



# Embryonic BPA Exposure Causes Liver Disease in Multiple Generations of Fish

Presented

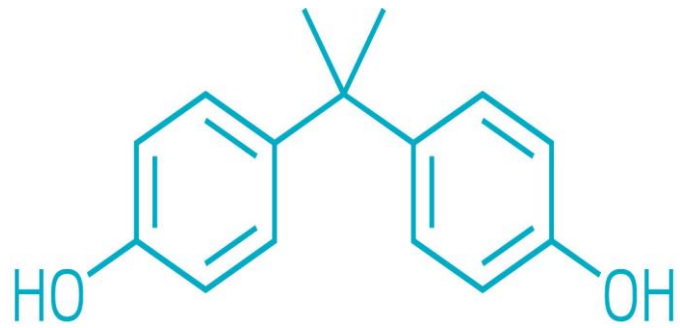
by

Sourav Chakraborty

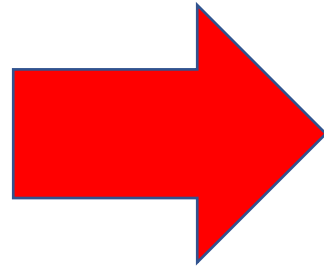
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# Direct Exposure Effects of Bisphenol A



**Bisphenol A**



- Estrogen receptor - **Reproductive & metabolic disorder, breast cancer**
- Androgen receptor- **Sperm count & motility**
- Thyroid receptor - **Thyroid cell proliferation**
- Glucocorticoid receptor - **Adipogenesis**
- GPR 30 - **Insulin resistance**
- Transcription factor - PPAR,C/EBPs, and Nrf2

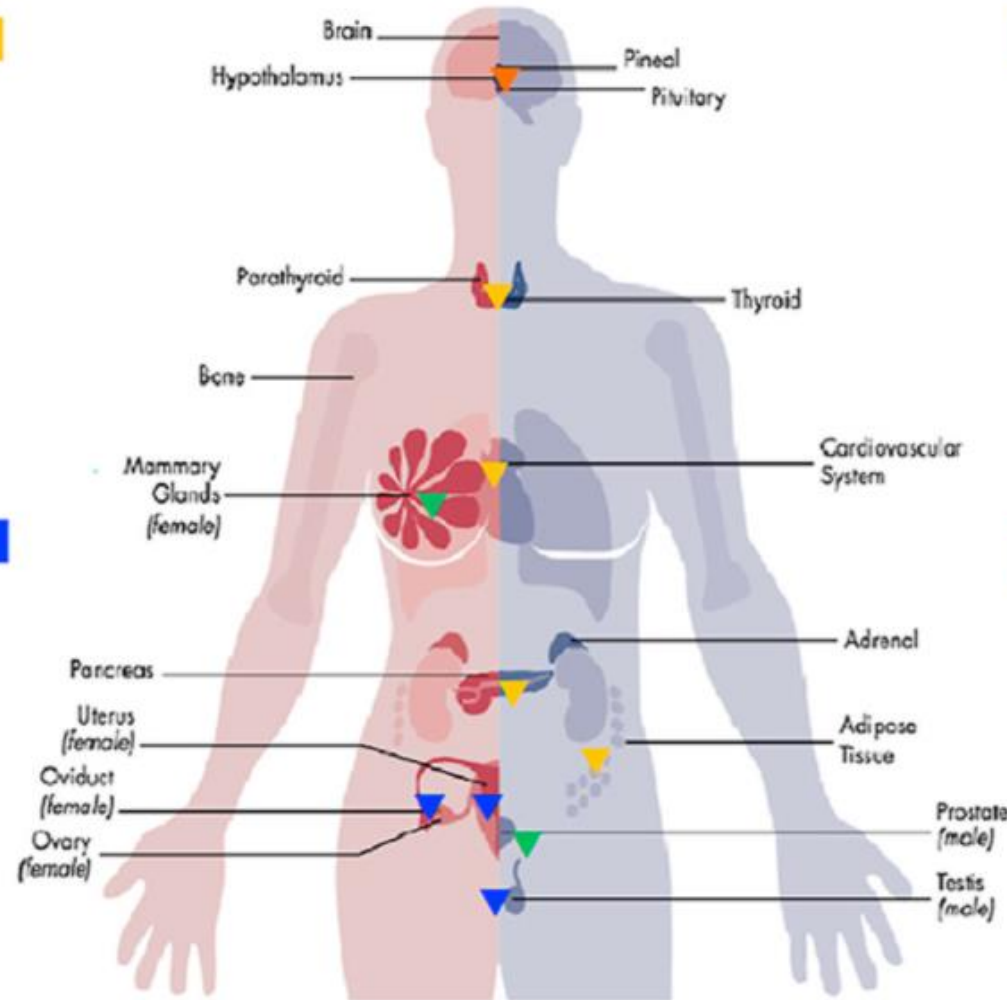
# Effects of BPA in Humans

## Metabolic alterations

- Overweight and obesity
- Fat tissue dysfunction
- Increase of body fat mass
- Hyperglycemia
- Insulin resistance
- Type 2 diabetes mellitus
- Thyroid dysregulation
- Hypertension
- Coronary heart disease

## Reproductive disorders

- Hormonal alterations
- Precocious puberty
- Fetal growth restriction
- Preterm births and abortions
- Decreased fertility
- Ovarian and uterine hypertrophy
- Premature ovarian failure
- Reduced semen quality



## Neurological disorders

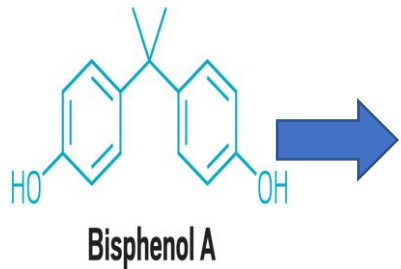
- Psychomotor and mental development alterations
- Reduced cognitive ability
- Depression and anxiety
- Internalizing and externalizing behavior alterations
- Reduction of sexually dimorphic behavior

## Endocrine Disorders

- Uterine leiomyoma
- Advanced endometriosis
- Malignant endometrial hyperplasia
- Endometrial, breast and prostate cancer

Modified from Gore et al., 2015.

