

6-month-long fast-food intake is associated with worse metabolic syndrome score and higher ecDNA levels in female rats

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Obesity

- = **abnormal or excessive fat accumulation** (general, regional, ectopic) **that presents a risk to health**
- **Incidence: Rising world-wide** (all age categories)
- **Prevalence - Slovakia** (2024; <https://data.worldobesity.org>)
 - **15+ years** (2019): **overweight: 38%, obesity: 19%**
- **Obesity-associated**
 - **Morbidity:** T2DM; HT; dyslipidemia; MetS; heart, cerebrovascular, respiratory, gastrointestinal, kidney, bone, gynecologic, psychiatric diseases; cancer; obstetric, anesthesiologic complications, ...
 - **Mortality:** deaths from NCDs due to obesity

Obesity - low-grade inflammation

- **A state of chronic low-grade fat-induced inflammation causing chronic health condition that progresses over time**
- **Classical soluble markers:**
 - ↑ pro-inflammatory cytokines/adipokines (CRP, TNF- α , IL-6, IL-18, resistin, leptin,...)
 - ↓ anti-inflammatory cytokines/adipokines (IL-10, IL-4, IL-13, IL-1Ra, TGF- β , adiponectin, ...)
- **New marker:**
 - ↑ **ecDNA – DAMP recognized by PRRs** (Nishimoto et al., 2020)
 - Obese pregnant women: ↑ maternal cfDNA vs. non-obese; \approx with BMI (Haghiac et al., 2012)
 - Viscerally obese adults: ↑ cfDNA vs. lean; \approx with visceral fat area, IR (Nishimoto et al., 2016)
 - HFD-induced obese mice: ↑ cfDNA vs. lean; \approx with glycemia (Nishimoto et al., 2016)
 - Healthy adolescents: ecDNA, mtDNA, ncDNA: \approx ↑ continuous MetS score (Celec et al., 2021)

Obesity

- **Pathogenesis**

- **Mostly imbalance: calories intake vs. expenditure**
- **Humans (life span - decades):**
 - Prenatal – intrauterine – perinatal - childhood - adolescence - adulthood
- **⇒ Animal models (rodents) – diet-induced obesity: TRICKY!**
 - ad libitum ↑ sugar beverage + chow/FFD → compensated caloric intake → no excess Bwt gain
 - HFD (40%-60% caloric intake from lard, cocoanut oil) – Bwt gain / diet not corresponding to human
 - Western diets – thermally processed, pre-processed, highly palatable (attractive taste and odor) → obesity

