**HGGA, Volume *4***

## Supplemental information

# The mitochondrial genome as a modifier of autism versus cancer phenotypes in *PTEN* hamartoma tumor syndrome

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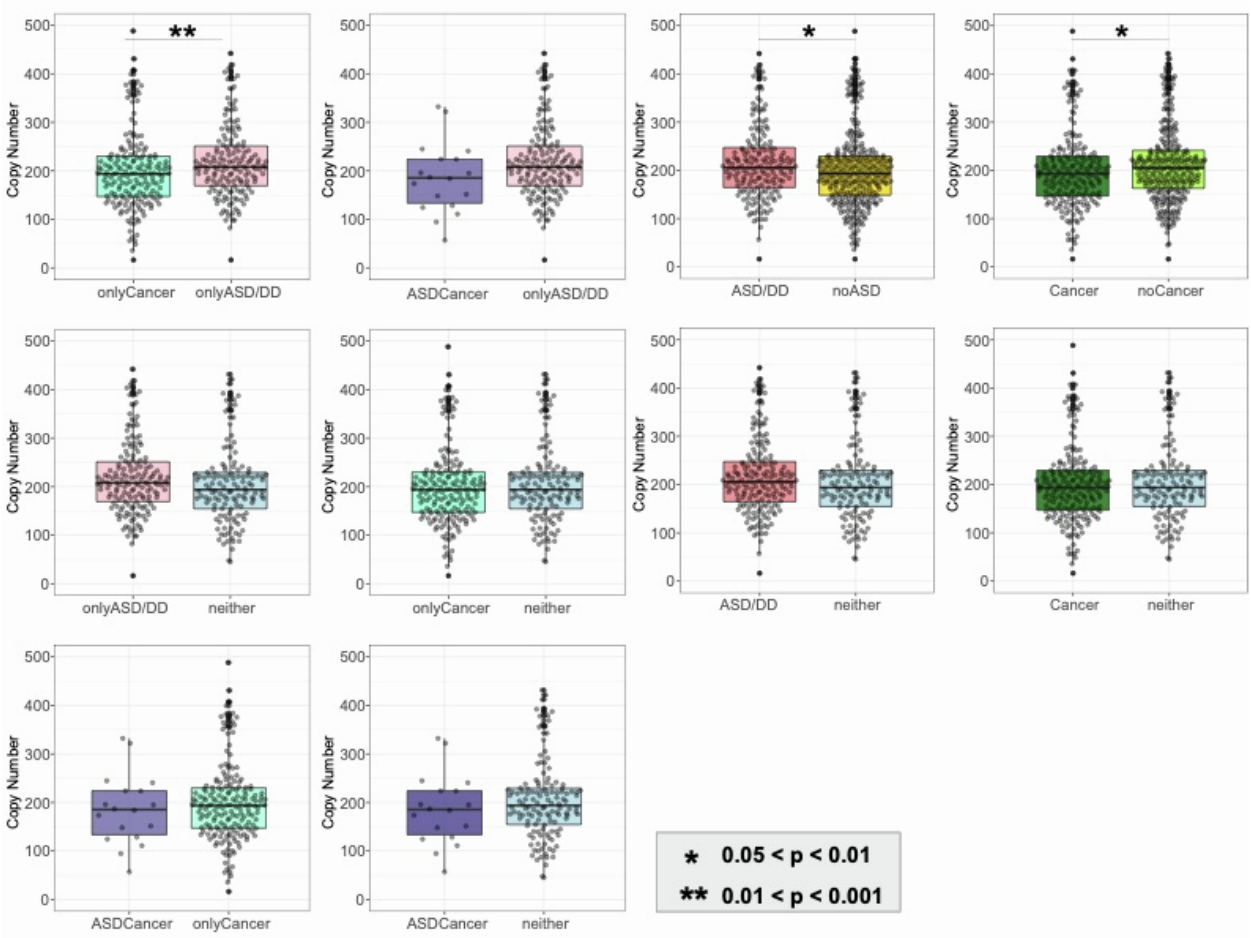
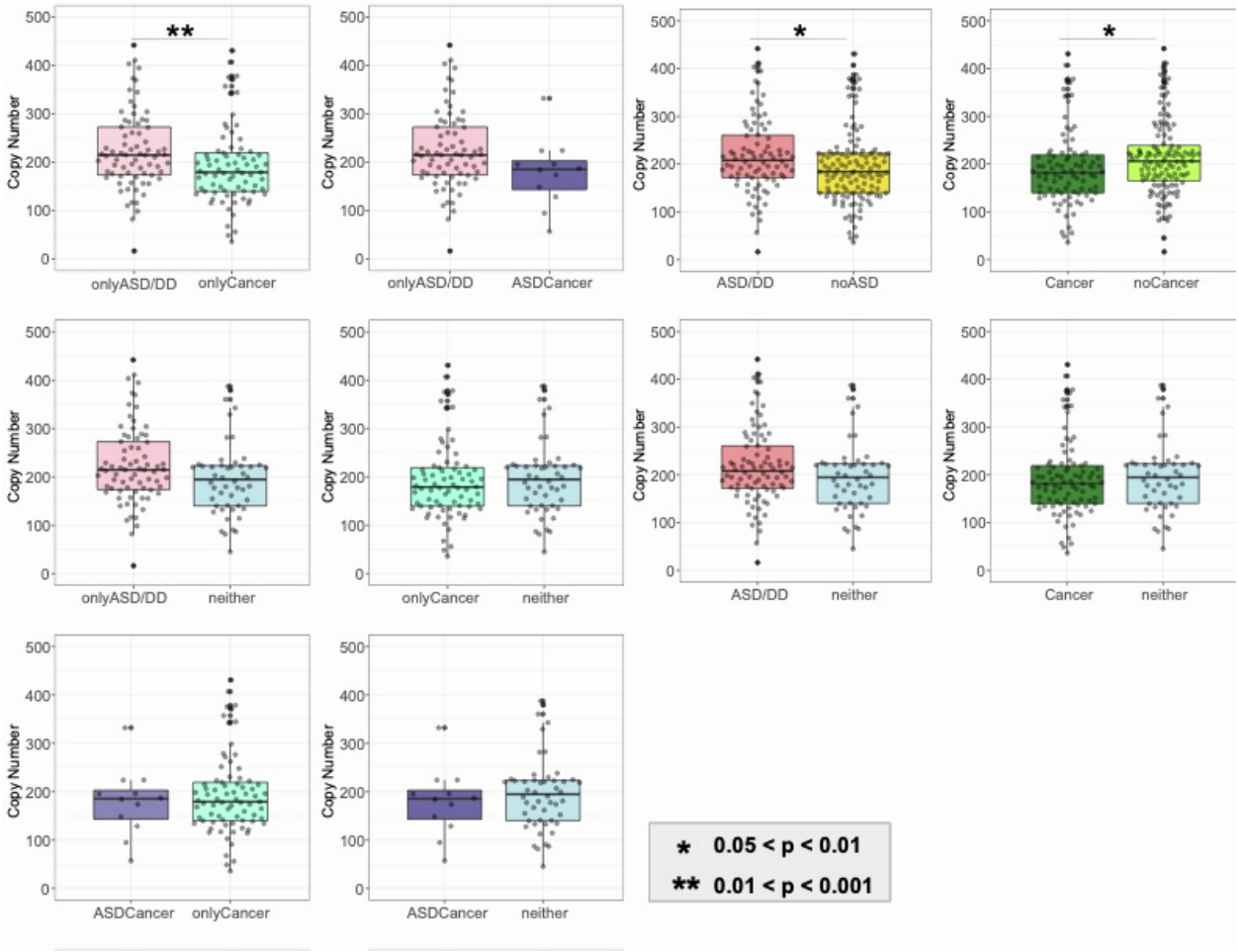
**Figure S1.** Beeswarm plots of mtDNA CN differences between different PHTS phenotypes within all research participants (n=498)



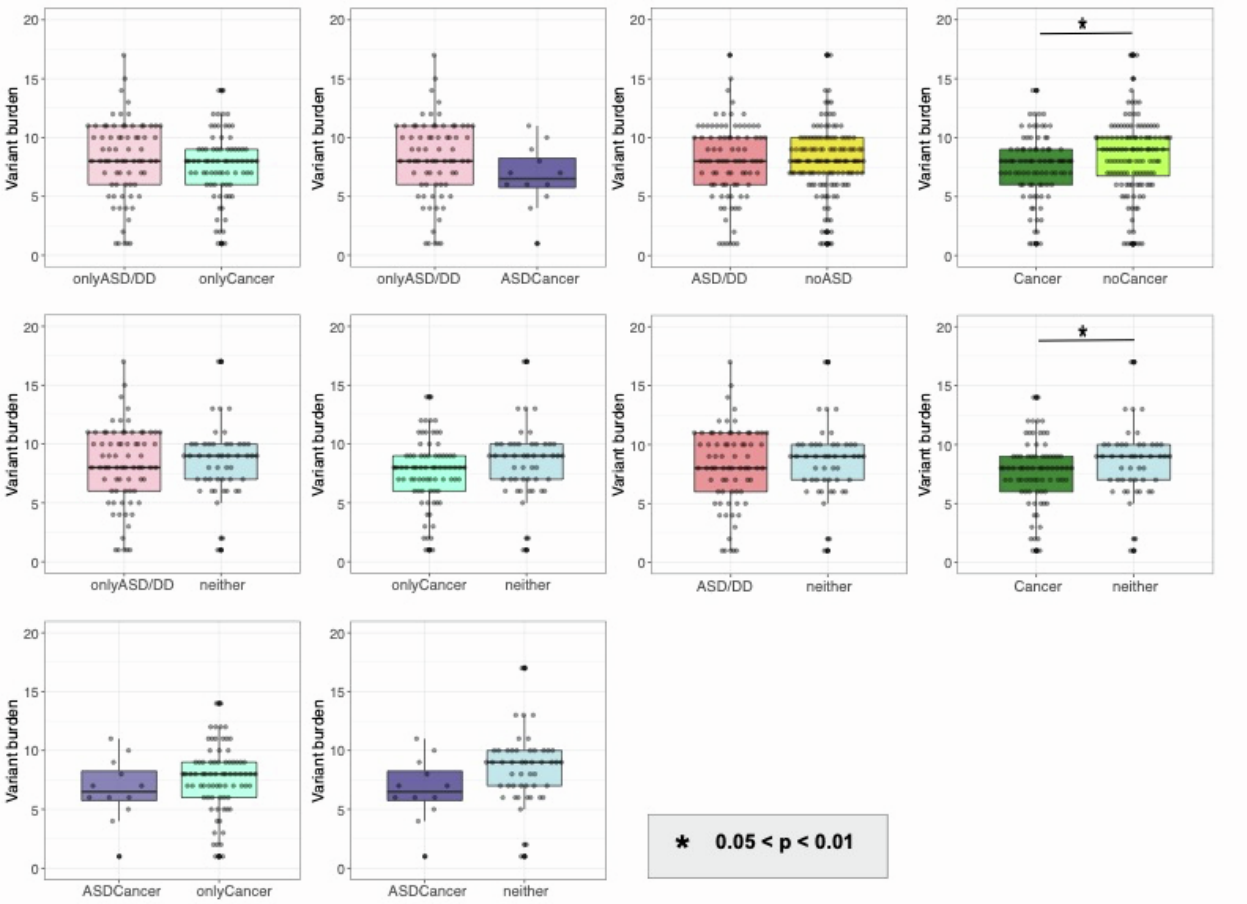

The beeswarm plots represent 10 mtDNA CN comparisons between different PHTS phenotypes within all PHTS samples. Each dot represents one sample's mtDNA CN value. The upper whisker extends from the hinge to the largest value no further than 1.5 * inter-quartile range (IQR) from the hinge. The lower whisker extends from the hinge to the smallest value at most 1.5 * IQR of the hinge. Data beyond the end of the whiskers are "outlying" points and are plotted individually. Different colors indicate different PHTS phenotypes. PHTS-ASD/DD group has higher mtDNA CN than PHTS individuals without ASD/DD.

**Figure S2.** Beeswarm plots of mtDNA CN differences between different PHTS phenotypes within the H haplogroup (n=243)



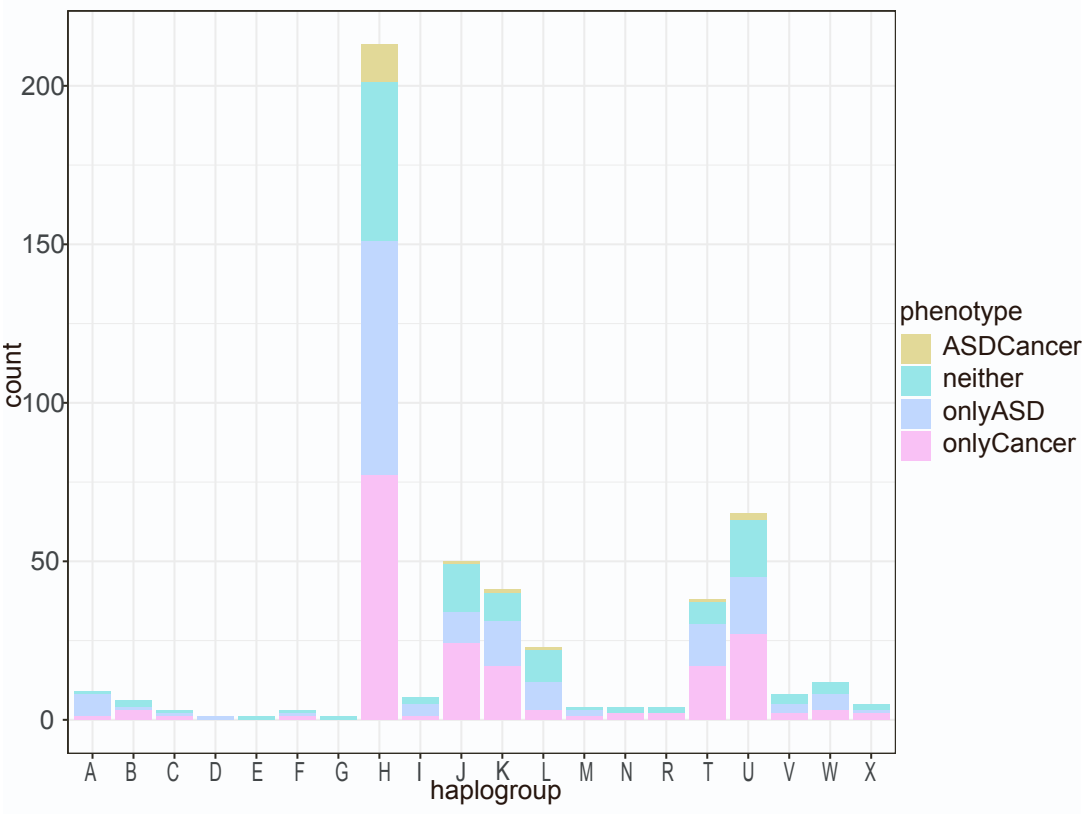

The beeswarm plots represent 10 mtDNA CN comparisons between different PHTS phenotypes within the H haplogroup. Each dot represents one sample's mtDNA CN value. The upper whisker extends from the hinge to the largest value no further than 1.5 * inter-quartile range (IQR) from the hinge. The lower whisker extends from the hinge to the smallest value at most 1.5 * IQR of the hinge. Data beyond the end of the whiskers are "outlying" points and are plotted individually. Different colors indicate different PHTS phenotypes. PHTS-ASD/DD group has higher mtDNA CN than PHTS individuals without ASD/DD.