# Indirect Exposure Effects of Bisphenol A



Epimutations  
in germ cell



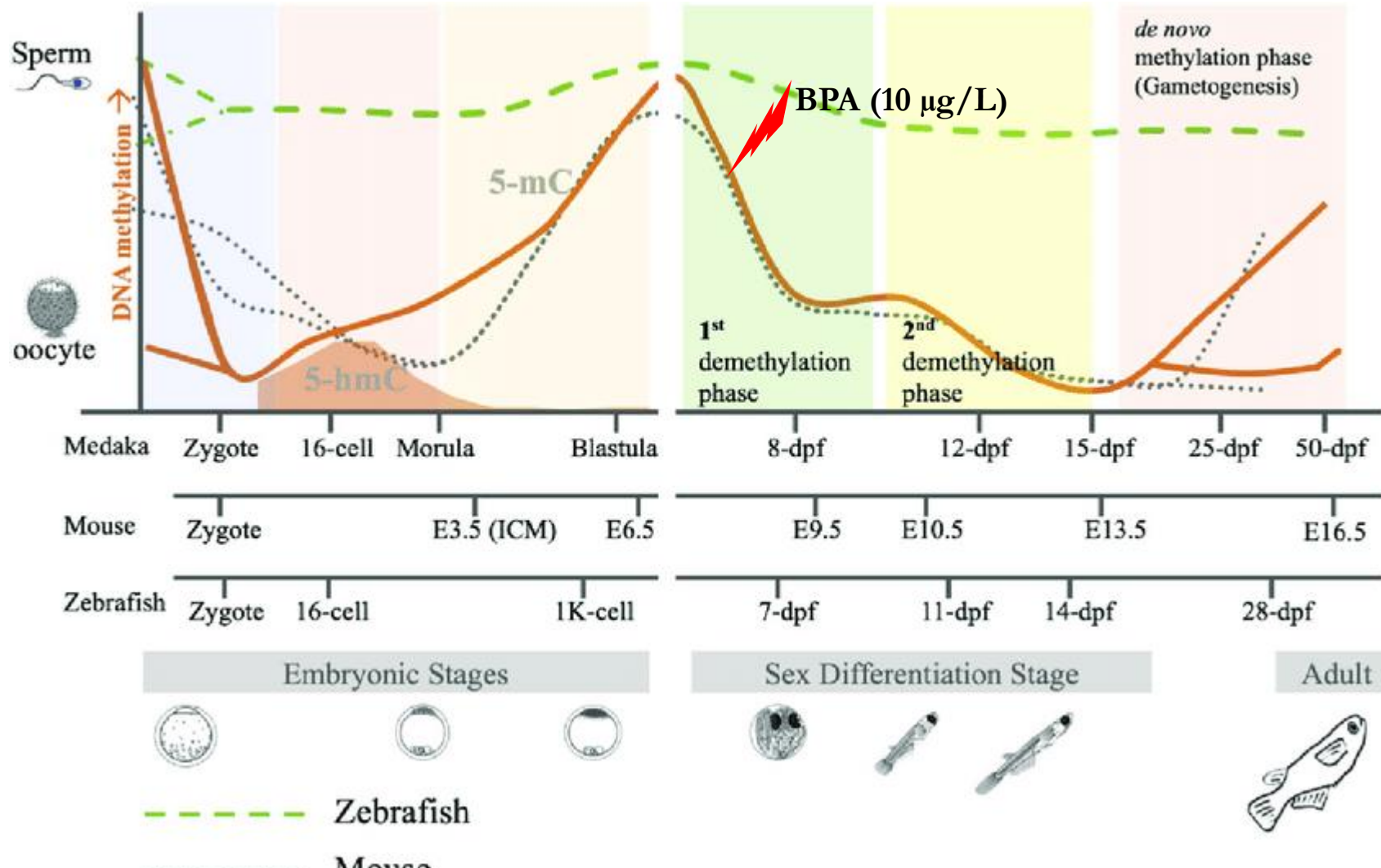
Ancestral Exposure

Inherited effects in absence of BPA  
in grandchildren generation

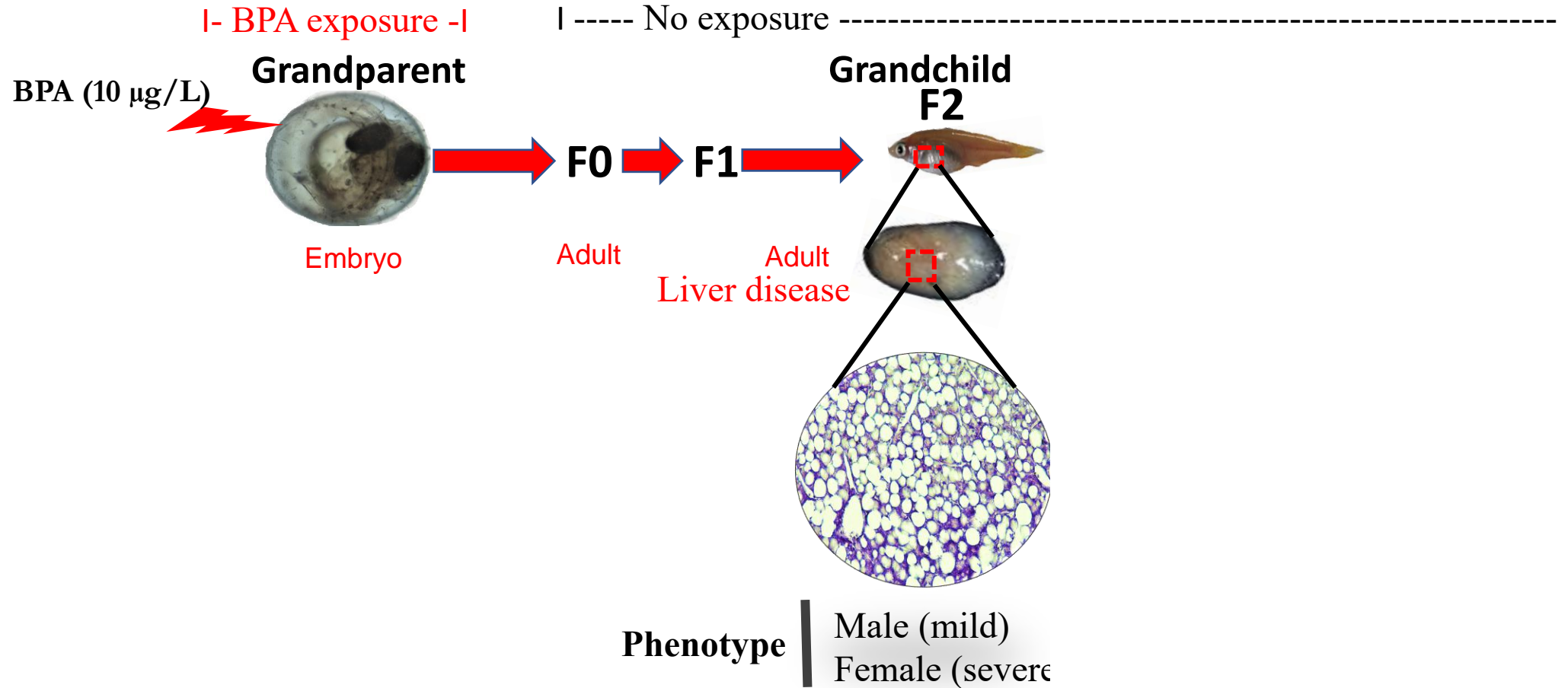
- Metabolic disorder (Obesity)
- Reproductive disorder
- Neurological disorder
- Hormonal defect
- Congenital disorder

