Is there a genetic basis for pelvic organ prolapse?

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Identification of the Genetic Basis of Sow Pelvic Organ Prolapse

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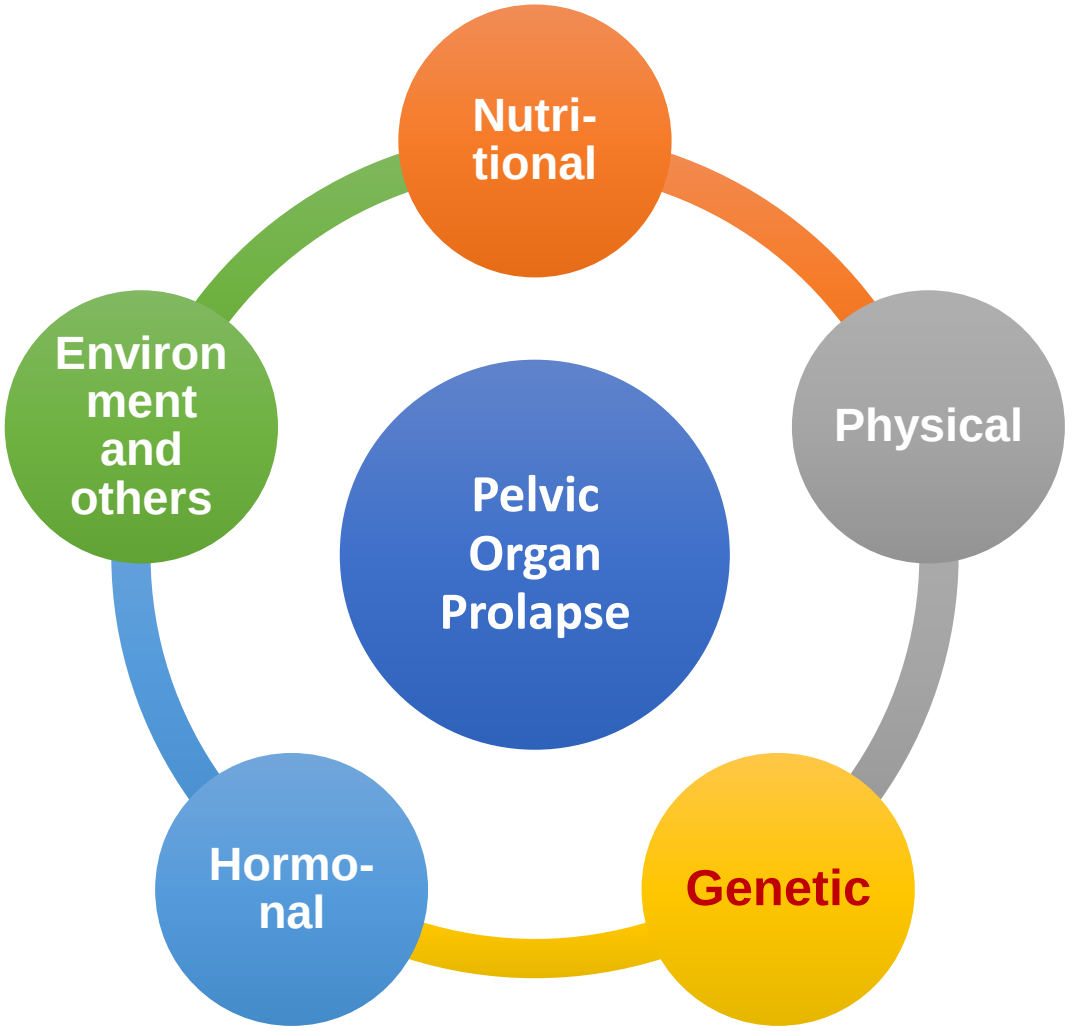
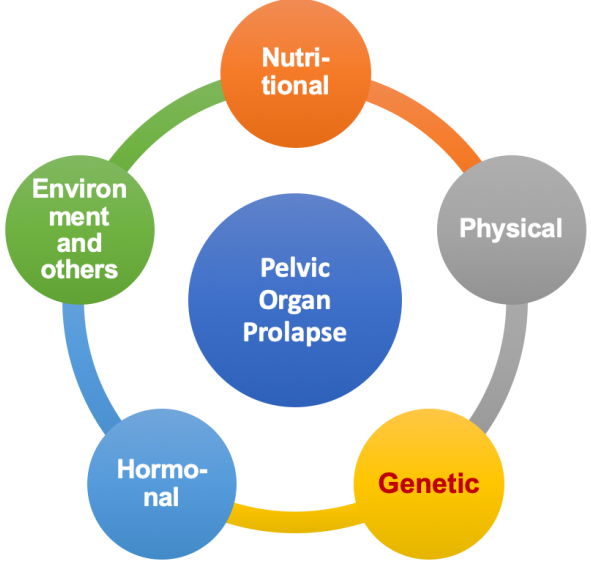
Background

