positivity	0.19	0.14	1.34	0.18
	HDAC8	Sex *x HDAC8 x* Aβ positivity	-0.05	0.15	-0.31	0.76
Longitudinal Cognition	*SLC10A3*	Sex *x SLC10A3 x* tau positivity	-0.04	0.02	-1.92	0.06
	FTX	Sex *x FTX x* tau positivity	0.03	0.03	1.11	0.27

All presented p-values are uncorrected. P-values for sensitivity analyses are not corrected. Bolded values represent significant values. Abbreviations: SE = standard error, T = t-value.

Supplementary Table 6: Linear model estimates for *sex x X-linked gene x* diagnosis interaction analyses

Outcome	Gene	Analysis	β	SE	T	$P_{uncorrected}$
Tau Tangles	*MCF2*	Sex x *MCF2* x Diagnosis	0.10	0.08	1.24	0.22
	HDAC8	Sex *x HDAC8* x Diagnosis	-0.08	0.08	-1.03	0.31
Longitudinal Cognition	*SLC10A3*	**Sex *x SLC10A3 x* Diagnosis**	**0.02**	**0.01**	**2.74**	**0.01**
		NC-stratified				
		Sex *x SLC10A3*	-0.003	0.01	-0.47	0.64
		MCI-stratified				
		Sex *x SLC10A3*	0.01	0.01	1.42	0.16
		AD-stratified				
		Sex *x SLC10A3*	**0.04**	**0.02**	**2.54**	**0.01**
		Female-stratified	-0.005	0.01	-0.46	0.64
		Male-stratified	**0.03**	**0.01**	**2.68**	**0.01**
	FTX	Sex *x FTX x* Diagnosis	0.01	0.01	1.38	0.17

All presented p-values are uncorrected. P-values for sensitivity analyses are not corrected. Bolded values represent significant values. Abbreviations: NC = normal cognition, MCI = mild cognitive impairment, AD = Alzheimer's disease, SE = standard error, T = t-value.