**Figure S3.** Beeswarm plots of SNV burden differences between different PHTS phenotypes within the H haplogroup (n=243)



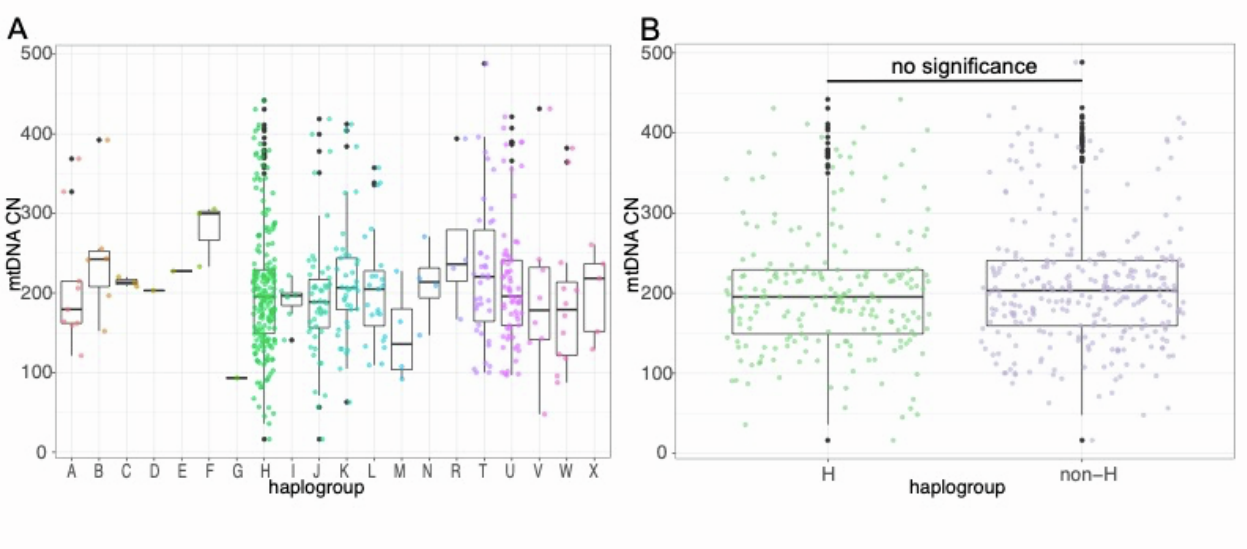

The beeswarm plots represent 10 mtDNA SNV burden comparisons between different PHTS phenotypes within the H haplogroup. Each dot represents one sample's mtDNA CN value. The upper whisker extends from the hinge to the largest value no further than 1.5 * inter-quartile range (IQR) from the hinge. The lower whisker extends from the hinge to the smallest value at most 1.5 * IQR of the hinge. Data beyond the end of the whiskers are "outlying" points and are plotted individually. Different colors indicate different PHTS phenotypes. PHTS-noCancer group has higher SNV burden than those PHTS individuals who have cancer or who have both ASD/DD and cancer.

**Figure S4.** mtDNA phenotype distribution among each haplogroup




The bar plot represents the phenotype distribution across the different PHTS phenotypes within all samples (n = 498).

**Figure S5.** mtDNA CN distribution among the haplogroups



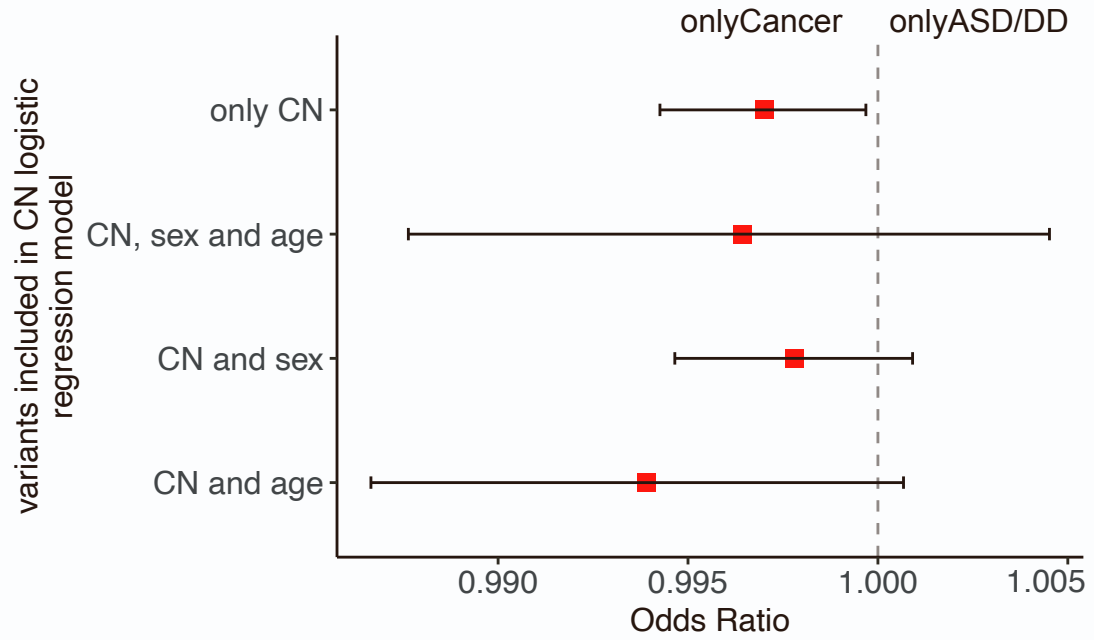

A. Beeswarm plots of copy number among all haplogroups in our sample set (n=498).

B. Beeswarm plots of copy number among H and non-H haplogroups in our sample set (n=498).

There are no statistically significant differences in mtDNA CN between the H haplogroup and non-H haplogroup.

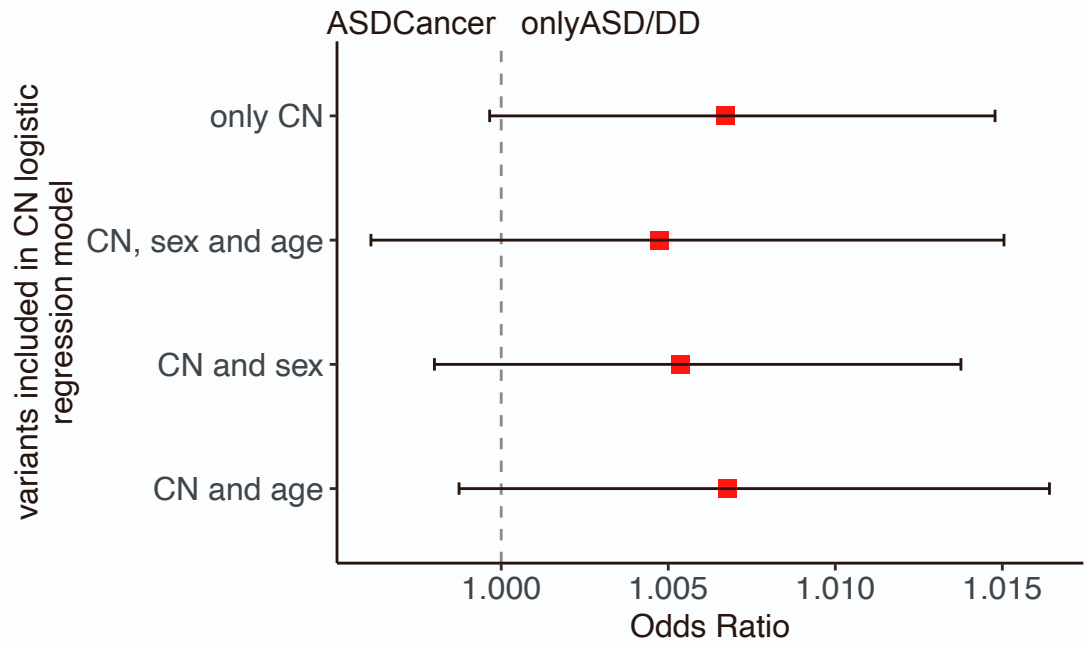
Each dot represents one sample's mtDNA CN value. The upper whisker extends from the hinge to the largest value no further than 1.5 * inter-quartile range (IQR) from the hinge. The lower whisker extends from the hinge to the smallest value at most 1.5 * IQR of the hinge. Data beyond the end of the whiskers are "outlying" points and are plotted individually.

**Figure S6.** Forest plot of mtDNA CN analysis among PHTS-onlyASD/DD and PHTS-onlyCancer groups within all haplogroups (n = 498).



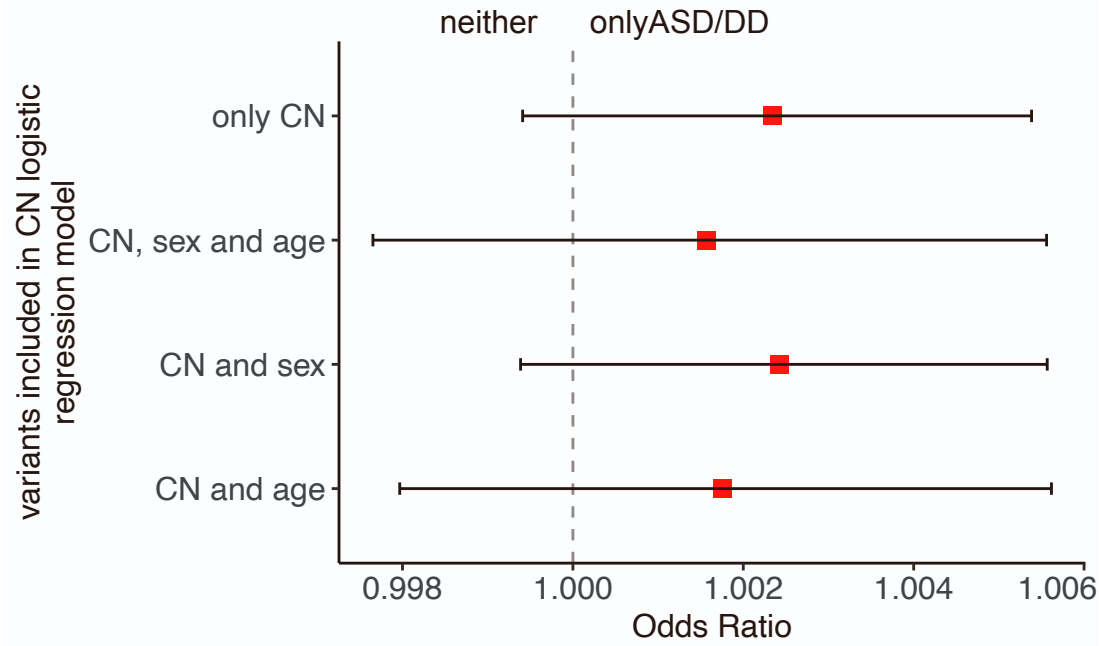

The red squares indicate the odds ratios, error bars indicate the 95% of confidential intervals of the odds ratios. Clinical phenotype groups are indicated at the top of each forest plot. Corresponding p values and odds ratios can be located in Table S1 and Table S2, respectively.

**Figure S7.** Forest plot of mtDNA CN analysis among PHTS-onlyASD/DD and PHTS-ASDCancer groups within all haplogroups (n = 498).



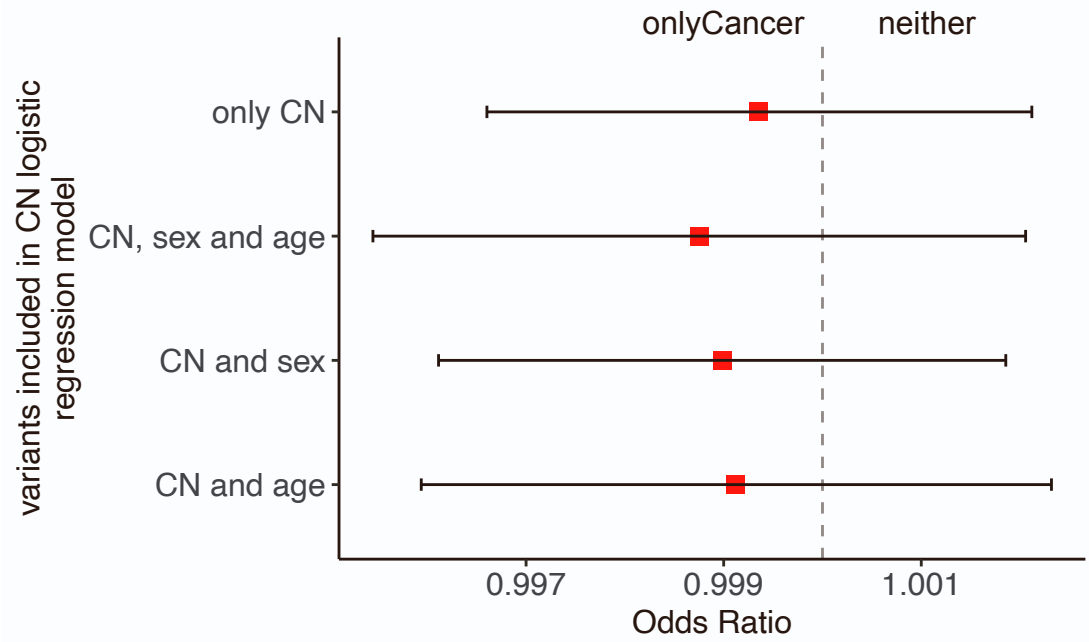

The red squares indicate the odds ratios, error bars indicate the 95% of confidential intervals of the odds ratios. Clinical phenotype groups are indicated at the top of each forest plot. Corresponding p values and odds ratios can be located in Table S1 and Table S2, respectively.

**Figure S8.** Forest plot of mtDNA CN analysis among PHTS-onlyASD/DD and PHTS-neither groups within all haplogroups (n = 498).



