Epigenetic changes with *T. gondii* in brains of people with HIV and their possible link to gliomas

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Introduction

- *Toxoplasma gondii* (***T. gondii***) is an **opportunistic parasitic infection** with a global infection prevalence of 32.5% in all people, and about 42.1% in **people with HIV (PWH)**.[1]
- In immunocompromised persons, *T. gondii* infection leads to a **fulminant neurological disease**. [2]
- Epidemiological research suggests Toxoplasmosis has the **highest comorbid association with HIV, followed by malignant brain neoplasms**, and then several neurocognitive conditions.[3]
- **PWH have an elevated occurrence of glioma and glioblastoma (GBM)** relative to the general population.[4]
- Murine and *in vitro* studies have suggested ***T. gondii* infection causes changes to DNA methylation in the brain**.[5,6]

Hypotheses

- There will be an association between **differential DNA methylation (DM)** and *T. gondii* infection in brains of PWH.
- Select **candidate genes containing DM** will indicate a **potential underlying mechanism for neurological comorbidities** in the brains of PWH and *T. gondii*.

Results

The correlation between differential DNA methylation found with *T. gondii* infection in genes with known expression changes in gliomas may have **clinical implications for addressing the risk of brain tumor development in people with *T. gondii*.**

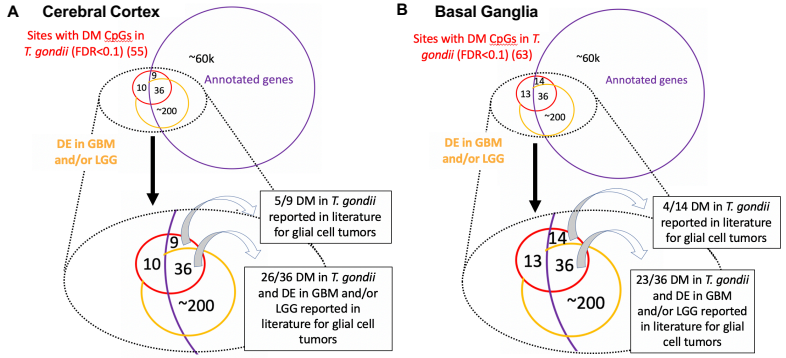


Fig. 1 Overlap of **detected DM sites** in (**A**) cerebral cortex and (**B**) basal ganglia with genes known to be **DE in GBM or LGG**.

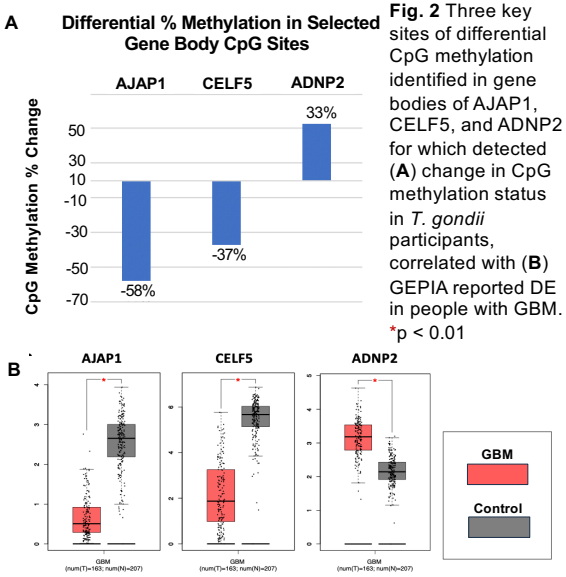


Fig. 2 Three key sites of differential CpG methylation identified in gene bodies of AJAP1, CELF5, and ADNP2 for which detected (**A**) change in CpG methylation status in *T. gondii* participants, correlated with (**B**) GEPIA reported DE in people with GBM. *p < 0.01

Materials, Methods, and Participants

1. Brain tissue from *T. gondii* positive participants were received from the California NeuroAIDS Tissue Network, and *T. gondii* negative participants from the Last Gift Rapid Autopsy Cohort at UC San Diego.
2. *T. gondii* infection status was validated via histopathology, serum IgG ELISA and quantitative PCR.
3. Reduced representation bisulfite sequencing (RRBS) was performed on basal ganglia and cerebral cortex.
4. Utilized Limma for deconvolution and to assess DM on CpG sites (FDR < 0.1, DM ≥ ±15%).
5. DM sites screened for location using UCSC Genome Browser. Gene Expression Profiling Interactive Analysis (GEPIA)[7] database was used to evaluate **differential expression (DE)** for DM genes of interest in GBM or **lower grade glioma (LGG)**.

Table 1. Participant characteristics.

Participant	*T. gondii* status	Sex	Race	Ethnicity	Age at death (Years)
CA192	Histopathology +	M	Caucasian	Non-Hispanic	52
CA346	IgG ELISA and histopathology +, self report	M	Caucasian	Non-Hispanic	57
CB239	qPCR (brain) +, self report	M	Caucasian	Hispanic	58
CC249	Histopathology +	M	Caucasian	Hispanic	43
CE167	Histopathology +	M	Caucasian	Non-Hispanic	43
CE234	IgG ELISA +	F	Native Alaskan	Hispanic	63
LG39	Neg	M	Caucasian	Non-Hispanic	51
LG38	Neg	M	Caucasian	Non-Hispanic	74
LG34	Neg	M	Caucasian	Non-Hispanic	30
LG29	Neg	M	Caucasian	Non-Hispanic	45

Conclusions and Future Directions

- The **epigenetic changes in the brains of PWH suggest that *T. gondii* infection influences DNA methylation patterns in humans**, as demonstrated in murine studies. [5,6]
- The identified correlation between genes with differentially methylated CpGs and expression changes linked to LGG and GBM points to a potential **connection between *T. gondii* infection and brain tumor development**.
- Evidence of potential brain neoplasm-related epigenetic changes warrants **further exploration of the mechanism** by which *T. gondii* impacts epigenetic pathways in the human brain to impact cell division and differentiation.

Acknowledgements

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Citations

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