- Cellular, molecular mechanisms in both germ line and liver?
- Transmission pattern across the generation?
- Germline transmission of exposure effects?
- Sex specific, Allele specific, Parent of origin specific?
- Health risks for future generations?

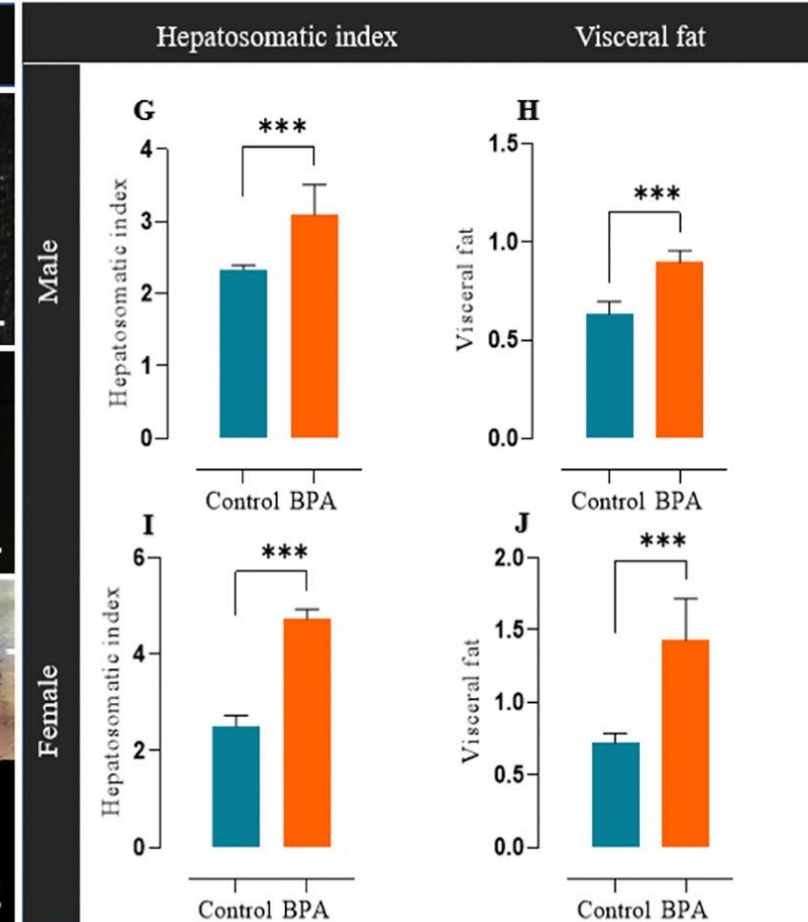
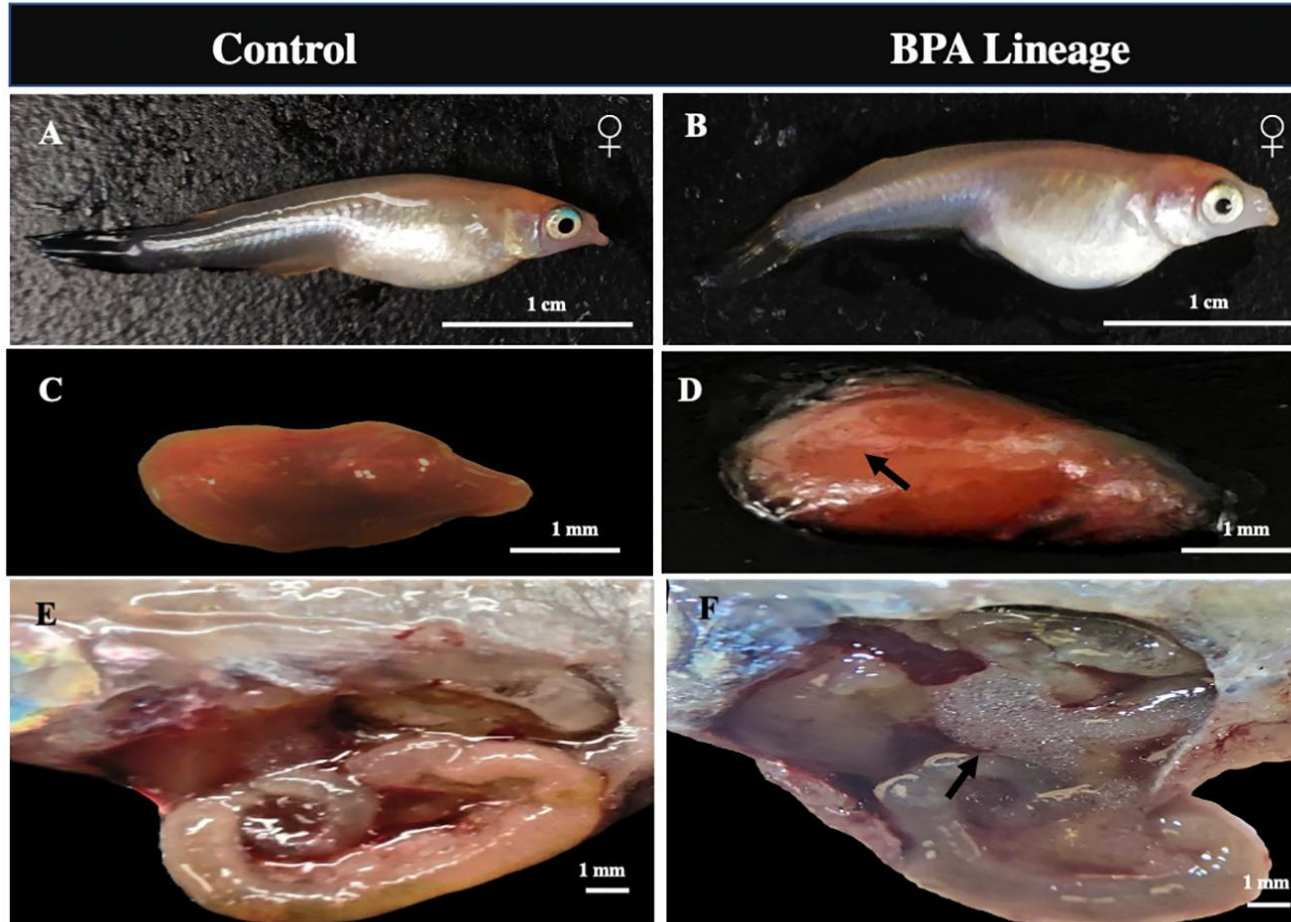
# Exposure window