- **AIM:**

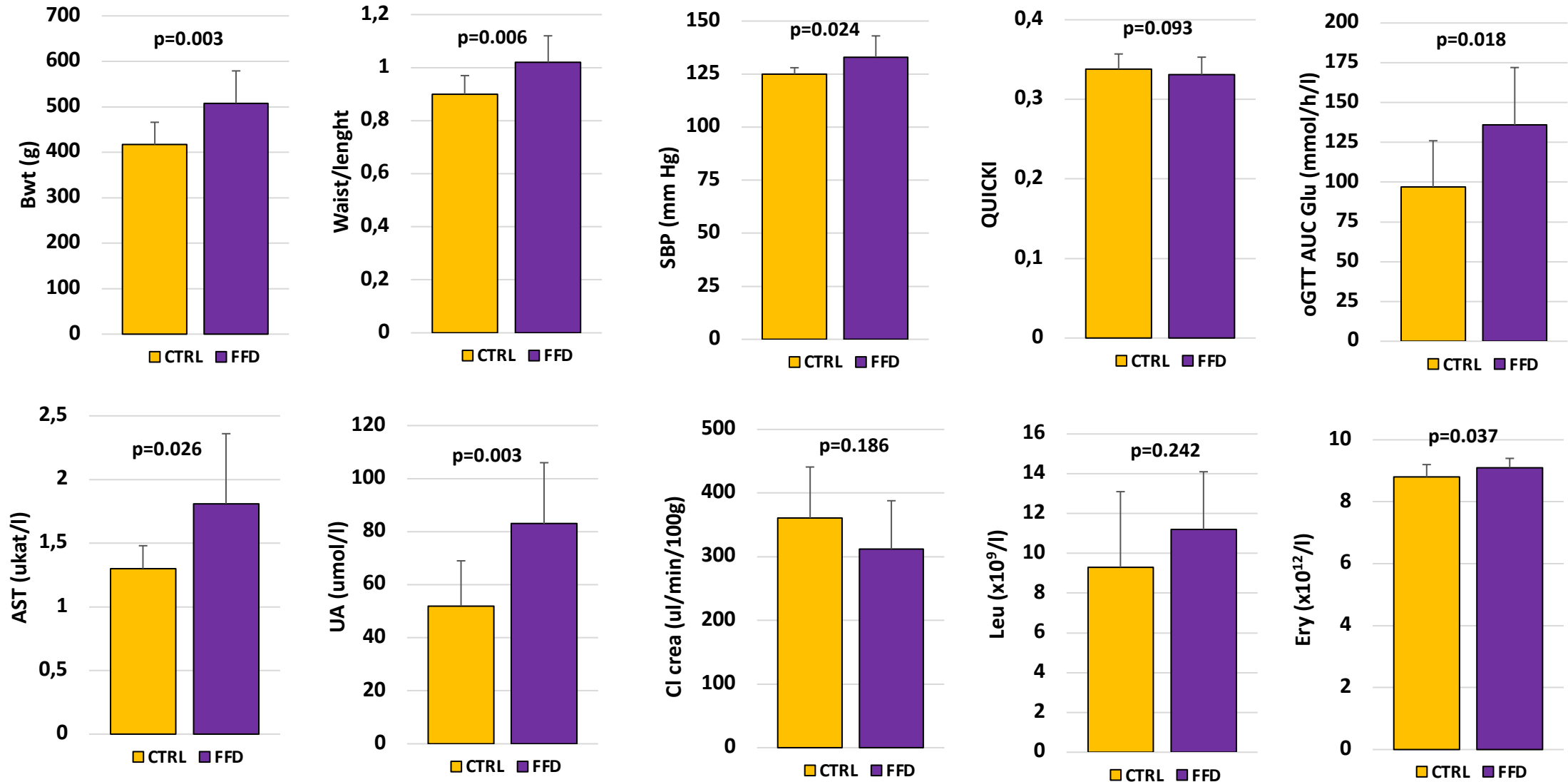
- **? Western-diet-induced obesity associates with higher ecDNA levels in rodent model**
- **= cheeseburgers (n=9) vs. control diet (n=10) fed female rats**
(isocaloric diet, 10% vs. 31% energy from fat), **6 months**



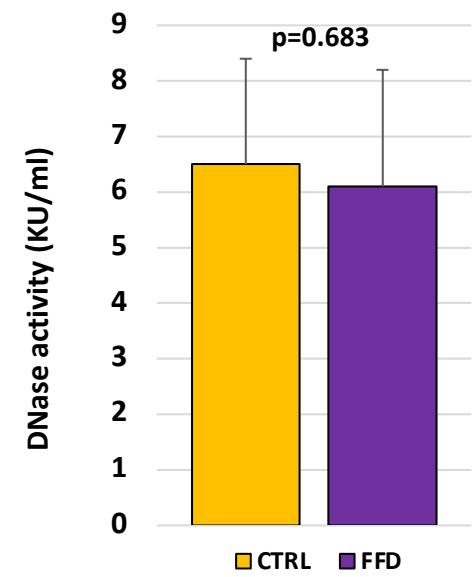
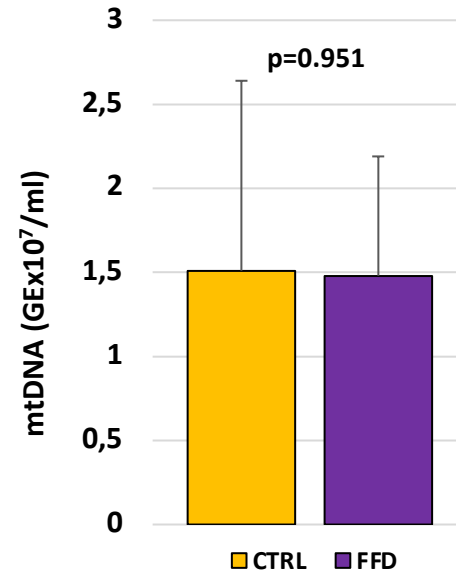
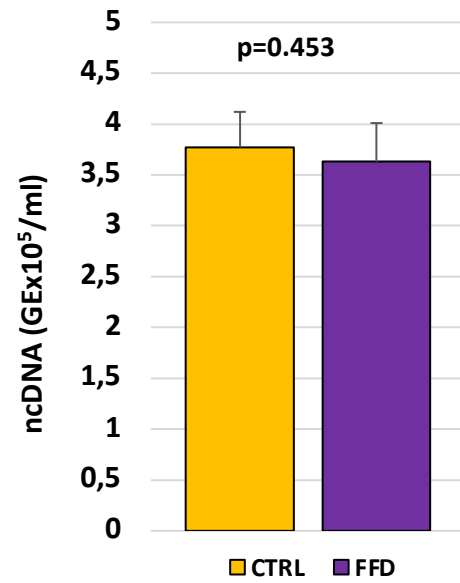
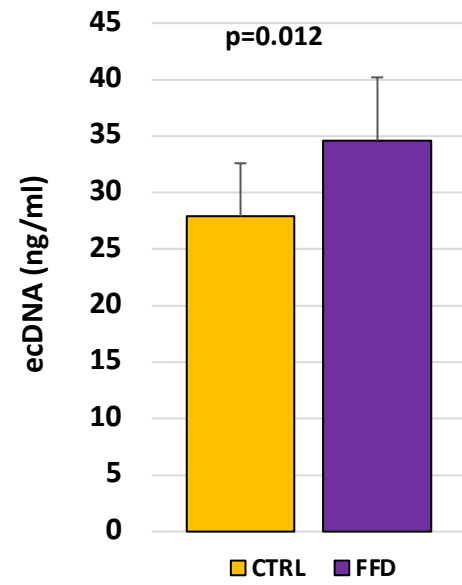
vs.