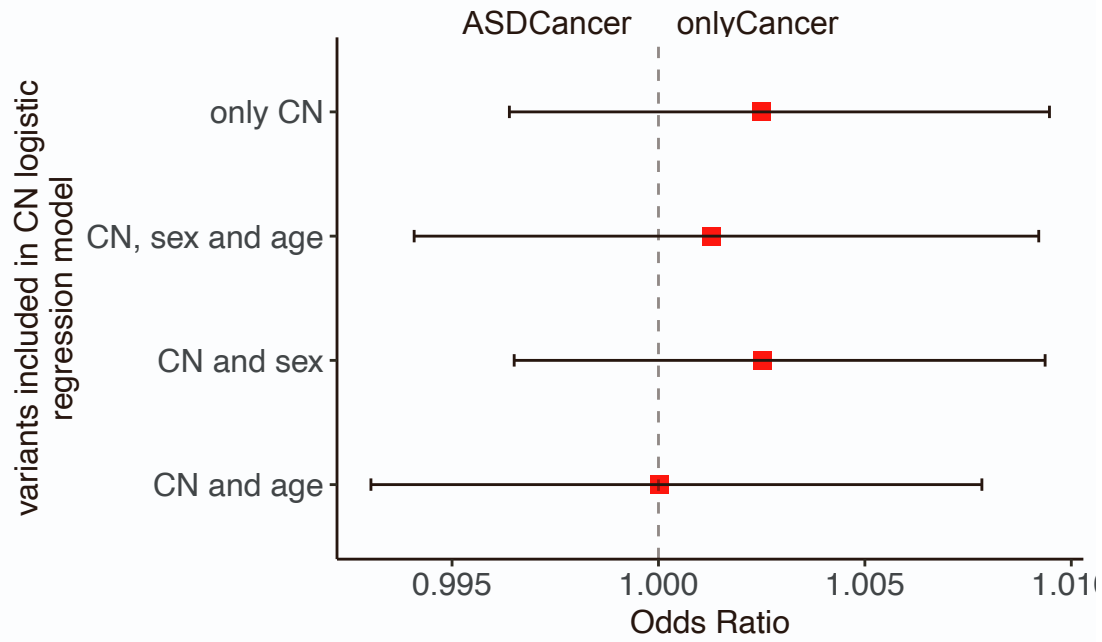

The red squares indicate the odds ratios, error bars indicate the 95% of confidential intervals of the odds ratios. Clinical phenotype groups are indicated at the top of each forest plot. Corresponding p values and odds ratios can be located in Table S1 and Table S2, respectively.

**Figure S9.** Forest plot of mtDNA CN analysis among PHTS-neither and PHTS-onlyCancer groups within all haplogroups (n = 498).



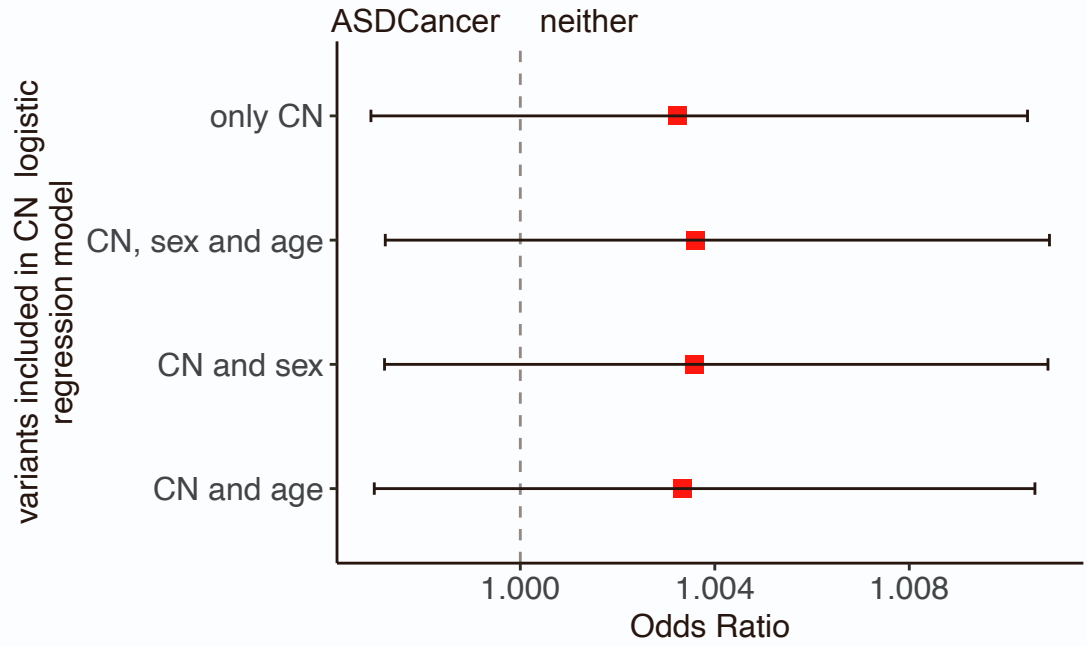

The red squares indicate the odds ratios, error bars indicate the 95% of confidential intervals of the odds ratios. Clinical phenotype groups are indicated at the top of each forest plot. Corresponding p values and odds ratios can be located in Table S1 and Table S2, respectively.

**Figure S10.** Forest plot of mtDNA CN analysis among PHTS-ASDCancer and PHTS-onlyCancer groups within all haplogroups (n = 498).



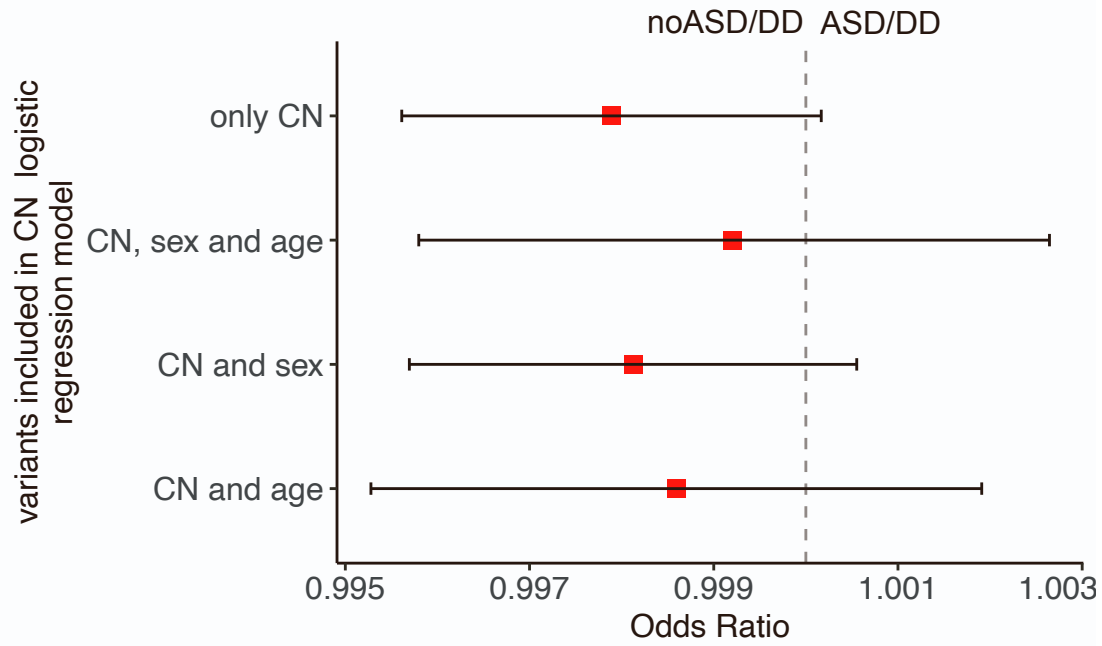

The red squares indicate the odds ratios, error bars indicate the 95% of confidential intervals of the odds ratios. Clinical phenotype groups are indicated at the top of each forest plot. Corresponding p values and odds ratios can be located in Table S1 and Table S2, respectively.

**Figure S11.** Forest plot of mtDNA CN analysis among PHTS-ASDCancer and PHTS-neither groups within all haplogroups (n = 498).



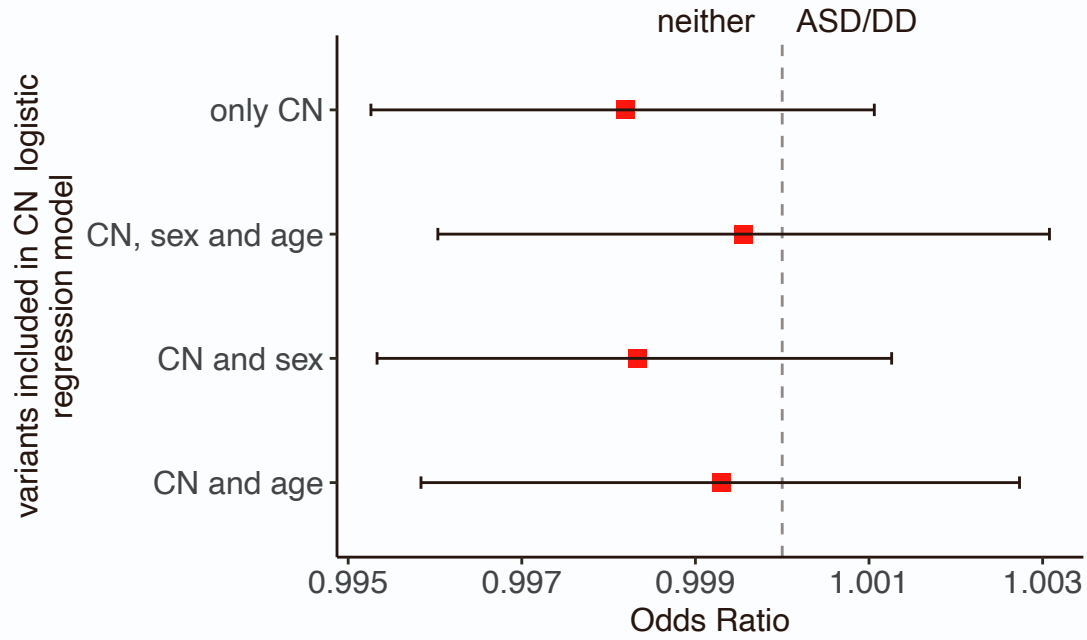

The red squares indicate the odds ratios, error bars indicate the 95% of confidential intervals of the odds ratios. Clinical phenotype groups are indicated at the top of each forest plot. Corresponding p values and odds ratios can be located in Table S1 and Table S2, respectively.

**Figure S12.** Forest plot of mtDNA CN analysis among PHTS-ASD/DD and PHTS-noASr groups within all haplogroups (n = 498).



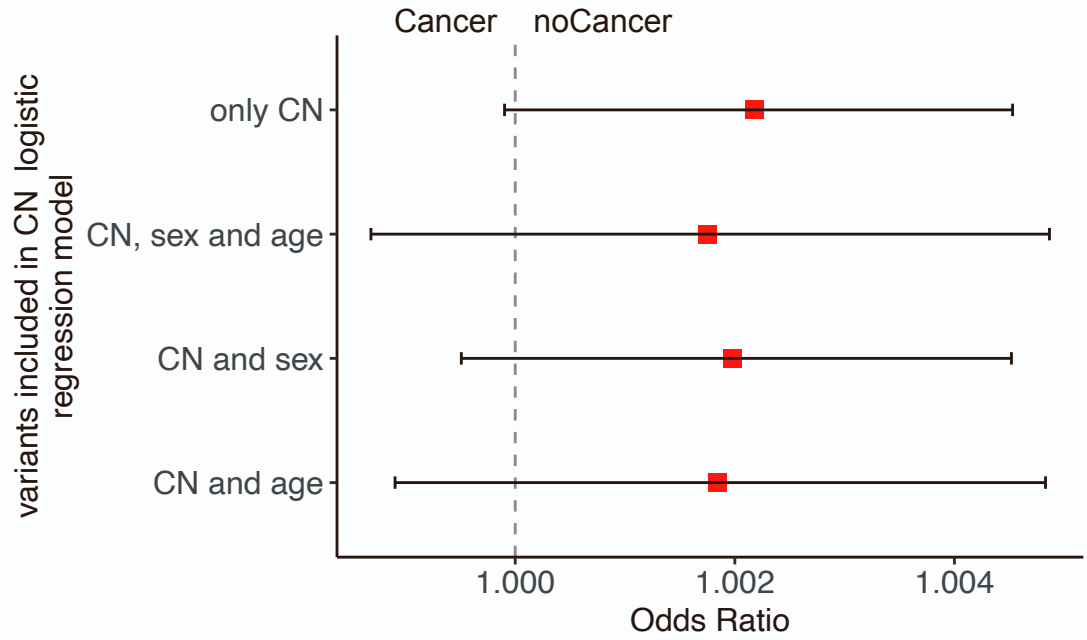

The red squares indicate the odds ratios, error bars indicate the 95% of confidential intervals of the odds ratios. Clinical phenotype groups are indicated at the top of each forest plot. Corresponding p values and odds ratios can be located in Table S1 and Table S2, respectively.

**Figure S13.** Forest plot of mtDNA CN analysis among PHTS-ASD/DD and PHTS-neither groups within all haplogroups (n = 498).



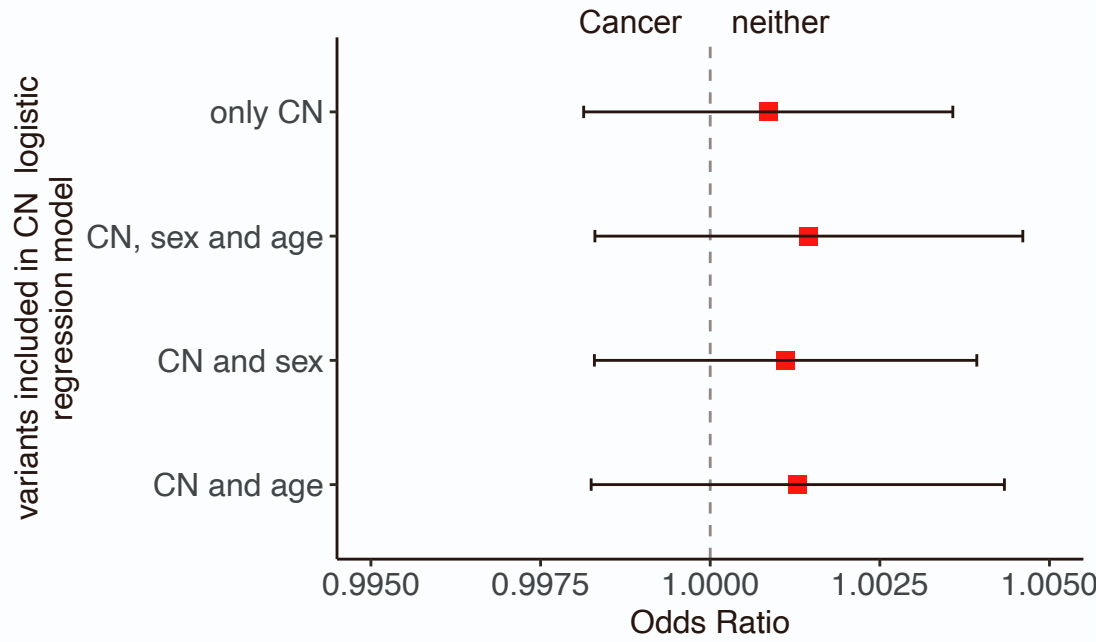

The red squares indicate the odds ratios, error bars indicate the 95% of confidential intervals of the odds ratios. Clinical phenotype groups are indicated at the top of each forest plot. Corresponding p values and odds ratios can be located in Table S1 and Table S2, respectively.