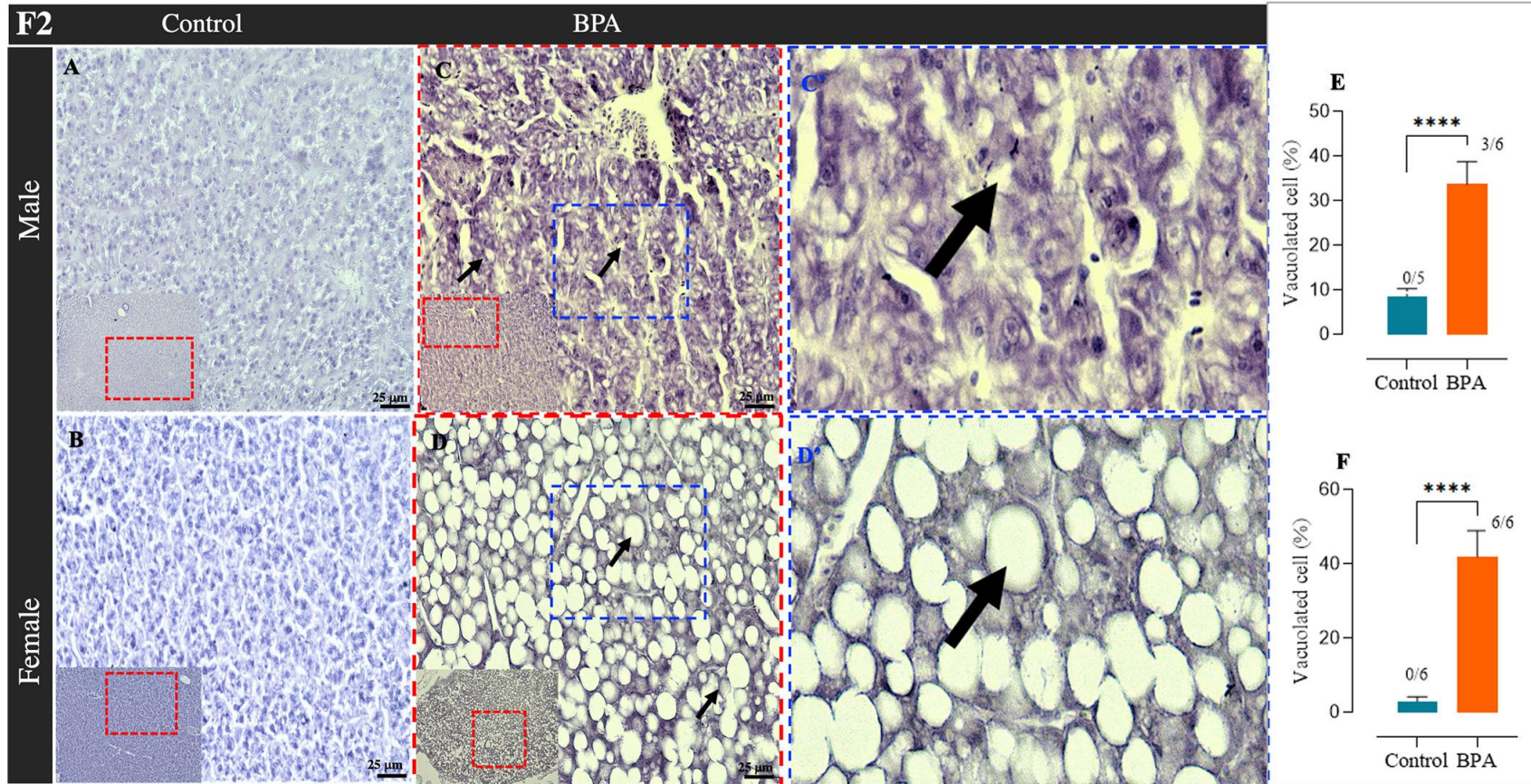
# Graphical Abstract



# Results



# Results

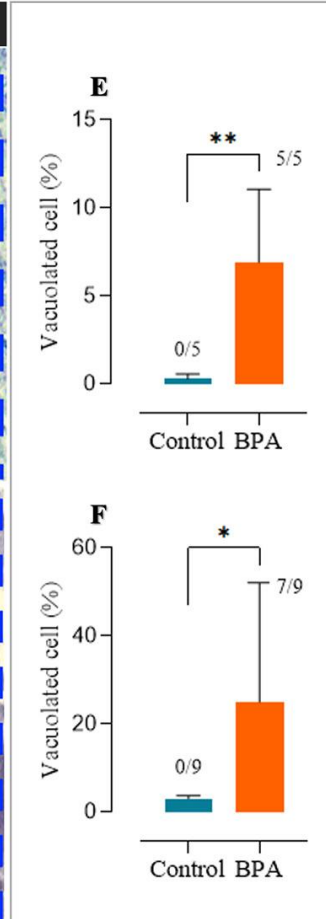
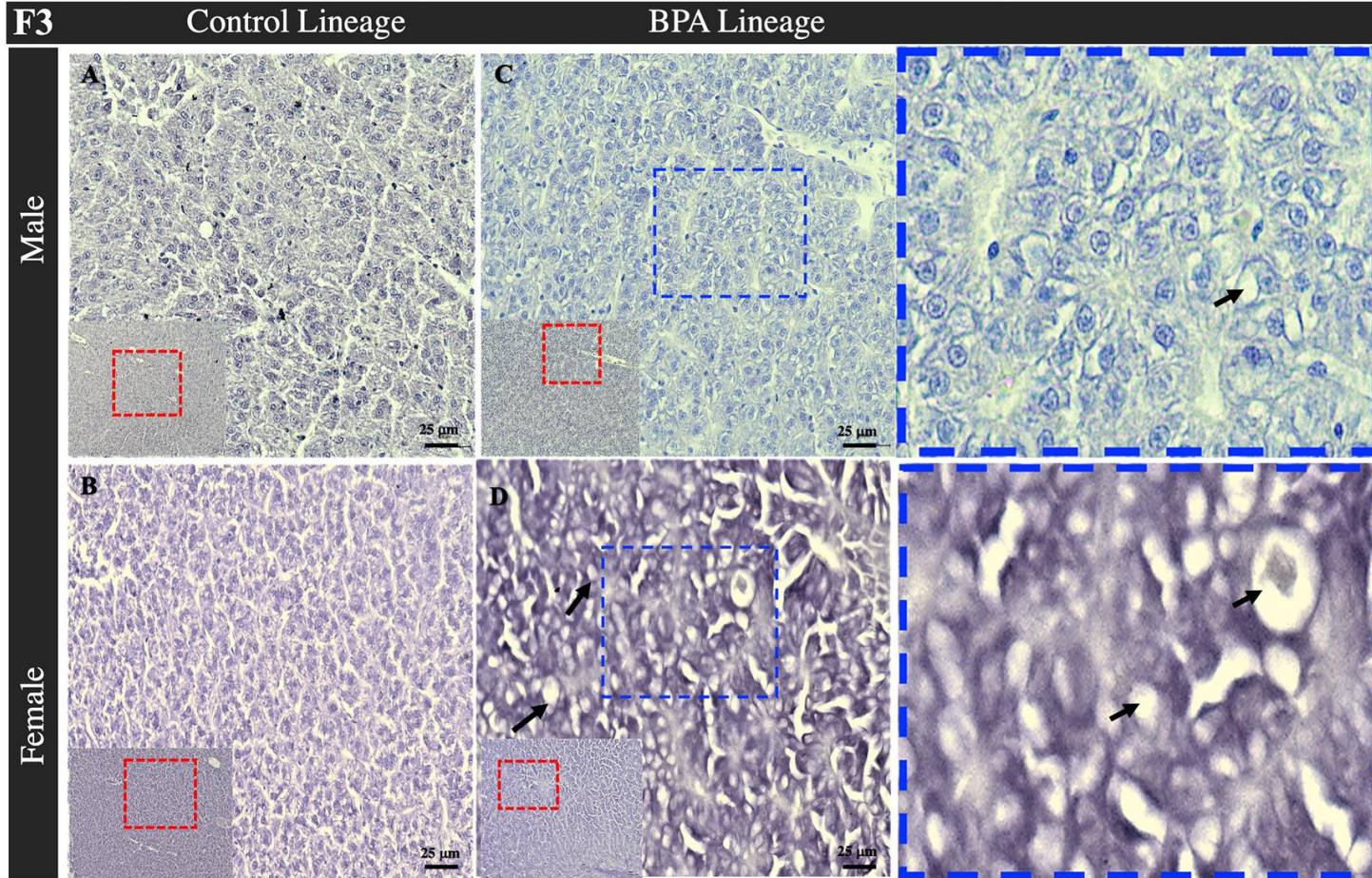


## Observations

- Macrovesicular steatosis-**Female**
- Microvesicular steatosis-**Male**