Results

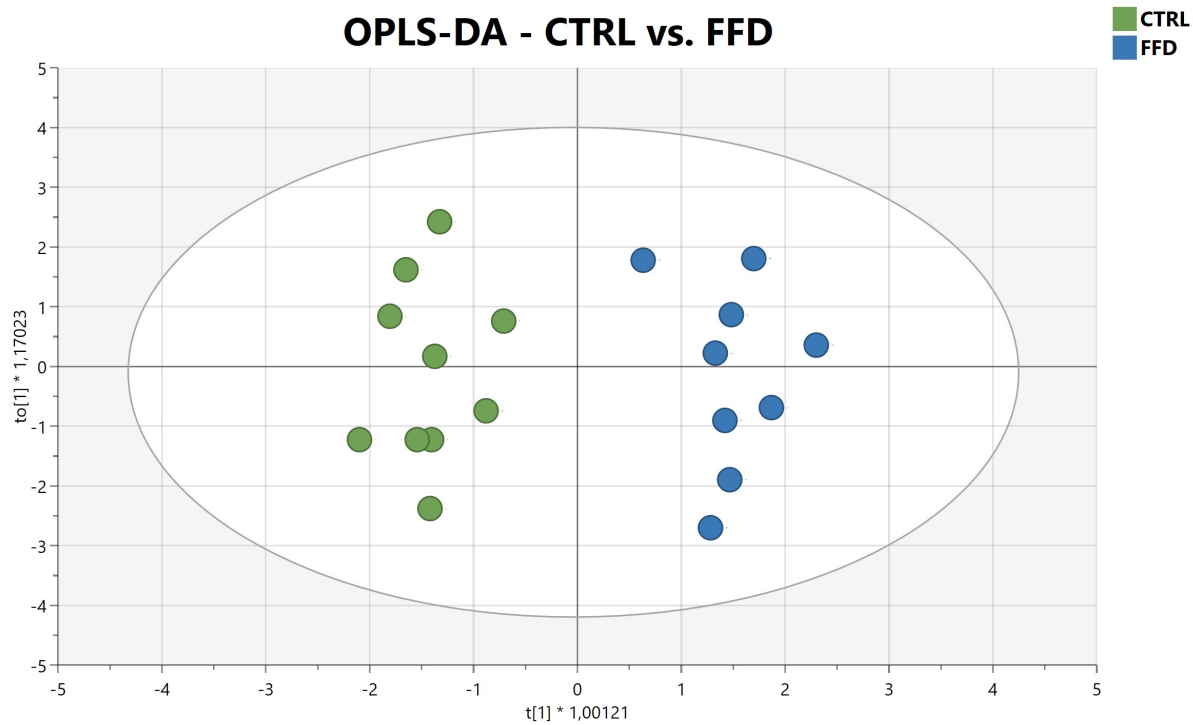


ecDNA

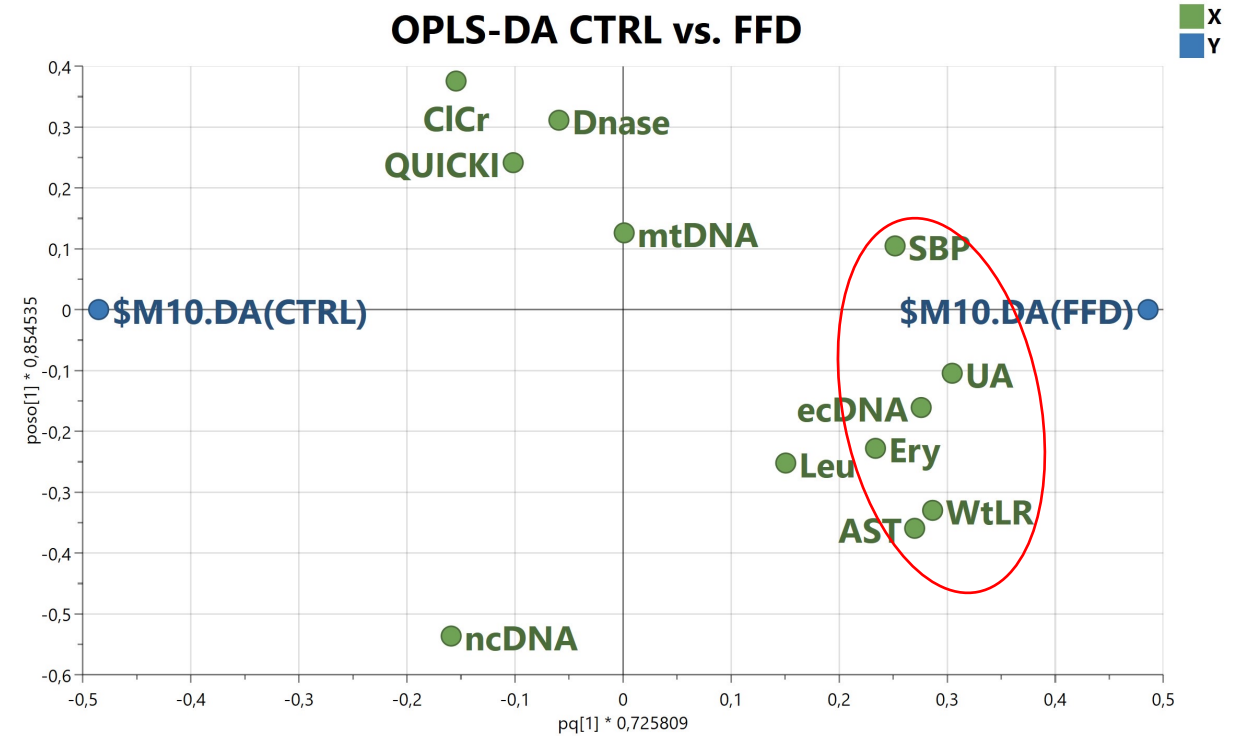


Multivariate analysis (OPLS-DA model)

