Elevated Mitochondrial DNA Content in HIV-Exposed Uninfected (HEU) Children with Autism

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Introduction

- In Canada, **nearly all** children born to HIV+ mothers receive perinatal cART exposure
- Many cART drugs that **cross the placenta and blood-brain barrier** have been associated with **adverse effects** on **mitochondrial DNA (mtDNA)**
- Mitochondrial dysfunction and maternal infections in pregnancy have been associated with **autism spectrum disorder (ASD)**
- **A high prevalence of ASD** (3-fold over general estimates of 1.5%) was seen in **HIV-exposed uninfected (HEU) children** enrolled in the pan-Canadian Children & Women AntiRetrovirals & Markers of Aging (**CARMA**) cohort (14/296, 4.7%)*
- Only 2/141 (1.4%) HIV+ children in CARMA were diagnosed with ASD
- **MtDNA abnormalities in HEU children are consistent with those also seen in ASD children: a possible association?**

*Since the submission of this abstract, two HEU children were determined to not meet criteria for ASD diagnosis and were excluded from this analysis (HEU + ASD n= 16→14).

Hypothesis

Leukocyte mtDNA content in HEU children diagnosed with ASD will be significantly different from that of well-matched HEU children without ASD, ASD children with no HIV/cART exposure, and controls

Materials & Methods

- Whole blood samples from **HIV-unexposed uninfected (HUU)** children with ASD and HUU non-ASD siblings were received from the BC Autism Spectrum Interdisciplinary Research (**ASPIRE**) program; all HEU samples were collected by CARMA; whole blood samples from HUU anonymous controls were left over from routine blood work

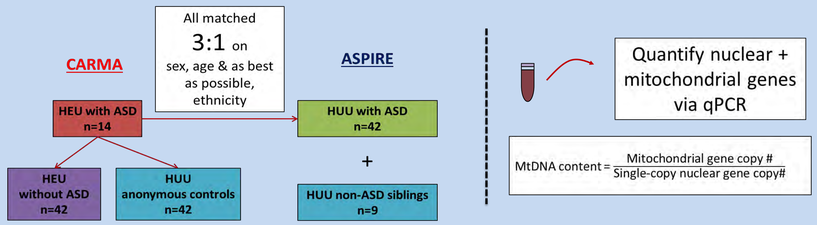


Figure 1. Schematic of study design and methodology

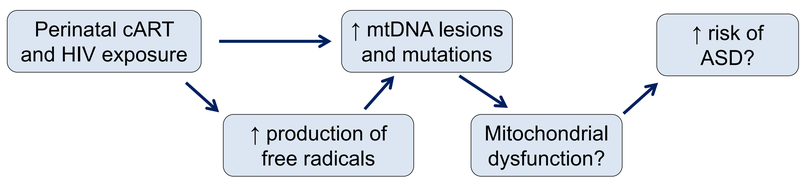


Figure 2. Potential model of the association between perinatal HIV/cART exposure and the observed elevated prevalence of ASD in HEU children

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Results

Table 1. Demographic characteristics of HEU/HUU children with and without ASD

	HEU with ASD n=14	HEU without ASD n=42	HUU with ASD n=42	HUU without ASD n=51
Male sex, n (%)	10 (71)	30 (71)	30 (71)	36 (71)
Age in years, median [Q1 – Q3] (range)	5.7 [3.9 – 8.3] (2.3 – 15.7)	5.8 [3.9 – 8.4] (2.2 – 15.7)	5.9 [3.7 – 8.1] (2.4 – 15.9)	5.9 [3.8 – 8.8] (2.2 – 15.7)
Ethnicity, n (%)				
Black	11 (79)	33 (79)	4 (10)	0
White	3 (21)	9 (21)	20 (48)	5(10)
Asian	0	0	6 (14)	4 (8)
Other	0	0	12 (29)	0
Unknown	0	0	0	42 (82)
Maternal cART, n (%)				
AZT+3TC+PI	7 (50)	19 (45)	-	-
TDF+FTC+PI	2 (14)	2 (5)	-	-
ABC+3TC+PI	0	9 (21)	-	-
None	3 (21)	2 (5)	-	-
Other/Unknown	2 (14)	10 (24)	-	-
Post-natal AZT prophylaxis, n (%)	13 (93)	42 (100)	-	-