- Severity – Significantly higher in **female**
- Prevalence – High in **female**



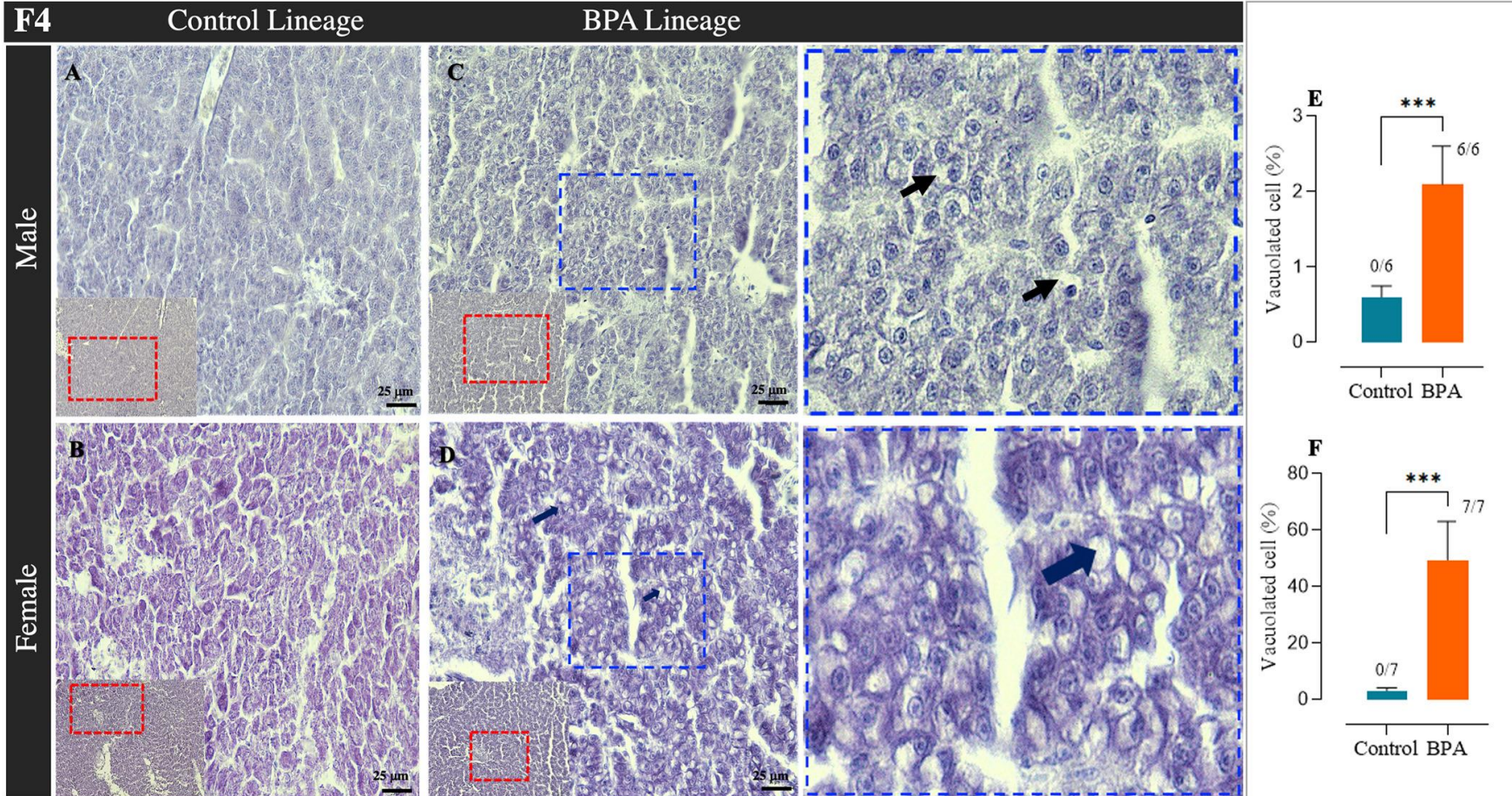
# Results



## Observation

- Microvesicular steatosis-**Female**
- Mild phenotype -**Male**
- Severity- Significantly higher in **female**