OPLS-DA - CTRL vs. FFD

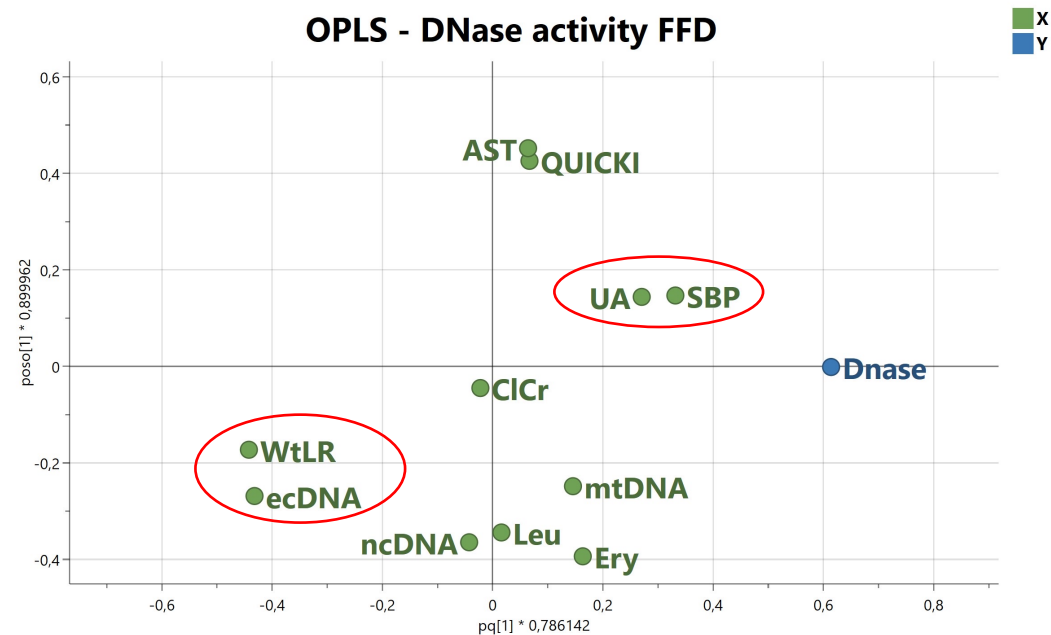
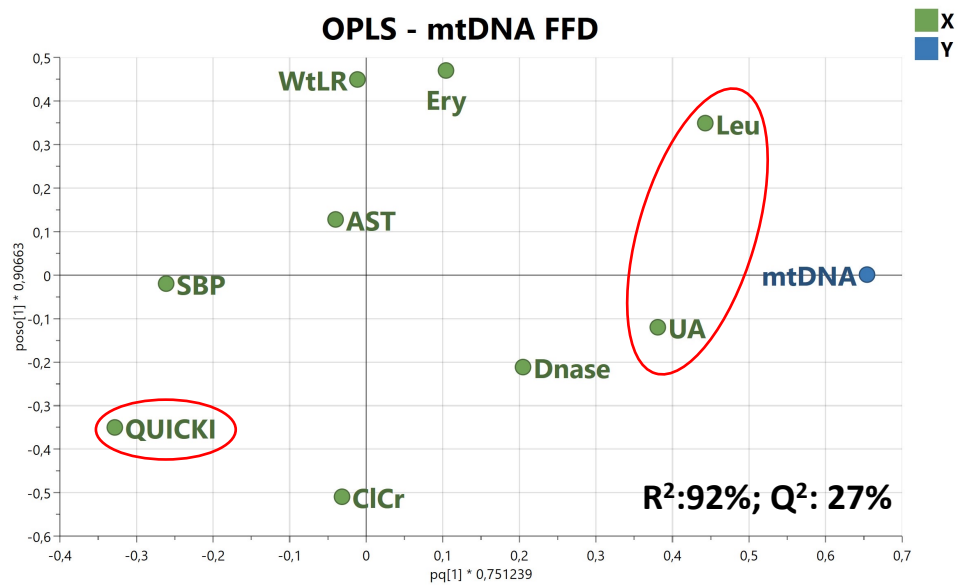