**Figure S14.** Forest plot of mtDNA CN analysis among PHTS-Cancer and PHTS-noCancer groups within all haplogroups (n = 498).



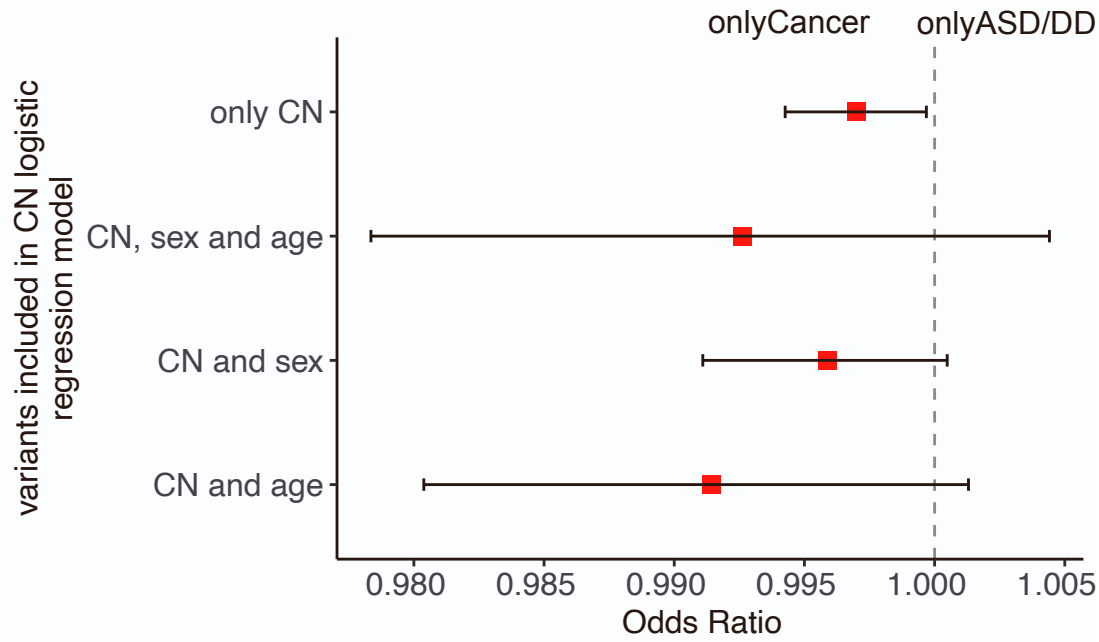

The red squares indicate the odds ratios, error bars indicate the 95% of confidential intervals of the odds ratios. Clinical phenotype groups are indicated at the top of each forest plot. Corresponding p values and odds ratios can be located in Table S1 and Table S2, respectively.

**Figure S15.** Forest plot of mtDNA CN analysis among PHTS-neither and PHTS-noCancer groups within all haplogroups (n = 498).



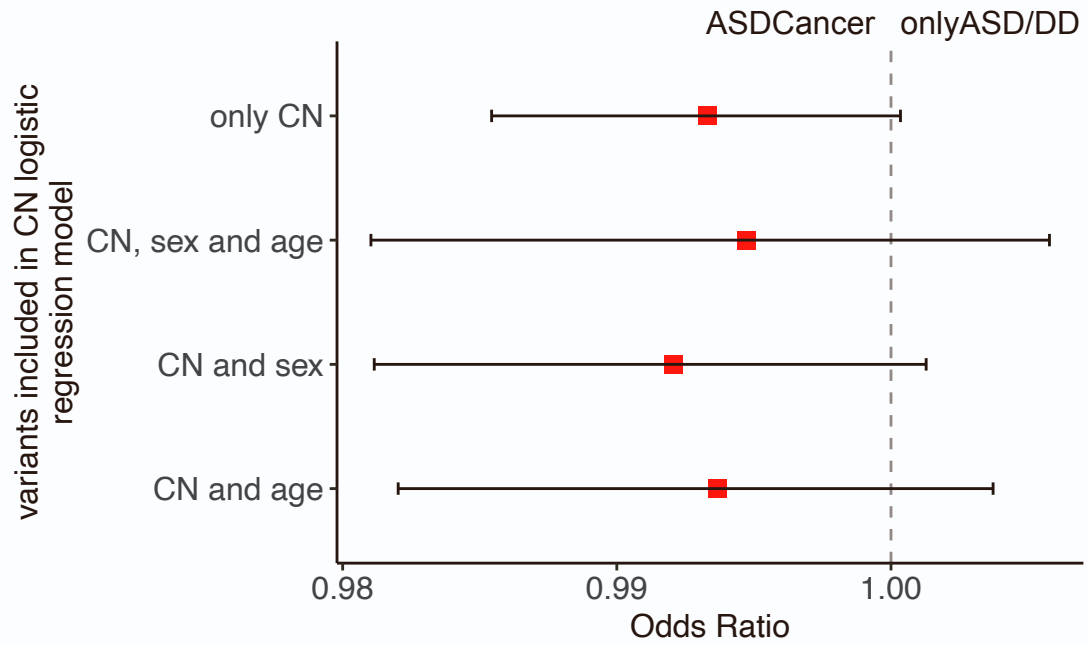

The red squares indicate the odds ratios, error bars indicate the 95% of confidential intervals of the odds ratios. Clinical phenotype groups are indicated at the top of each forest plot. Corresponding p values and odds ratios can be located in Table S1 and Table S2, respectively.

**Figure S16.** Forest plot of mtDNA CN analysis among PHTS-onlyASD/DD and PHTS-onlyCancer groups within the H haplogroup (n = 213).



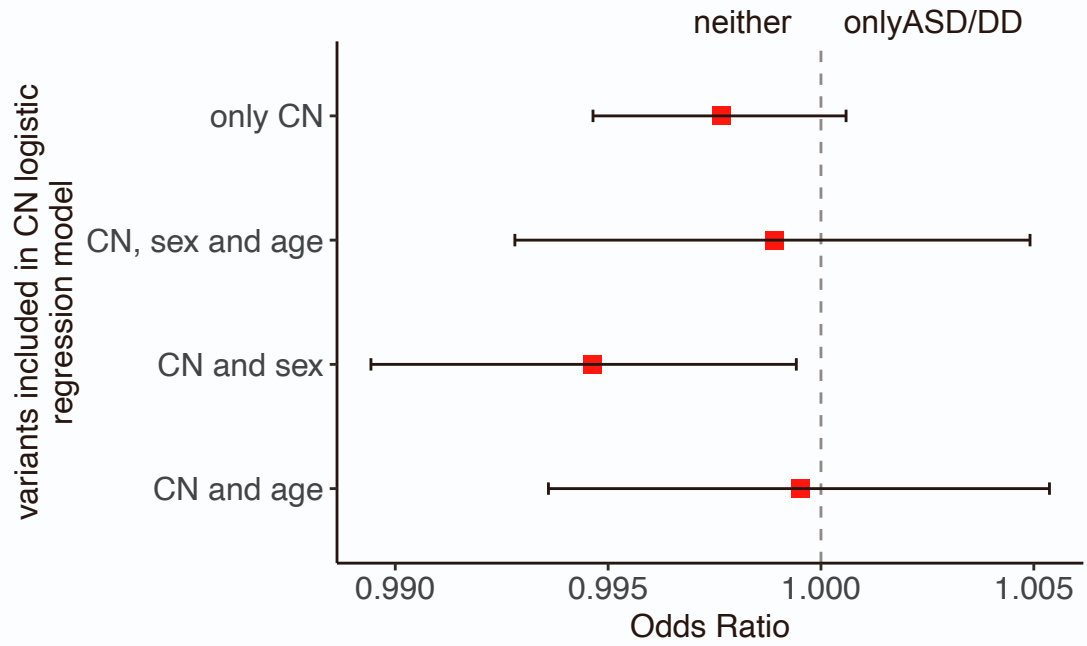

The red squares indicate the odds ratios, error bars indicate the 95% of confidential intervals of the odds ratios. Clinical phenotype groups are indicated at the top of each forest plot. Corresponding p values and odds ratios can be located in Table S1 and Table S2, respectively.

**Figure S17.** Forest plot of mtDNA CN analysis among PHTS-onlyASD/DD and PHTS-ASDCancer groups within the H haplogroup (n = 213).



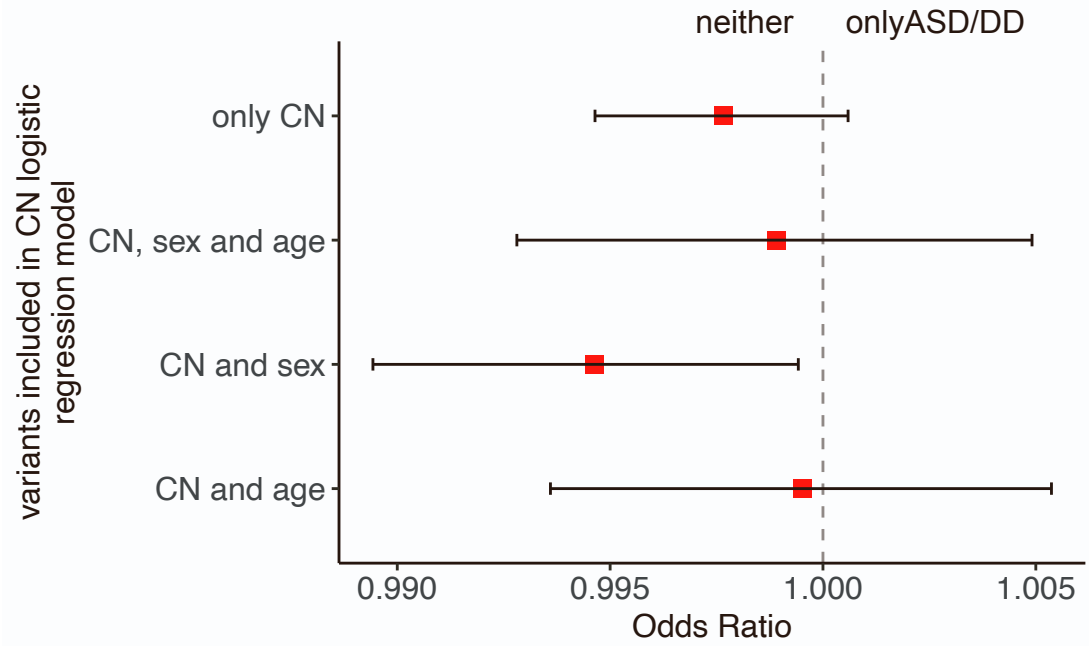

The red squares indicate the odds ratios, error bars indicate the 95% of confidential intervals of the odds ratios. Clinical phenotype groups are indicated at the top of each forest plot. Corresponding p values and odds ratios can be located in Table S1 and Table S2, respectively.

**Figure S18.** Forest plot of mtDNA CN analysis among PHTS-onlyASD/DD and PHTS-neither groups within the H haplogroup (n = 213).



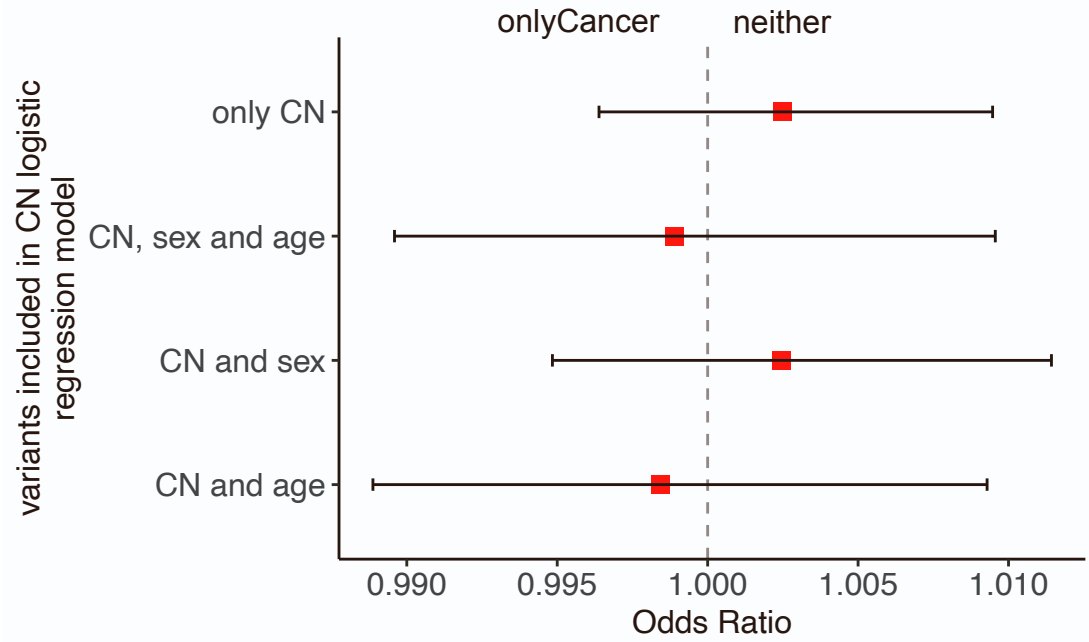

The red squares indicate the odds ratios, error bars indicate the 95% of confidential intervals of the odds ratios. Clinical phenotype groups are indicated at the top of each forest plot. Corresponding p values and odds ratios can be located in Table S1 and Table S2, respectively.

**Figure S19.** Forest plot of mtDNA CN analysis among PHTS-onlyASD/DD and PHTS-neither groups within the H haplogroup (n = 213).