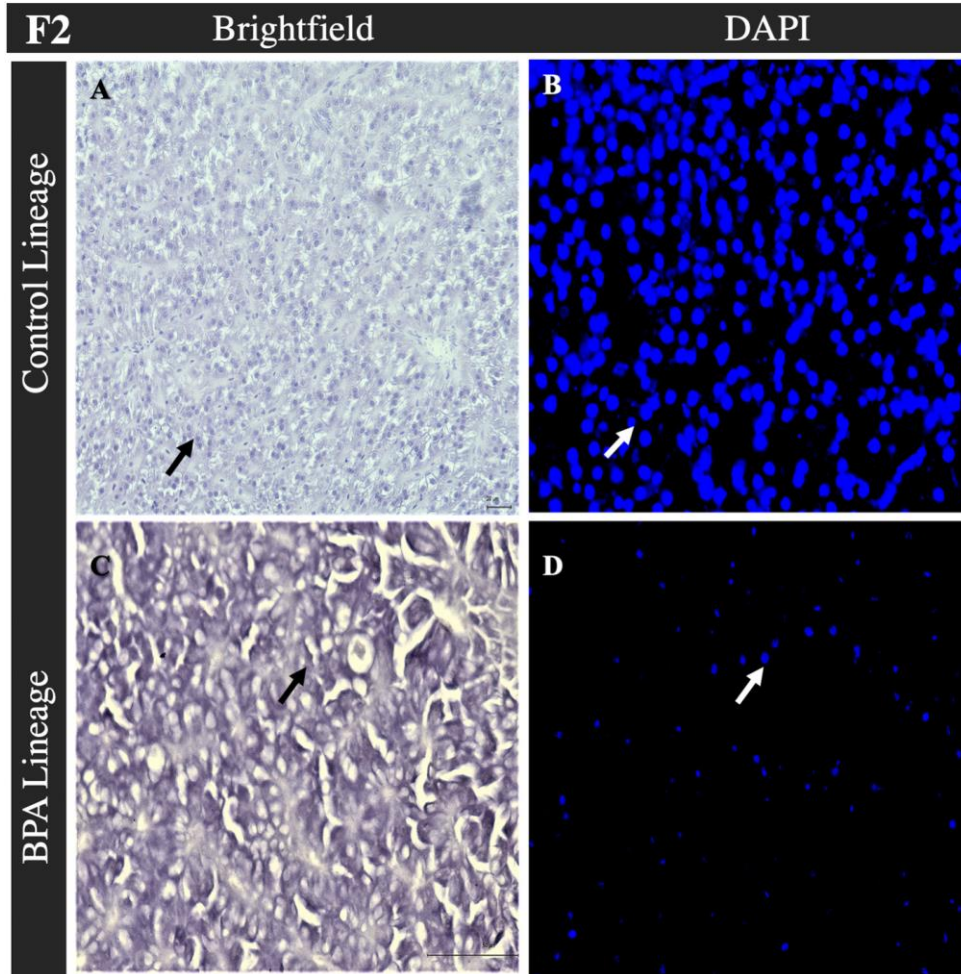
# Results



## Observation

- Microvesicular steatosis- **Female**
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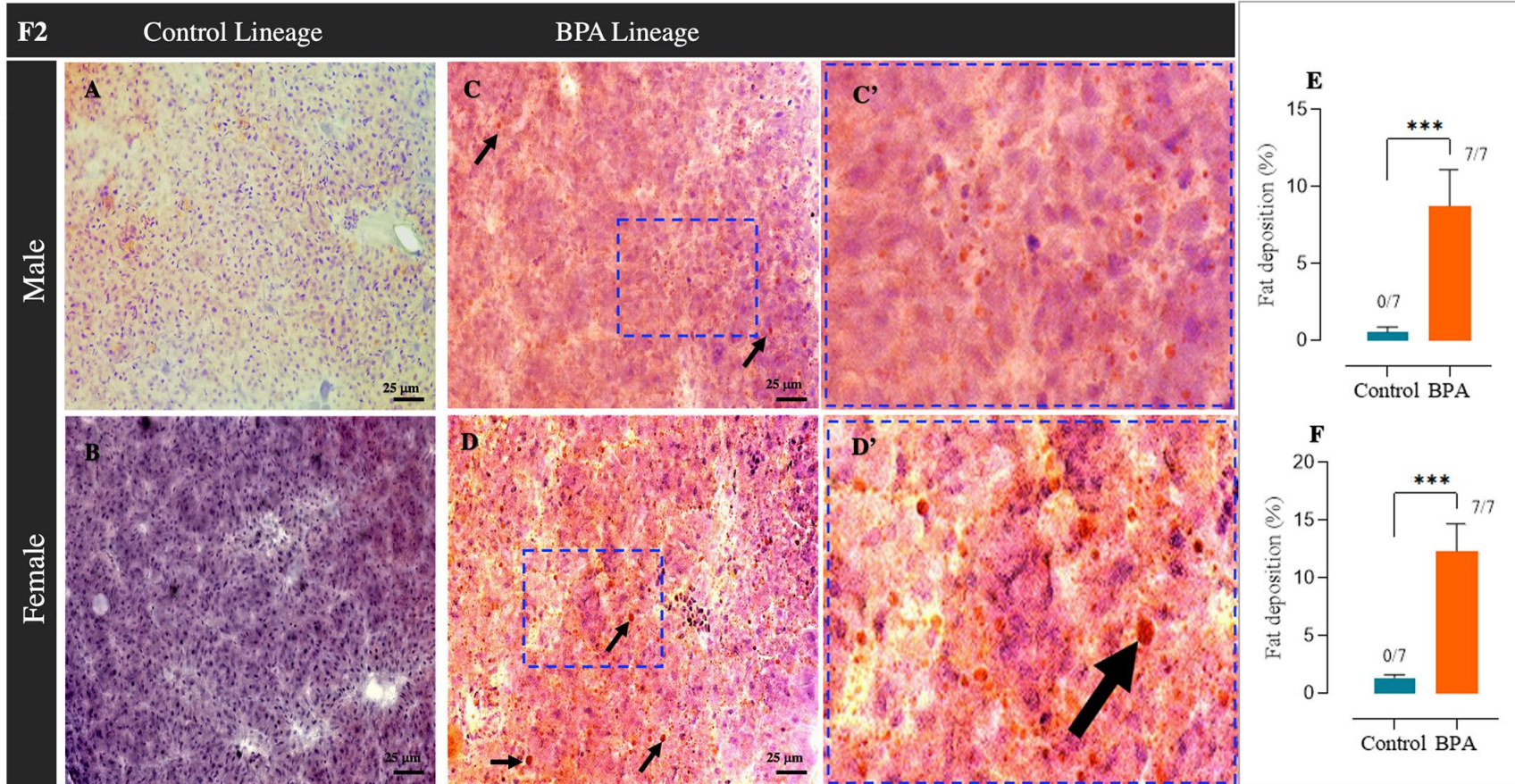
# Results