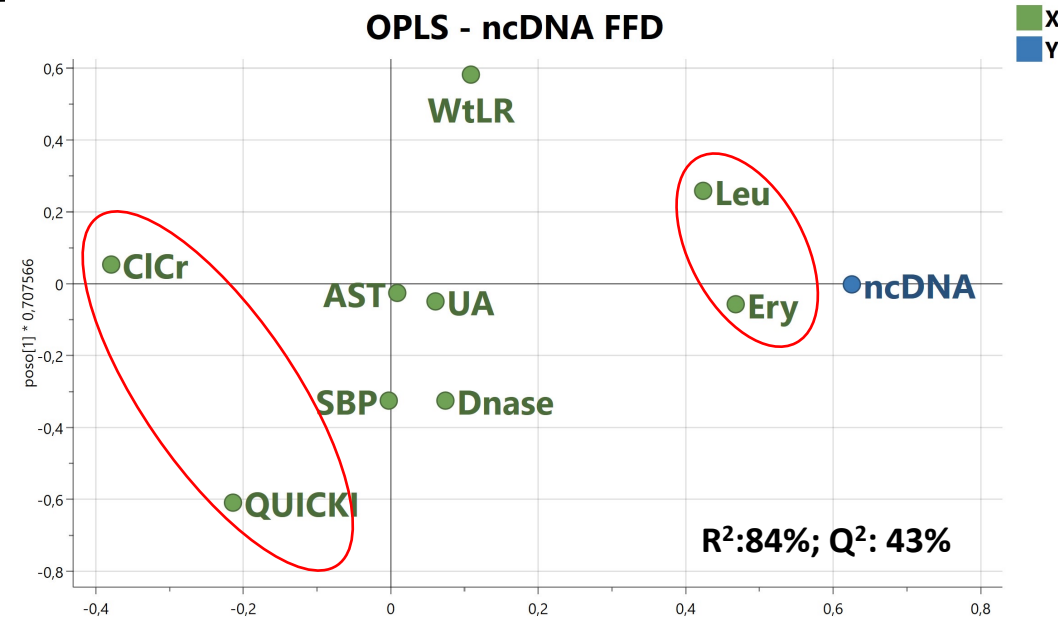
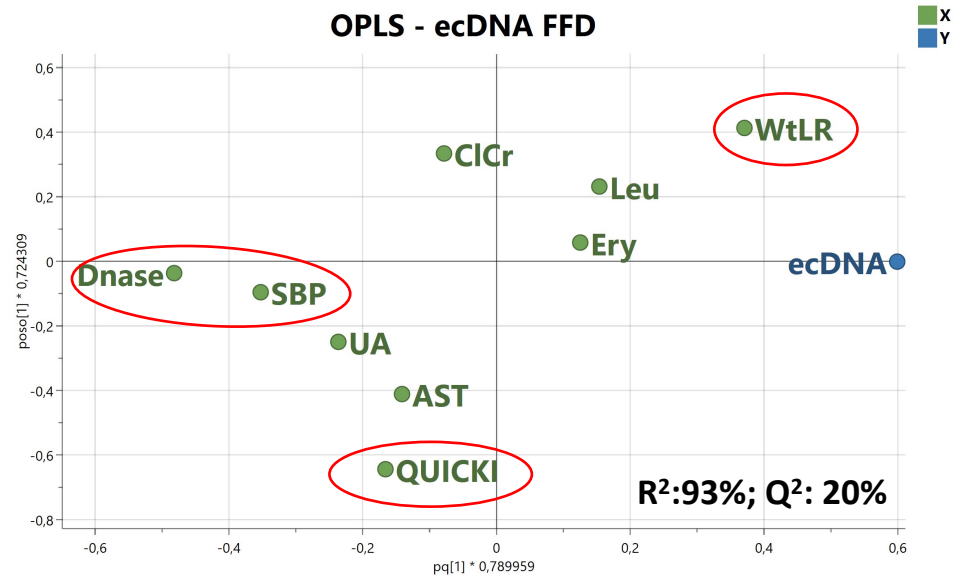