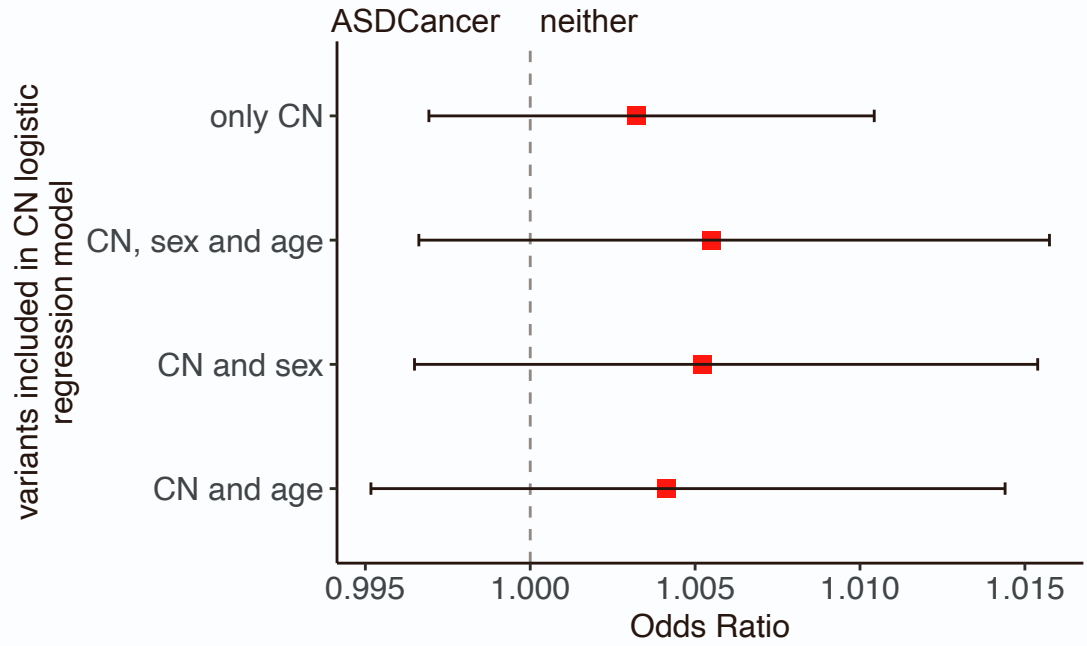

The red squares indicate the odds ratios, error bars indicate the 95% of confidential intervals of the odds ratios. Clinical phenotype groups are indicated at the top of each forest plot. Corresponding p values and odds ratios can be located in Table S1 and Table S2, respectively.

**Figure S20.** Forest plot of mtDNA CN analysis among PHTS-neither and PHTS-onlyCancer groups within the H haplogroup (n = 213).



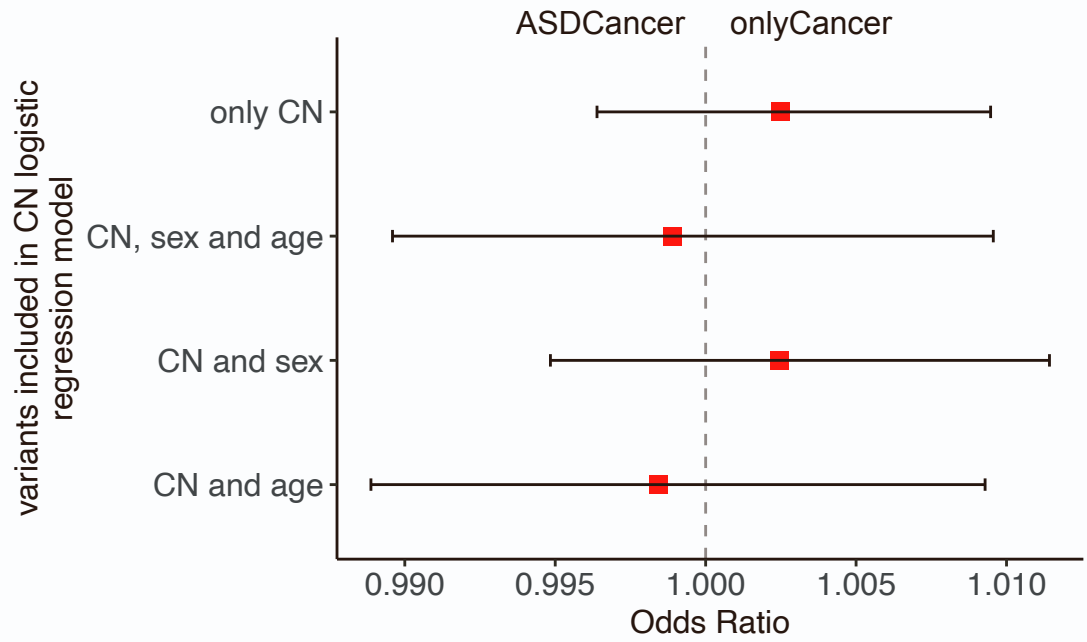

The red squares indicate the odds ratios, error bars indicate the 95% of confidential intervals of the odds ratios. Clinical phenotype groups are indicated at the top of each forest plot. Corresponding p values and odds ratios can be located in Table S1 and Table S2, respectively.

**Figure S21.** Forest plot of mtDNA CN analysis among PHTS-ASDCancer and PHTS-neither groups within the H haplogroup (n = 213).



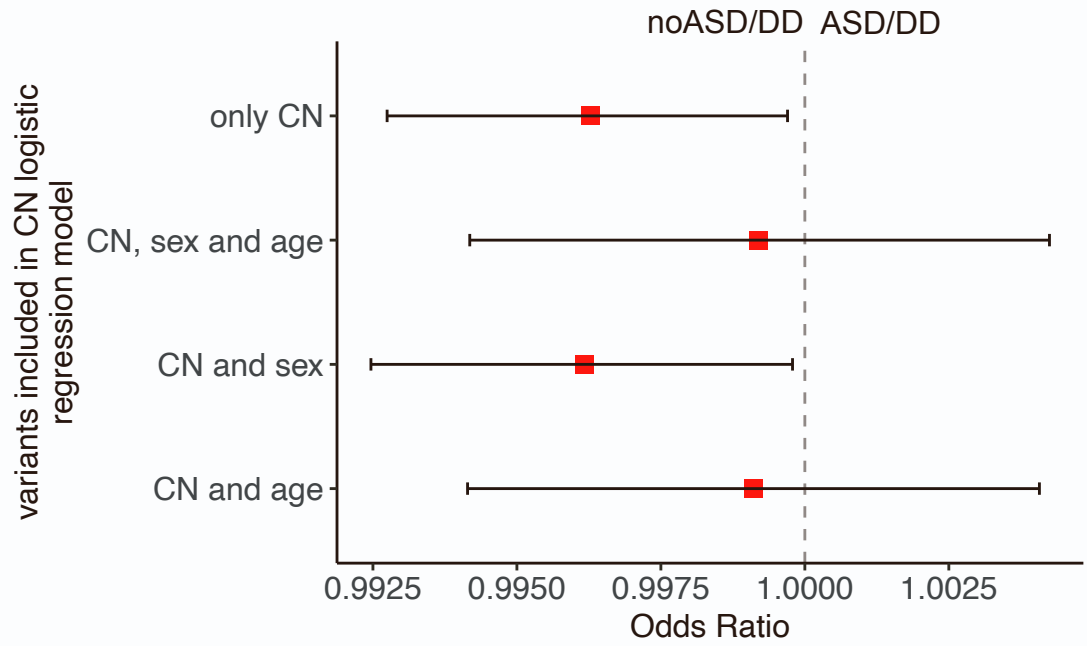

The red squares indicate the odds ratios, error bars indicate the 95% of confidential intervals of the odds ratios. Clinical phenotype groups are indicated at the top of each forest plot. Corresponding p values and odds ratios can be located in Table S1 and Table S2, respectively.

**Figure S22.** Forest plot of mtDNA CN analysis among PHTS-ASDCancer and PHTS-onlyCancer groups within the H haplogroup (n = 213).



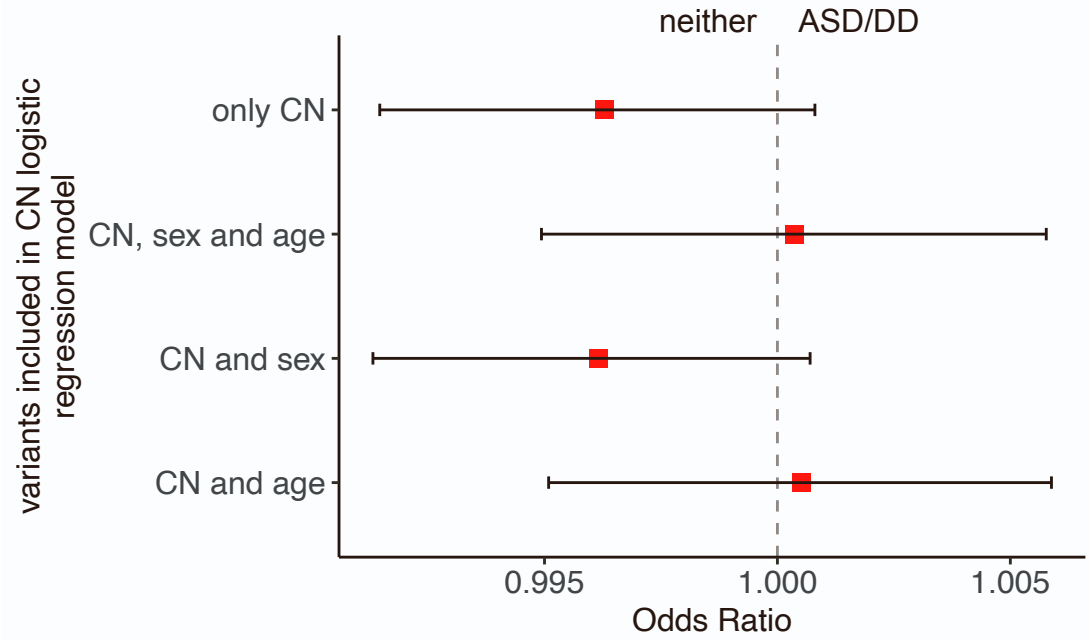

The red squares indicate the odds ratios, error bars indicate the 95% of confidential intervals of the odds ratios. Clinical phenotype groups are indicated at the top of each forest plot. Corresponding p values and odds ratios can be located in Table S1 and Table S2, respectively.

**Figure S23.** Forest plot of mtDNA CN analysis among PHTS-ASD/DD and PHTS-noASD/DD groups within the H haplogroup (n = 213).



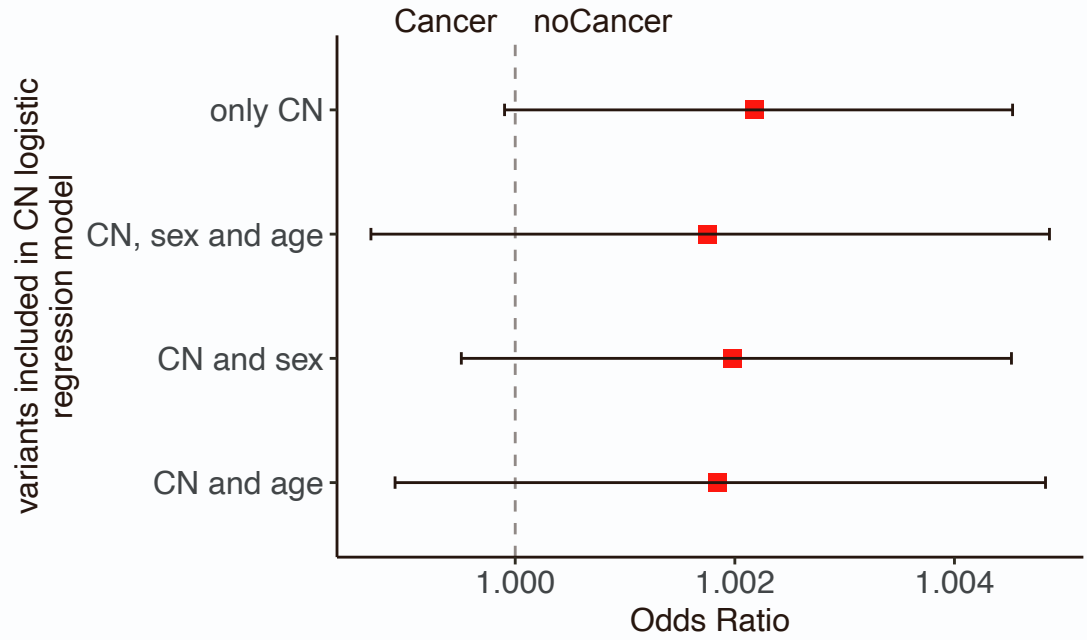

The red squares indicate the odds ratios, error bars indicate the 95% of confidential intervals of the odds ratios. Clinical phenotype groups are indicated at the top of each forest plot. Corresponding p values and odds ratios can be located in Table S1 and Table S2, respectively.

**Figure S24.** Forest plot of mtDNA CN analysis among PHTS-ASD/DD and PHTS-neither groups within the H haplogroup (n = 213).



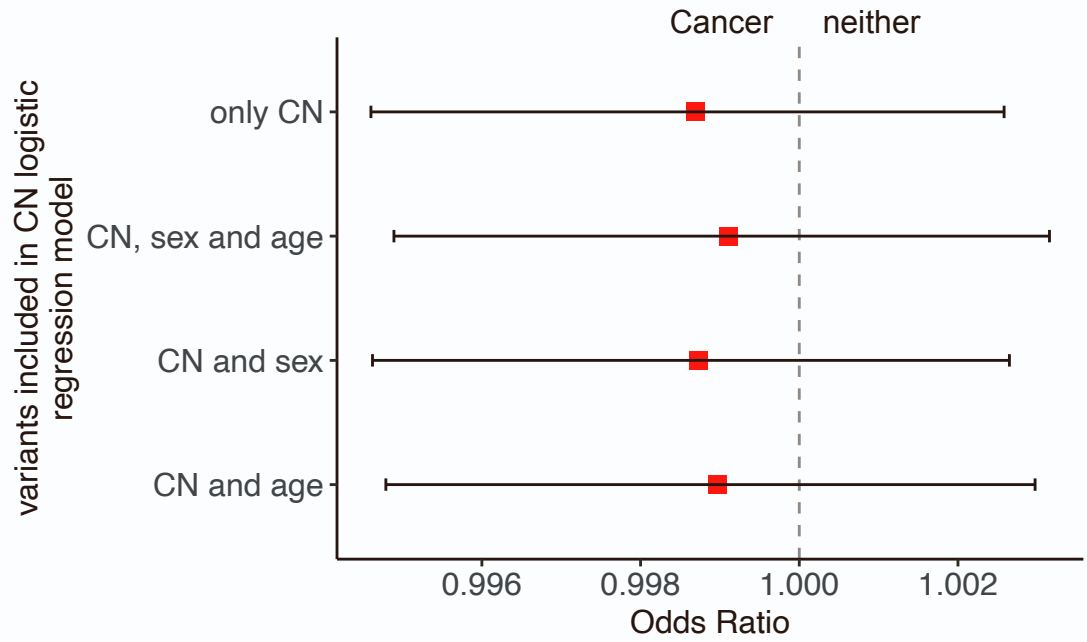

The red squares indicate the odds ratios, error bars indicate the 95% of confidential intervals of the odds ratios. Clinical phenotype groups are indicated at the top of each forest plot. Corresponding p values and odds ratios can be located in Table S1 and Table S2, respectively.