## Observation

- **High DAPI** signal found in **control liver**
- **Less DAPI** signal observed in **female BPA lineage** fish showing abnormality in nuclear content

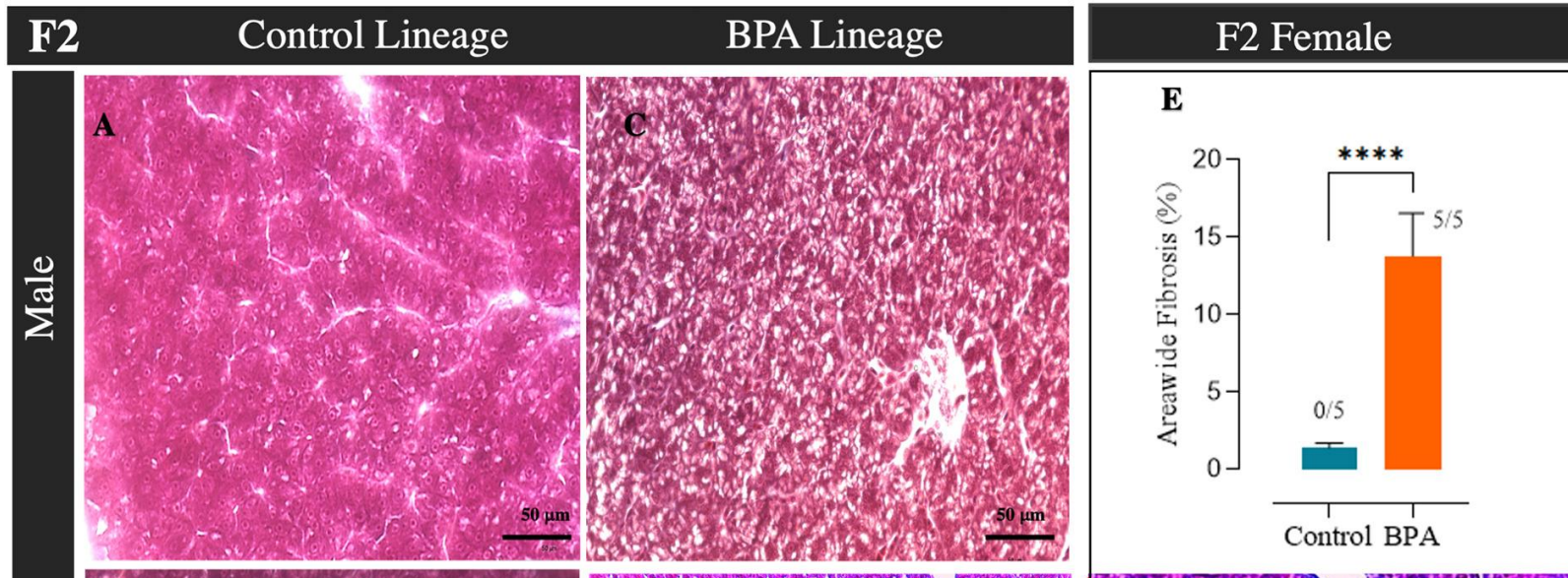
# Results



## Observations

- Fat droplet (orange color) – Significantly higher in **females**
- Percentage of fat deposition in **males** is 8% but in **females** is 13%