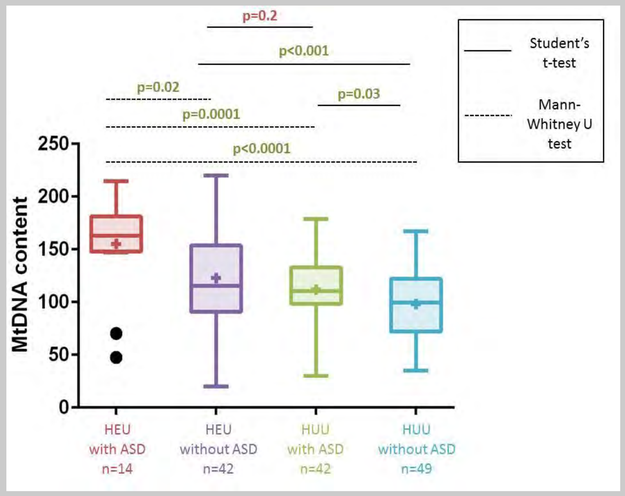


Figure 3: Between-group comparisons of mtDNA content between HEU/HUU children with and without ASD

- **HEU children with ASD had higher leukocyte mtDNA content** than all other groups. HEU status and ASD were also associated with elevated mtDNA content compared to controls

Table 2. Multivariable linear regression analysis of factors (HEU status, ASD, maternal and child age) possibly associated with mtDNA content (model R^2=0.124)

Explanatory variables	Effect size	Standard error	P value
ASD diagnosis (vs. non-ASD)	24.7	9.4	0.010
HEU status (vs. HUU)	33.4	9.3	0.001
Child's age at sample collection, years	-0.1	1.1	0.911
Maternal age at childbirth, years	0.6	0.7	0.388

(n=106; HEU with ASD=14, HEU without ASD=41, HUU with ASD=42, HUU without ASD= 9)

- **HEU status and ASD** were significantly associated with mtDNA content after controlling for maternal and child age

Results

Table 3. Multivariable linear regression analysis among ASD children, including HIV/cART exposure and factors previously described in ASD (model R^2=0.312)

Explanatory variables	Effect size	Standard error	P value
HEU status (vs. HUU)	53.7	14.0	<0.001
Age at visit, years	-1.3	1.6	0.422
Developmental delay *(language, motor, global)*	3.5	10.7	0.745
Chronic gastrointestinal abnormalities *(constipation, diarrhoea, reflux)*	-17.8	14.0	0.211
Maternal age at childbirth, years	-0.09	0.9	0.926
History of seizures and/or epilepsy	-5.0	16.5	0.765
Low muscle tone	1.1	11.9	0.928

(n=52; HEU with ASD=14, HUU with ASD=38)

- **Only HEU status** was independently associated with mtDNA content
- Other factors do not appear to be associated, but there may be other maternal factors which could explain our results and which are not accounted for by our model

Study Limitations

- This was a small exploratory study with limited power
- Incomplete information is available on maternal factors (e.g. smoking, other infections during pregnancy, substance use and non-HIV medication)
- Matching on ethnicity could not be done for HUU children, and may confound our results

Conclusions/Discussion

- There were no obvious differences between groups with respect to type of maternal cART taken during pregnancy
- Both HEU status and ASD are independently associated with elevated leukocyte mtDNA content
- HEU children with ASD had higher mtDNA content than all other groups, suggesting a possible cumulative effect
- Elevated mtDNA content may indicate a physiological response to mitochondrial dysfunction and/or oxidative stress
- Further work is needed to determine the effects of other maternal characteristics, and whether this increased prevalence of ASD in HEUs is seen in other cohorts

Acknowledgements

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