**Figure S25.** Forest plot of mtDNA CN analysis among PHTS-Cancer and PHTS-noCancer groups within the H haplogroup (n = 213).



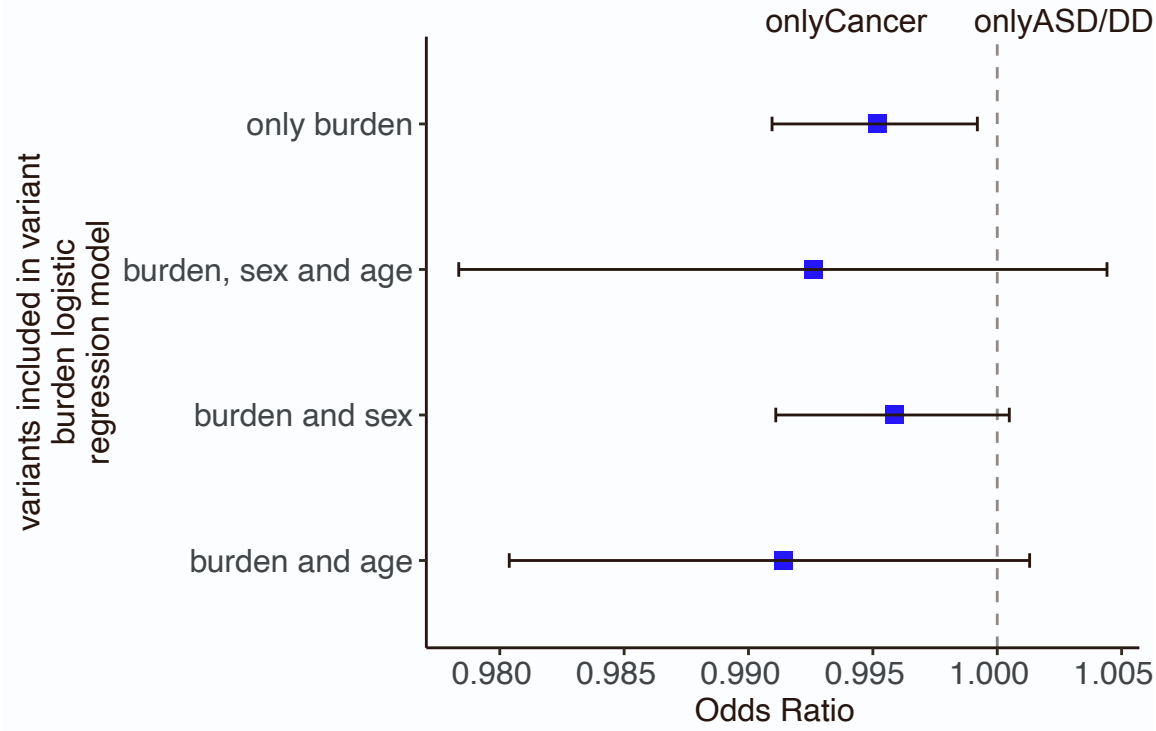

The red squares indicate the odds ratios, error bars indicate the 95% of confidential intervals of the odds ratios. Clinical phenotype groups are indicated at the top of each forest plot. Corresponding p values and odds ratios can be located in Table S1 and Table S2, respectively.

**Figure S26.** Forest plot of mtDNA CN analysis among PHTS-Cancer and PHTS-neither groups within the H haplogroup (n = 213).



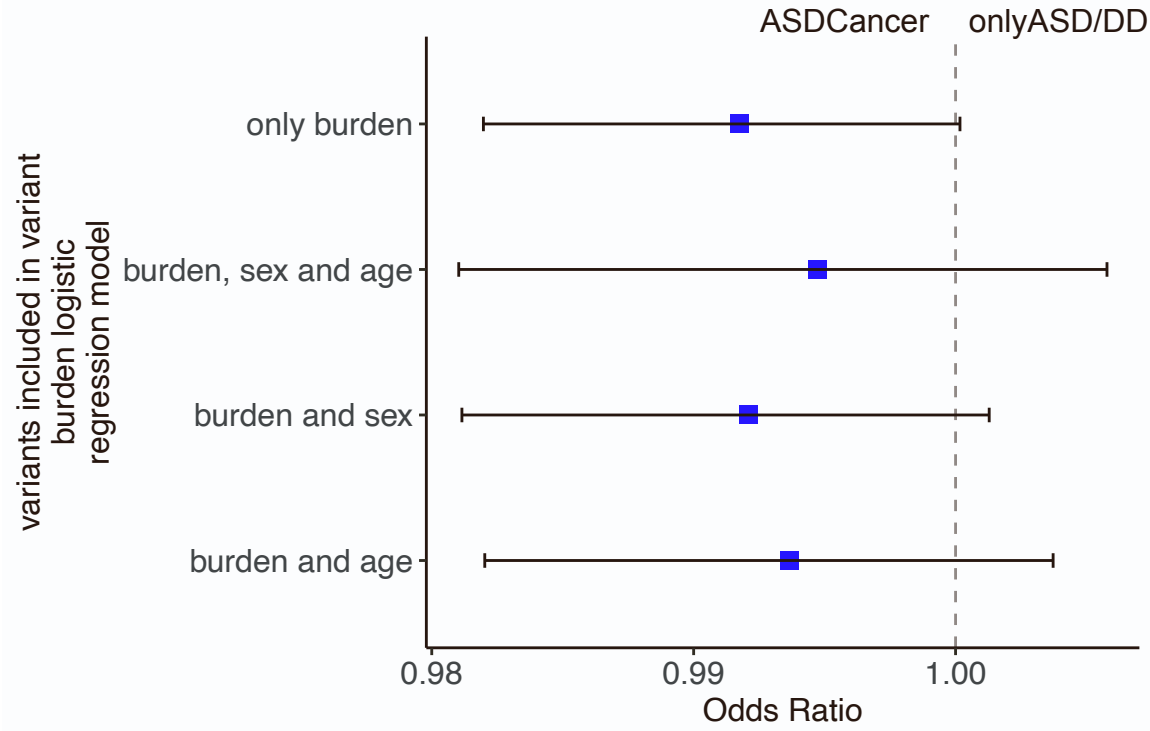

The red squares indicate the odds ratios, error bars indicate the 95% of confidential intervals of the odds ratios. Clinical phenotype groups are indicated at the top of each forest plot. Corresponding p values and odds ratios can be located in Table S1 and Table S2, respectively.

**Figure S27.** Forest plot of mtDNA variant burden analysis among PHTS-onlyASD/DD and PHTS-onlyCancer groups within the H haplogroup (n = 213).



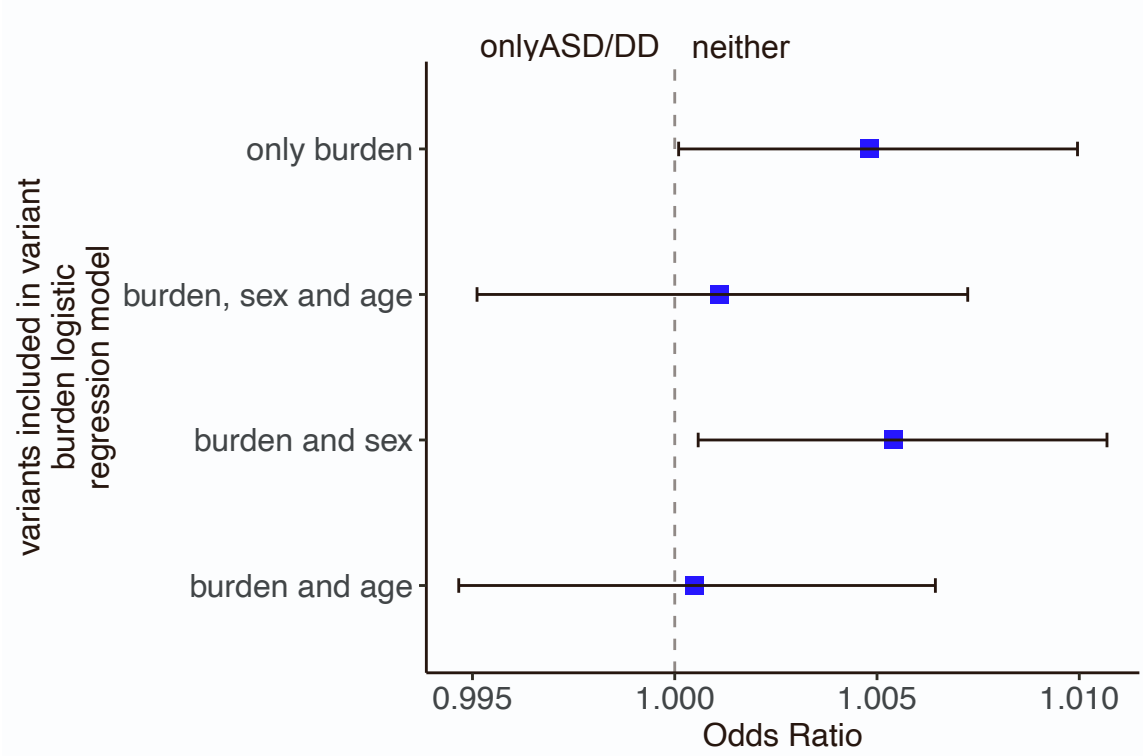

The blue squares indicate the odds ratios, error bars indicate the 95% of confidential intervals of the odds ratios. Clinical phenotype groups are indicated at the top of each forest plot. Corresponding p values and odds ratios can be located in Table S1 and Table S2, respectively.

**Figure S28.** Forest plot of mtDNA variant burden analysis among PHTS-ASD/DD and PHTS-ASDCancer groups within the H haplogroup (n = 213).



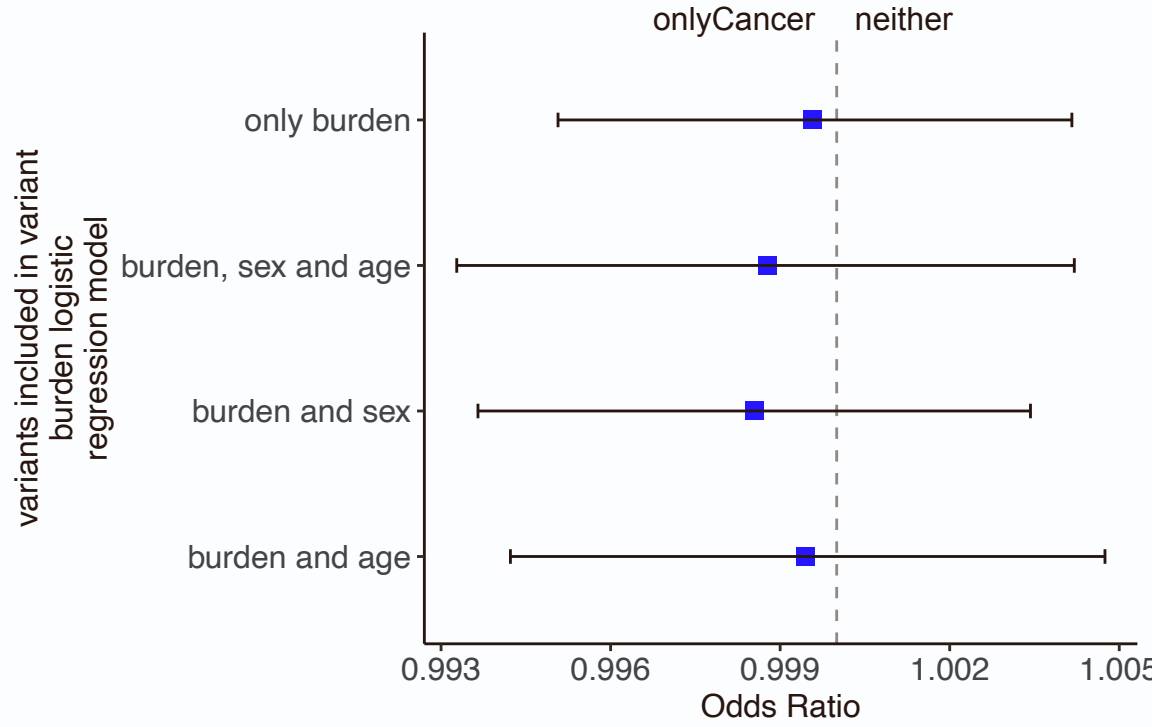

The blue squares indicate the odds ratios, error bars indicate the 95% of confidential intervals of the odds ratios. Clinical phenotype groups are indicated at the top of each forest plot. Corresponding p values and odds ratios can be located in Table S1 and Table S2, respectively.

**Figure S29.** Forest plot of mtDNA variant burden analysis among PHTS-onlyASD/DD and PHTS-neither groups within the H haplogroup (n = 213).



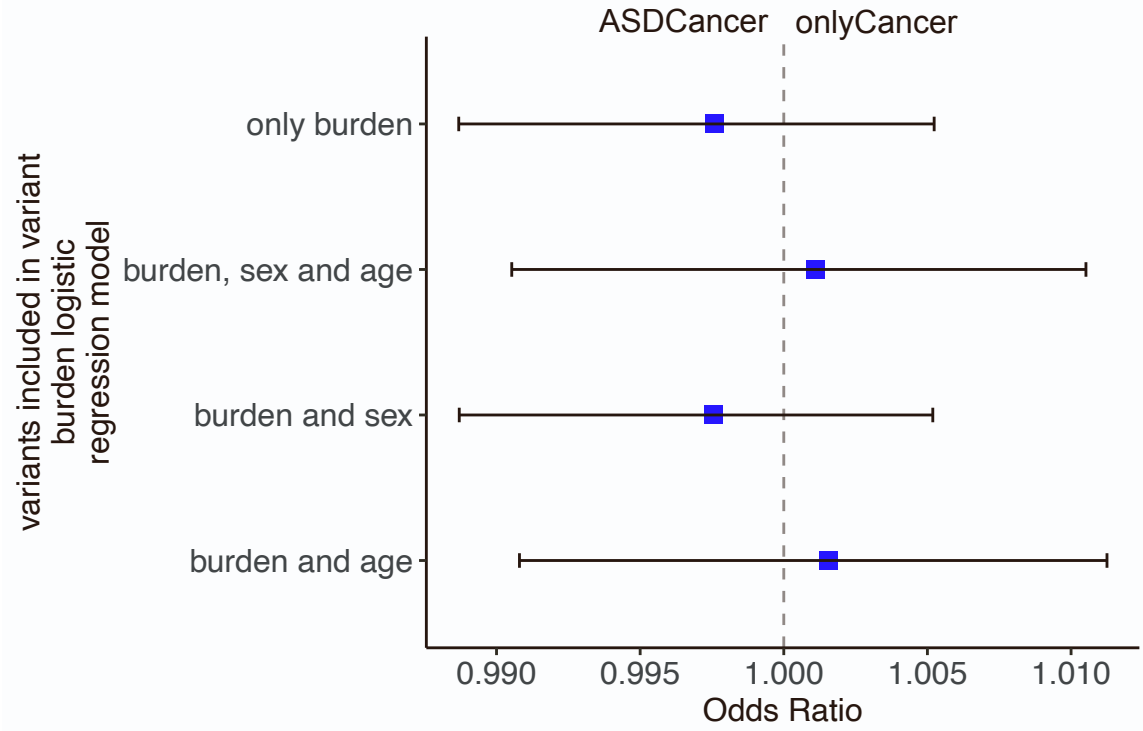

The blue squares indicate the odds ratios, error bars indicate the 95% of confidential intervals of the odds ratios. Clinical phenotype groups are indicated at the top of each forest plot. Corresponding p values and odds ratios can be located in Table S1 and Table S2, respectively.