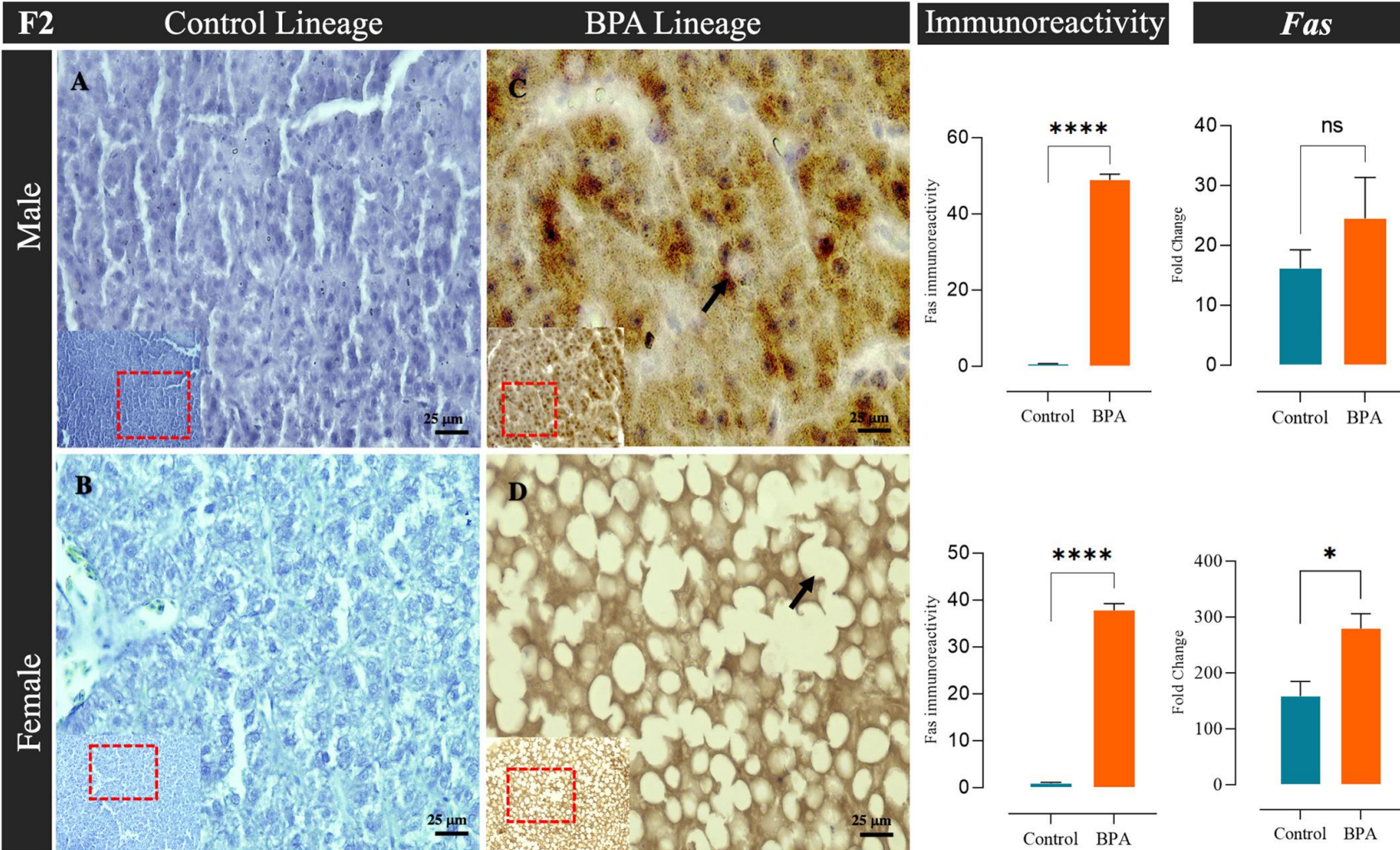
# Results



## Observations

- Collagen deposition identified in female liver from BPA lineage
- **Showing transgenerational NAFLD is progressive to NASH in female**

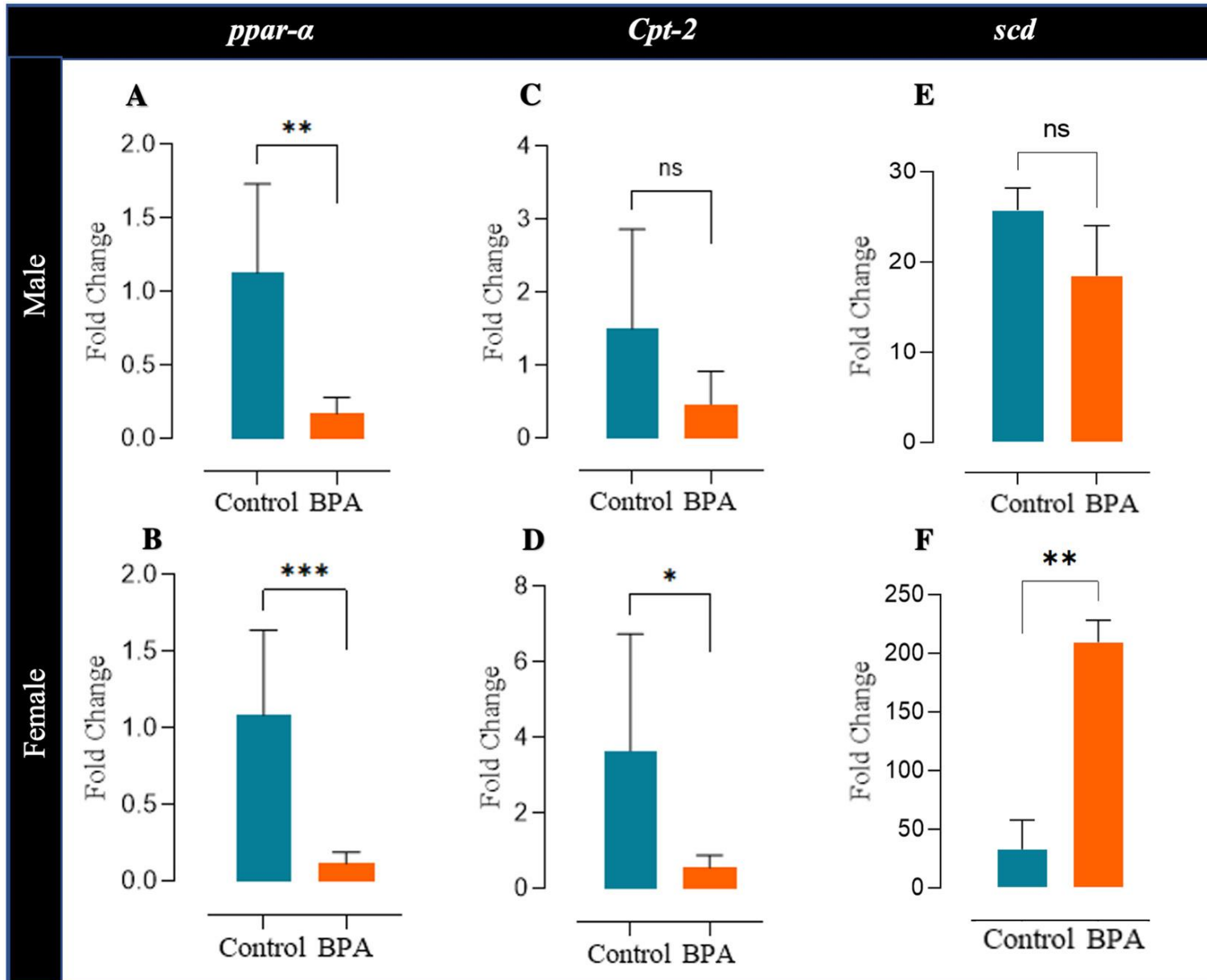
# Results



## Observation

- Fas positive signal found indicating **apoptosis**

# Results



## Observations

- **Lipolytic gene** (*ppar-α* and *cpt2*) were significantly **downregulated** and **lipogenic gene** (*scd1*) expression was **upregulated**

## Ongoing work...

- Finding BPA-specific epigenetic marks on germ cells and their passage to somatic cells (Liver) in subsequent generations.
- Finding a mitigation strategy for removal of epigenetic effects in liver and germline before the onset of phenotype





Thank You for your attention!

Questions???

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([R01ES032452](#), [R21ES027123](#), [R21HD098621](#))