OPLS-DA CTRL vs. FFD



R2:93%; Q2: 81%

Multivariate regression FFD



FFD rats: variables significantly associated with cfDNA (multivariate regression: OPLS model)

	ecDNA	ncDNA	mtDNA
UA	0.86	0.21	↑ 1.29
Ery	0.42	↑ 1.57	0.83
Clcr	0.54	↓ 1.27	0.82
DNase	↓ 1.58	0.54	0.76
Leu	0.60	↑ 1.47	↑ 1.58
WtLR	↑ 1.35	0.94	0.72
QUICKI	↓ 1.07	↓ 1.16	↓ 1.23

Conclusions: FFD-induced obesity

- ↑ ecDNA vs. similar ncDNA, mtDNA GE
 - Fragmentation?
 - Bacterial DNA? (16s rRNA, LPS)
 - Western type diet = AGEs-rich food
 - Dietary AGEs partially absorbed into circulation;
 - in gut (Phuong-Nguyen et al., 2023)
 - Change gut microbiota
 - Increase intestinal permeability (D-lactate, indols,...)



- **AGEs x RAGE interaction → insulin resistance** (Unoki & Yamagishi, 2008)
 - ecDNA x RAGE interaction (receptor for advanced glycation end-products) (Tian et al., 2019)
 - Proof of the concept:
 - Administration of DNase
 - Administration of anti-RAGE ab
 - RAGE -/- mouse
 - Bacterial ecDNA? - ATB