**Figure S30.** Forest plot of mtDNA variant burden analysis among PHTS-onlyCancer and PHTS-neither groups within the H haplogroup (n = 213).



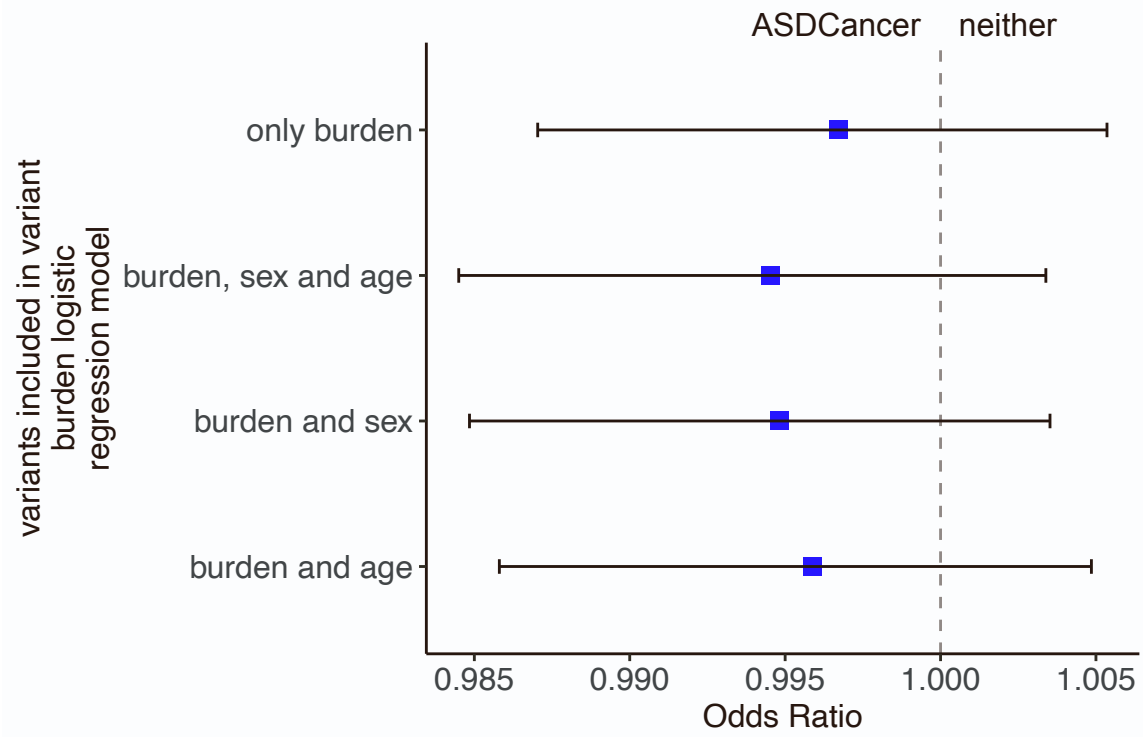

The blue squares indicate the odds ratios, error bars indicate the 95% of confidential intervals of the odds ratios. Clinical phenotype groups are indicated at the top of each forest plot. Corresponding p values and odds ratios can be located in Table S1 and Table S2, respectively.

**Figure S31.** Forest plot of mtDNA variant burden analysis among PHTS-onlyCancer and PHTS-ASDCancer groups within the H haplogroup (n = 213).



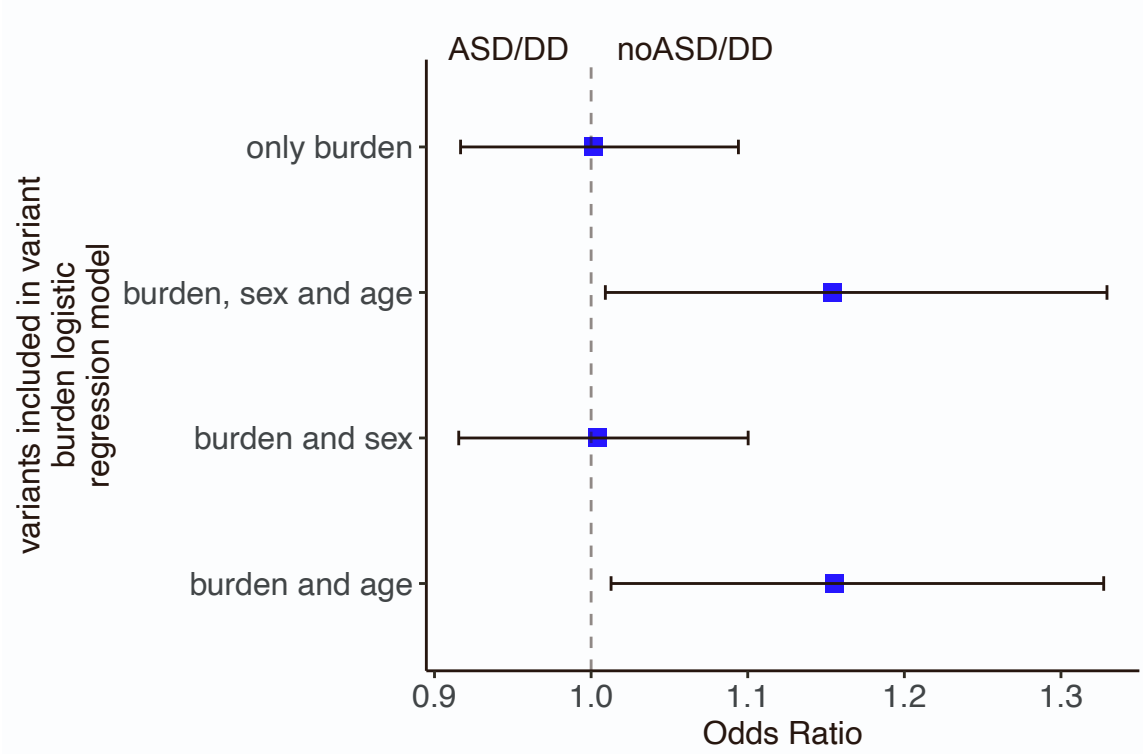

The blue squares indicate the odds ratios, error bars indicate the 95% of confidential intervals of the odds ratios. Clinical phenotype groups are indicated at the top of each forest plot. Corresponding p values and odds ratios can be located in Table S1 and Table S2, respectively.

**Figure S32.** Forest plot of mtDNA variant burden analysis among PHTS-ASDCancer and PHTS-neither groups within the H haplogroup (n = 213).



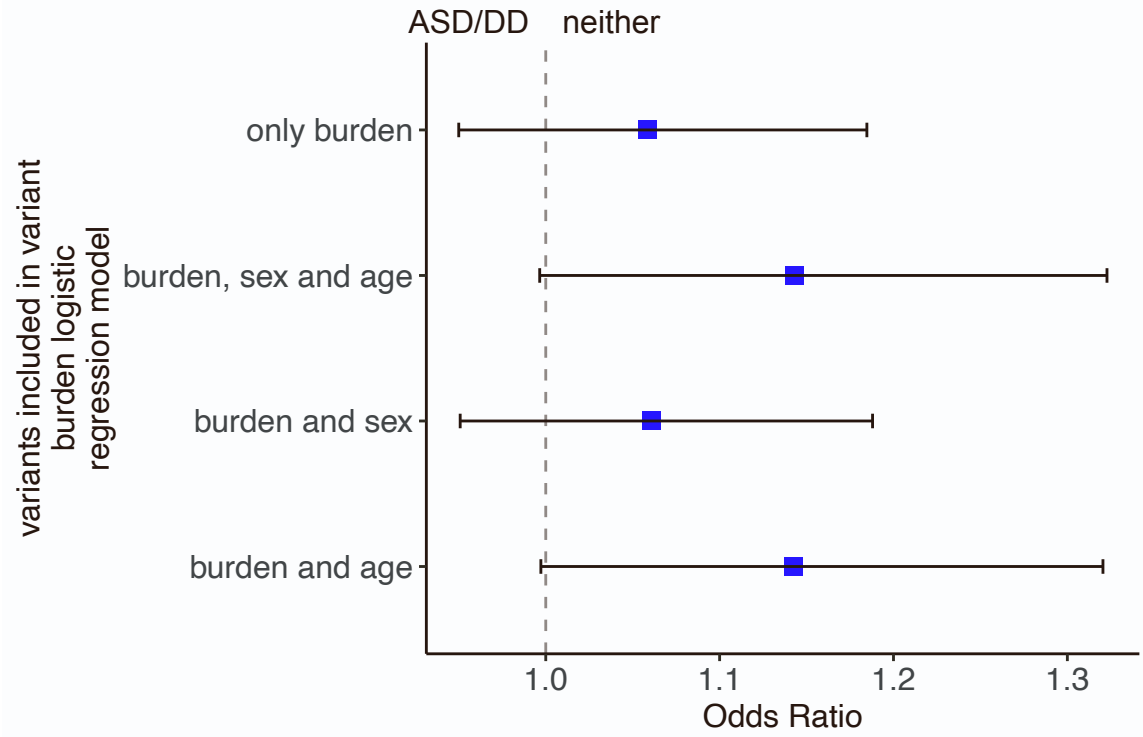

The blue squares indicate the odds ratios, error bars indicate the 95% of confidential intervals of the odds ratios. Clinical phenotype groups are indicated at the top of each forest plot. Corresponding p values and odds ratios can be located in Table S1 and Table S2, respectively.

**Figure S33.** Forest plot of mtDNA variant burden analysis among PHTS-ASD/DD and PHTS-noASD/DD groups within the H haplogroup (n = 213).



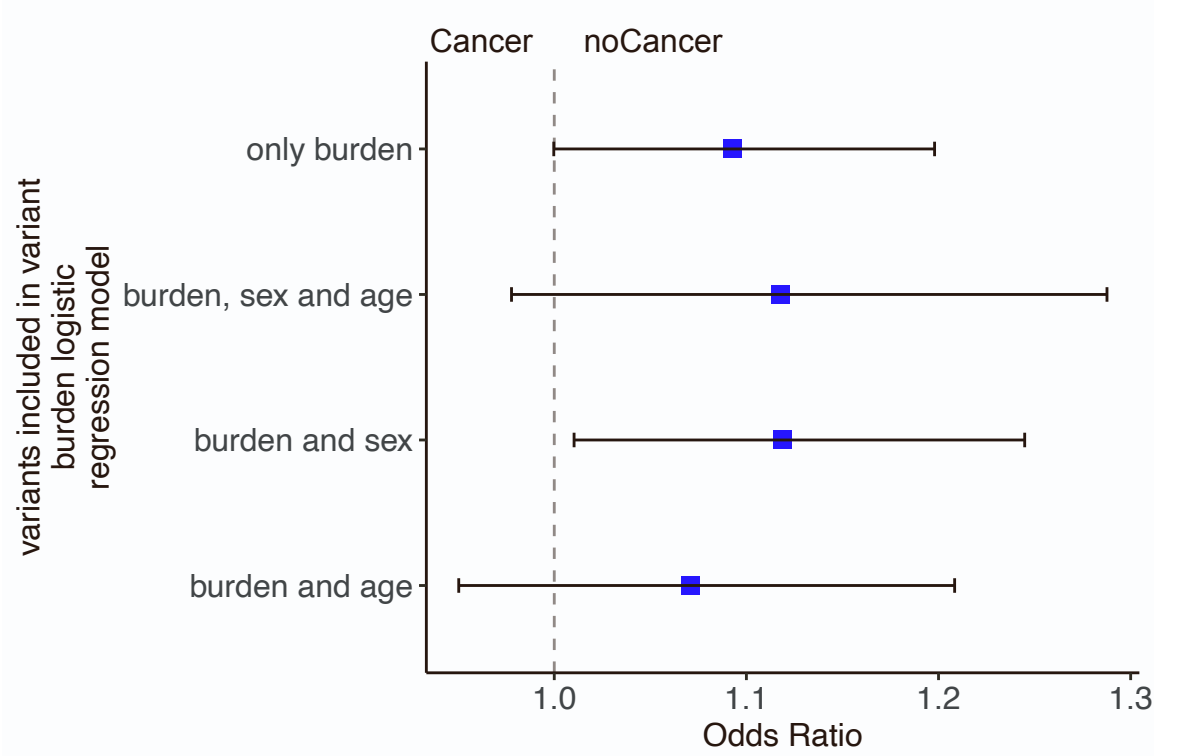

The blue squares indicate the odds ratios, error bars indicate the 95% of confidential intervals of the odds ratios. Clinical phenotype groups are indicated at the top of each forest plot. Corresponding p values and odds ratios can be located in Table S1 and Table S2, respectively.

**Figure S34.** Forest plot of mtDNA variant burden analysis among PHTS-ASD/DD and PHTS-neither groups within the H haplogroup (n = 213).



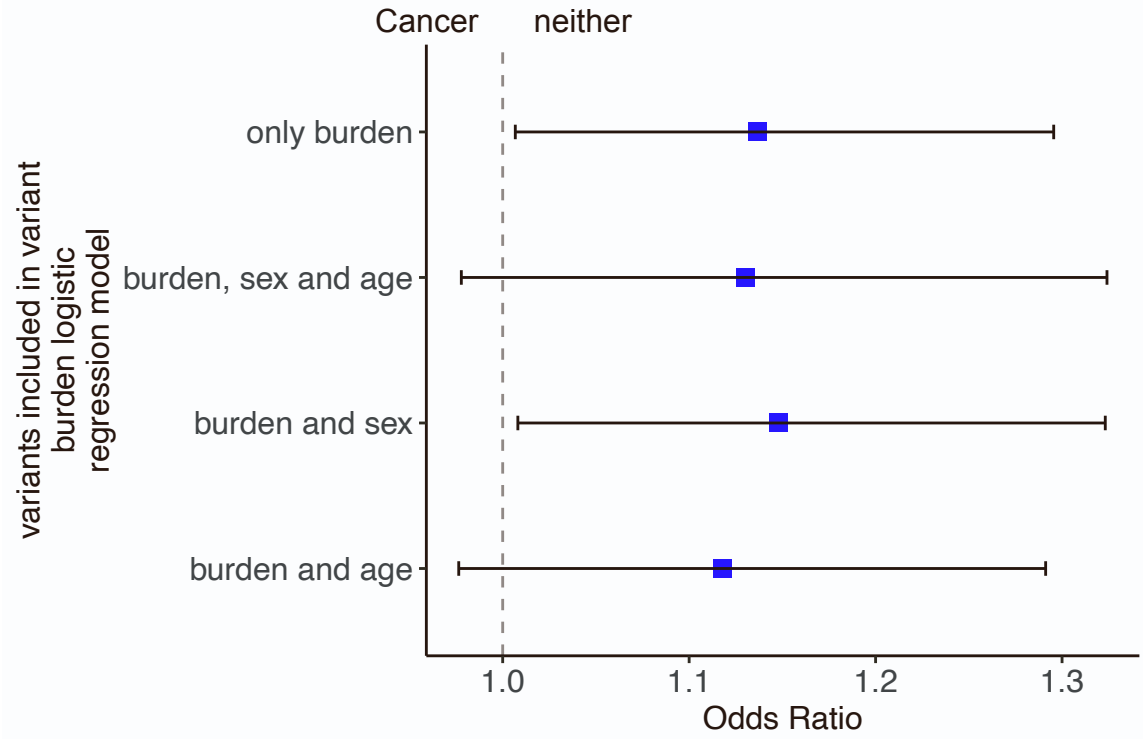

The blue squares indicate the odds ratios, error bars indicate the 95% of confidential intervals of the odds ratios. Clinical phenotype groups are indicated at the top of each forest plot. Corresponding p values and odds ratios can be located in Table S1 and Table S2, respectively.

**Figure S35.** Forest plot of mtDNA variant burden analysis among PHTS-Cancer and PHTS-noCancer groups within the H haplogroup (n = 213).




The blue squares indicate the odds ratios, error bars indicate the 95% of confidential intervals of the odds ratios. Clinical phenotype groups are indicated at the top of each forest plot. Corresponding p values and odds ratios can be located in Table S1 and Table S2, respectively.

**Figure S36.** Forest plot of mtDNA variant burden analysis among PHTS-Cancer and PHTS-neither groups within the H haplogroup (n = 213).




The blue squares indicate the odds ratios, error bars indicate the 95% of confidential intervals of the odds ratios. Clinical phenotype groups are indicated at the top of each forest plot. Corresponding p values and odds ratios can be located in Table S1 and Table S2, respectively.

**Table S1.** Statistical results of the comparisons of mtDNA copy number and SNV burden across all PHTS phenotype groups

| Comparisons/Test | Mann-Whitney test | Controlling for neither age nor sex | Controlling for age[a] and sex) | Controlling for sex | Controlling for age |
|---|---|---|---|---|---|
| **mtDNA copy number across all PHTS phenotype groups (n = 498)** | | | | | |
| onlyASD/DD vs. onlyCancer (n = 348) | 0.00918[b]** | 0.03* | 0.407 | 0.167 | 0.0862 |
| onlyASD/DD vs. ASDCancer (n = 182) | 0.0841 | 0.079 | 0.319 | 0.179 | 0.128 |
| onlyASD/DD vs. neither (n = 296) | 0.0666 | 0.12 | 0.433 | 0.122 | 0.368 |
| onlyCancer vs. ASDCancer (n = 202) | 0.492 | 0.45 | 0.739 | 0.440 | 0.994 |
| onlyCancer vs. neither (n = 316) | 0.591 | 0.64 | 0.458 | 0.488 | 0.586 |
| ASDCancer vs. neither (n = 150) | 0.433 | 0.433 | 0.296 | 0.299 | 0.332 |
| ASD/DD vs. noASD (n = 498) | 0.0242*[c] | 0.069 | 0.650 | 0.130 | 0.405 |
| ASD/DD vs. neither (n = 498) | 0.129 | 0.221 | 0.851 | 0.268 | 0.689 |
| Cancer vs. noCancer (n = 498) | 0.0323* | 0.064 | 0.265 | 0.120 | 0.220 |
| Cancer vs. neither (n = 498) | 0.511 | 0.54 | 0.367 | 0.441 | 0.405 |
| **mtDNA copy number among the phenotype groups with the H haplogroup (n=213)** | | | | | |
| onlyASD/DD vs. onlyCancer (n = 151) | 0.00418** | 0.03* | 0.257 | 0.0833 | 0.103 |
| onlyASD/DD vs. ASDCancer (n = 86) | 0.0670 | 0.08 | 0.397 | 0.121 | 0.249 |
| onlyASD/DD vs. neither (n = 124) | 0.0545 | 0.122 | 0.720 | 0.0340* | 0.872 |
| onlyCancer vs. ASDCancer (n = 89) | 0.805 | 0.645 | 0.825 | 0.556 | 0.759 |
| onlyCancer vs. neither (n = 127) | 0.520 | 0.451 | 0.658 | 0.556 | 0.836 |
| ASDCancer vs. neither (n = 62) | 0.527 | 0.344 | 0.249 | 0.267 | 0.390 |
| ASD/DD vs. noASD (n = 213) | 0.0135* | 0.035* | 0.750 | 0.0400* | 0.724 |
| ASD/DD vs. neither (n = 213) | 0.123 | 0.117 | 0.891 | 0.852 | 0.107 |
| Cancer vs. noCancer (n = 213) | 0.0146* | 0.0635 | 0.265 | 0.120 | 0.220 |
| Cancer vs. neither (n = 213) | 0.465 | 0.519 | 0.672 | 0.535 | 0.622 |
| **mtDNA variant burden within the H haplogroup (n = 213)** | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| onlyASD/DD vs. onlyCancer (n = 151) | 0.190 | 0.0221* | 0.906 | 0.139 | 0.301 |
| onlyASD/DD vs. ASDCancer (n = 86) | 0.100 | 0.0732 | 0.253 | 0.599 | 0.941 |
| onlyASD/DD vs. neither (n = 124) | 0.882 | 0.0531 | 0.153 | 0.504 | 0.158 |
| onlyCancer vs. ASDCancer (n = 89) | 0.226 | 0.853 | 0.109 | 0.343 | 0.0655 |
| onlyCancer vs. neither (n = 127) | 0.0843 | 0.563 | 0.338 | 0.133 | 0.266 |
| ASDCancer vs. neither (n = 62) | 0.0457* | 0.476 | 0.0964 | 0.0984 | 0.0656 |
| ASD/DD vs. noASD (n = 213) | 0.805 | 0.973 | 0.0399* | 0.934 | 0.0348* |
| ASD/DD vs. neither (n = 213) | 0.524 | 0.308 | 0.0619 | 0.296 | 0.0607 |
| Cancer vs. noCancer (n = 213) | 0.0329* | 0.054 | 0.111 | 0.0342* | 0.263 |
| Cancer vs. neither (n = 213) | 0.0843 | 0.0448* | 0.110 | 0.0452* | 0.115 |

[a]Age represents age at consent

[b]** $0.001 < p \text{ value} \leqslant 0.01$

[c]* $p \text{ value} < 0.05$

**Table S2.** Odds ratios of the comparisons of mtDNA copy number and SNV burden across all PHTS phenotype groups

| Comparisons/Test | Controlling for neither age nor sex (Odd Ratio, 95% confidence interval) | Controlling for age[a] and sex (Odd Ratio, 95% confidence interval) | Controlling for sex (Odd Ratio, 95% confidence interval) | Controlling for age (Odd Ratio, 95% confidence interval) |
|---|---|---|---|---|
| **mtDNA copy number across all PHTS phenotype groups (n = 498)** | | | | |
| onlyASD/DD vs. onlyCancer (n = 348) | 0.997 (0.994-1.000) | 0.996 (0.988-1.005) | 0.998 (0.995-1.001) | 0.998 (0.995-1.001) |
| onlyASD/DD vs. ASDCancer (n = 182) | 1.007 (1.000-1.015) | 1.005 (0.996-1.015) | 0.998 (0.995-1.001) | 1.007 (0.999-1.016) |
| onlyASD/DD vs. neither (n = 296) | 1.002 (0.999-1.005) | 1.002 (0.998-1.006) | 0.998 (0.995-1.001) | 1.002 (0.998-1.006) |
| onlyCancer vs. ASDCancer (n = 202) | 0.999 (0.997-1.002) | 1.001 (0.994-1.009) | 0.998 (0.995 1.001) | 1.000 (0.993-1.008) |
| onlyCancer vs. neither (n = 316) | 0.999 (0.997-1.002) | 0.999 (0.995-1.002) | 0.998 (0.995-1.002) | 0.999 (0.996-1.002) |
| ASDCancer vs. neither (n = 150) | 1.003 (0.997-1.010) | 1.003 (0.997-1.011) | 0.998 (0.995-1.001) | 1.003 (0.997-1.011) |
| ASD/DD vs. noASD (n = 498) | 0.998 (0.996-1.000) | 0.999 (0.996-1.003) | 0.998 (0.996-1.001) | 0.999 (0.995-1.002) |
| ASD/DD vs. neither (n = 498) | 0.998 (0.995-1.001) | 1.000 (0.996-1.003) | 0.998 (0.995-1.001) | 0.999 (0.996-1.003) |
| Cancer vs. noCancer (n = 498) | 1.002 (1.000-1.005) | 1.002 (0.999,1.005) | 1.002 (1.000-1.005) | 1.002 (0.999-1.005) |
| Cancer vs. neither (n = 498) | 1.001 (0.998-1.004) | 1.001 (0.998-1.005) | 1.001 (0.998-1.004) | 1.001 (0.998-1.004) |
| **mtDNA copy number among the phenotype groups with the H haplogroup (n=213)** | | | | |
| onlyASD/DD vs. onlyCancer (n = 151) | 0.997 (0.994-1.000) | 0.9938 (0.978-1.004) | 0.996 (0.991-1.000) | 0.991 (0.980-1.001) |
| onlyASD/DD vs. ASDCancer (n = 86) | 0.993 (0.985-1.000) | 0.995 (0.981-1.006) | 0.992 (0.981-1.001) | 0.993 (0.982-1.003) |
| onlyASD/DD vs. neither (n = 124) | 0.998 (0.995-1.001) | 0.999 (0.993-1.005) | 0.995 (0.989-0.999) | 1.000 (0.994-1.005) |
| onlyCancer vs. ASDCancer (n = 89) | 1.001 (0.998-1.003) | 0.999 (0.990- 1.010) | 1.002 (0.995-1.011) | 1.001 (0.995-1.006) |
| onlyCancer vs. neither (n = 127) | 1.003 (0.996-1.009) | 1.001 (0.996-1.007) | 1.001 (0.997-1.006) | 1.002 (0.995-1.006) |
| ASDCancer vs. neither (n = 62) | 1.003 0.997-1.010) | 0.995 (0.981-1.006) | 1.005 (0.996-1.015) | 1.004 (0.995-1.014) |
| ASD/DD vs. noASD (n = 213) | 0.996 0.993-1.000) | 0.999 (0.994-1.004) | 0.996 (0.993,0.999) | 0.999 (0.995-1.003) |
| ASD/DD vs. neither (n = 213) | 0.996 (0.991-1.001) | 1.000 (0.995-1.006) | 0.996 (0.991-1.001) | 1.001 (0.995-1.006) |
| Cancer vs. noCancer (n = 213) | 1.002 (1.000-1.005) | 1.002 (0.999-1.005) | 1.002 (1.000-1.005) | 1.002 (0.999-1.005) |

| | | | | |
|---|---|---|---|---|
| Cancer vs. neither (n = 213) | 0.999 (0.995-1.003) | 0.999 (0.995-1.003) | 0.999 (0.995-1.003) | 0.999 (0.995-1.003) |
| **mtDNA variant burden within the H haplogroup (n = 213)** | | | | |
| onlyASD/DD vs. onlyCancer (n = 151) | 0.995 (0.991-0.999) | 1.017 (0.767-1.390) | 0.912 (0.804-1.029) | 1.140 (0.897-1.491) |
| onlyASD/DD vs. ASDCancer (n = 86) | 0.992 (0.982-1.000) | 0.829 (0.581-1.133) | 0.795 (0.613-0.999) | 0.991 (0.780 1.268) |
| onlyASD/DD vs. neither (n = 124) | 1.005 (1.000-1.010) | 1.119 (0.961-1.312) | 1.039 (0.929-1.166) | 1.114 (0.961-1.300) |
| onlyCancer vs. ASDCancer (n = 89) | 1.000 (0.995-1.004) | 1.292 (0.965-1.834) | 1.112 (0.894-1.392) | 1.35 (0.997-1.912) |
| onlyCancer vs. neither (n = 127) | 0.998 (0.989-1.005) | 1.080 (0.926-1.273) | 1.110 (0.973-1.282) | 1.086 (0.940-1.263) |
| ASDCancer vs. neither (n = 62) | 0.997 (0.987-1.005) | 1.223 (0.975-1.574) | 1.215 (0.973-1.558) | 1.248 (0.998-1.611) |
| ASD/DD vs. noASD (n = 213) | 1.002 (0.917-1.094) | 1.154 (1.009-1.329) | 1.004 (0.915-1.100) | 1.156 (1.013-1.327) |
| ASD/DD vs. neither (n = 213) | 1.059 (0.950-1.185) | 1.143 (0.997-1.323) | 1.061 (0.951-1.188) | 1.143 (0.997-1.320) |
| Cancer vs. noCancer (n = 213) | 1.093 (1.000-1.198) | 1.118 (0.978-1.288) | 1.119 (1.010-1.245) | 1.071 (0.950-1.208) |
| Cancer vs. neither (n = 213) | 1.136 (1.007-1.296) | 1.13 (0.978-1.324) | 1.148 (1.008-1.323) | 1.118 (0.976-1.291) |

[a]Age represents age at consent

**Table S3.** Clinical phenotypic characteristics of the 498 individuals with PHTS

| Clinical phenotypic characteristics | | Data |
|---|---|---|
| Sex, No. (%) | | |
| | Female | 266 (53.4%) |
| | Male | 232 (46.6%) |
| Age at consent, mean (SD)[range],years | | 31.19 (21.9) [0.5-85] |
| Autism spectrum disorder, No. (%) | | 182 (36.5%) |
| Cancer, No. (%) | | 202 (40.6%) |
| PHTS component malignant neoplasms, No. (%) | | 128 (25.7%) |
| | Breast cancer | 113 (22.7) |
| | Thyroid cancer | 62 (12.5) |
| | Renal cell cancer | 28 (5.6%) |
| | Endometrial cancer | 33 (6.6%) |
| | Colon cancer | 17 (3.4%) |
| | Melanoma | 10 (2.0%) |
| Other malignant neoplasms[a], No. (%) | | 74 (14.9%) |

[a] These are non-component cancers.