- Pelvic Organ Prolapse (POP) is characterized by loss of connective tissue support, leading to displacement of pelvic organs.
- POP can present itself in various forms, i.e., vaginal, rectal, or uterine prolapse.
- POP is a significant welfare and production issue due to its rising incidence.
- Multifactorial in nature; root cause of POP is still not known



Motivation and Objectives



Heritability estimates for sow prolapse

China Supakorn [a], Marcie I. Christianson [a], Jeremy Howard [b], Kent A. Gray [b], Kenneth J. Stalder [a]

Late-Breaking: Heritability and Validation of Sow Uterine Prolapse in the United States.

Tomas Stevens[1], Jenelle Dunkelberger[2], Egbert Knol[1], [1]*Topigs Norsvin*, [2]*Topigs Norsvin USA*

Pedigree based h^2 Estimates

0.03 ± 0.01 (Linear Model)

0.003 ± 0.01 (Threshold Model)

Heritability of sow uterine prolapse in a commercial maternal line

J. R. Dunkelberger,[1,2] PhD; T. Stevens,[1] MSc; and E. F. Knol,[1] PhD.
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Pedigree based h^2 Estimates

0.15 ± 0.02 (Linear Model)

0.22 ± 0.02 (Logit Model)

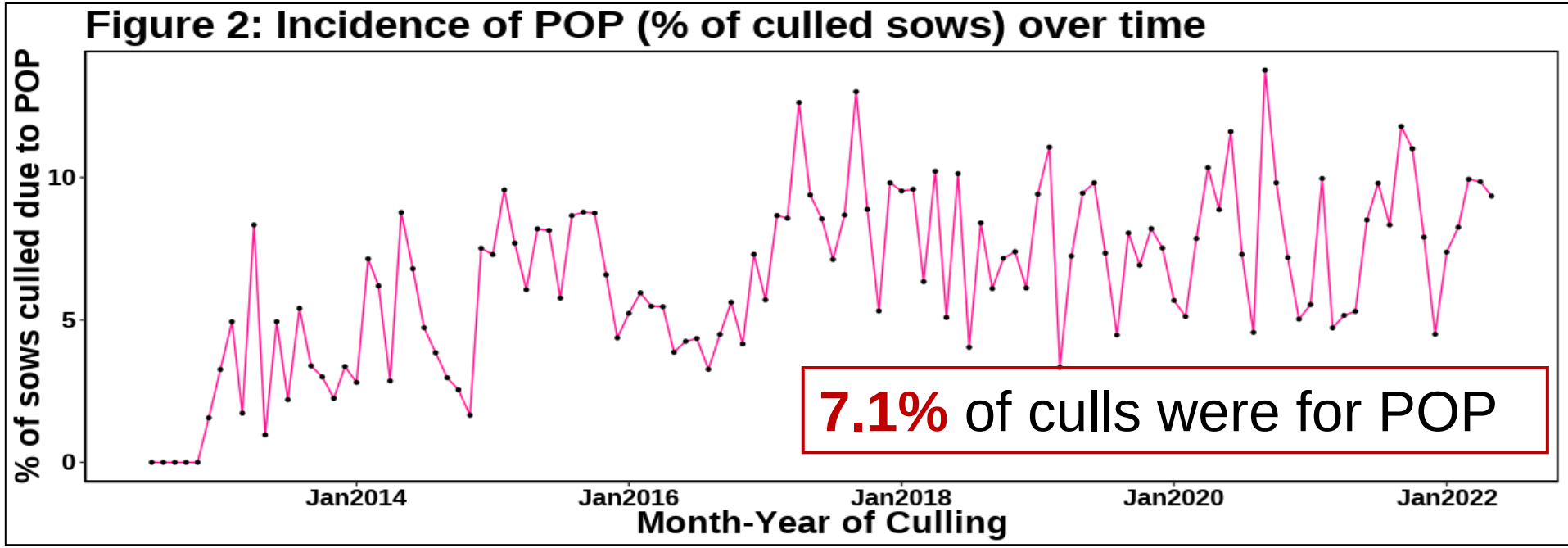
OBJECTIVES

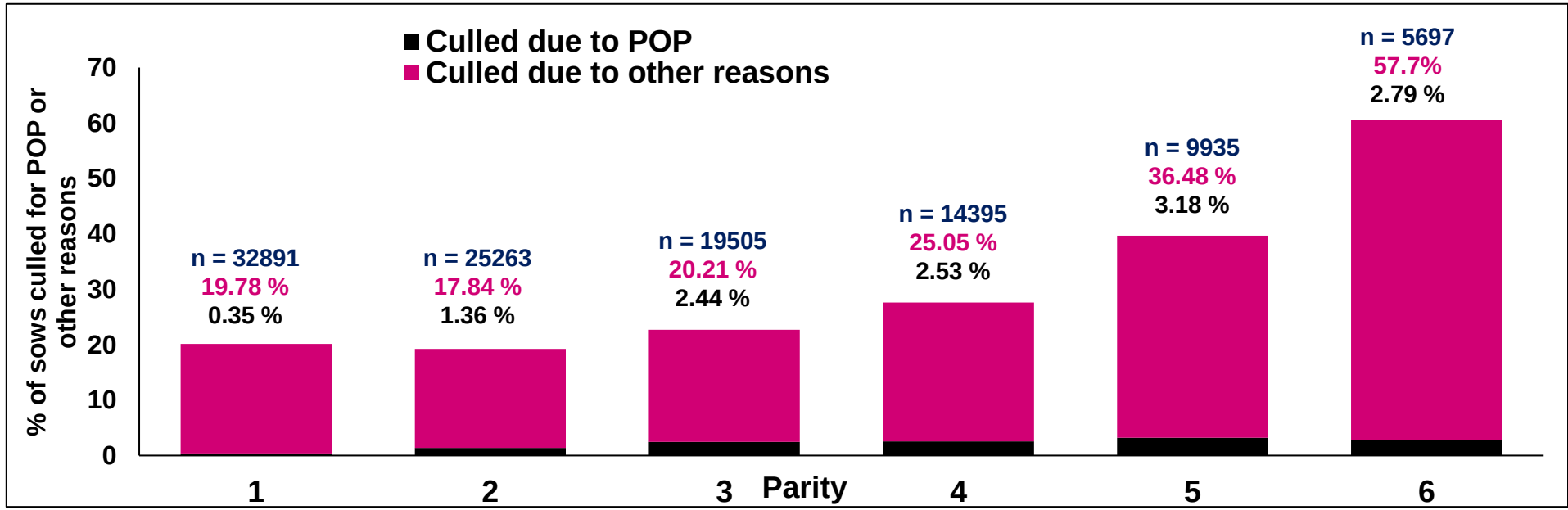
Investigate the role of genetics in susceptibility to POP using high-density SNP genotypes.	Identify genomics regions associated with susceptibility to POP and perform candidate gene analyses

Materials and Methods

- Data on 30,429 Topigs Norsvin purebred sows from two US multiplier farms, collected from 2012 to 2022.
- Only records on genotyped sows from parities 2 to 6 (n = 14,186) were used for analysis.

- Across parity analysis:
  1 = culled for POP
  0 = culled for other reason
- By parity analyses:
  1 = culled for POP
  0 = not culled or
  culled for other reason





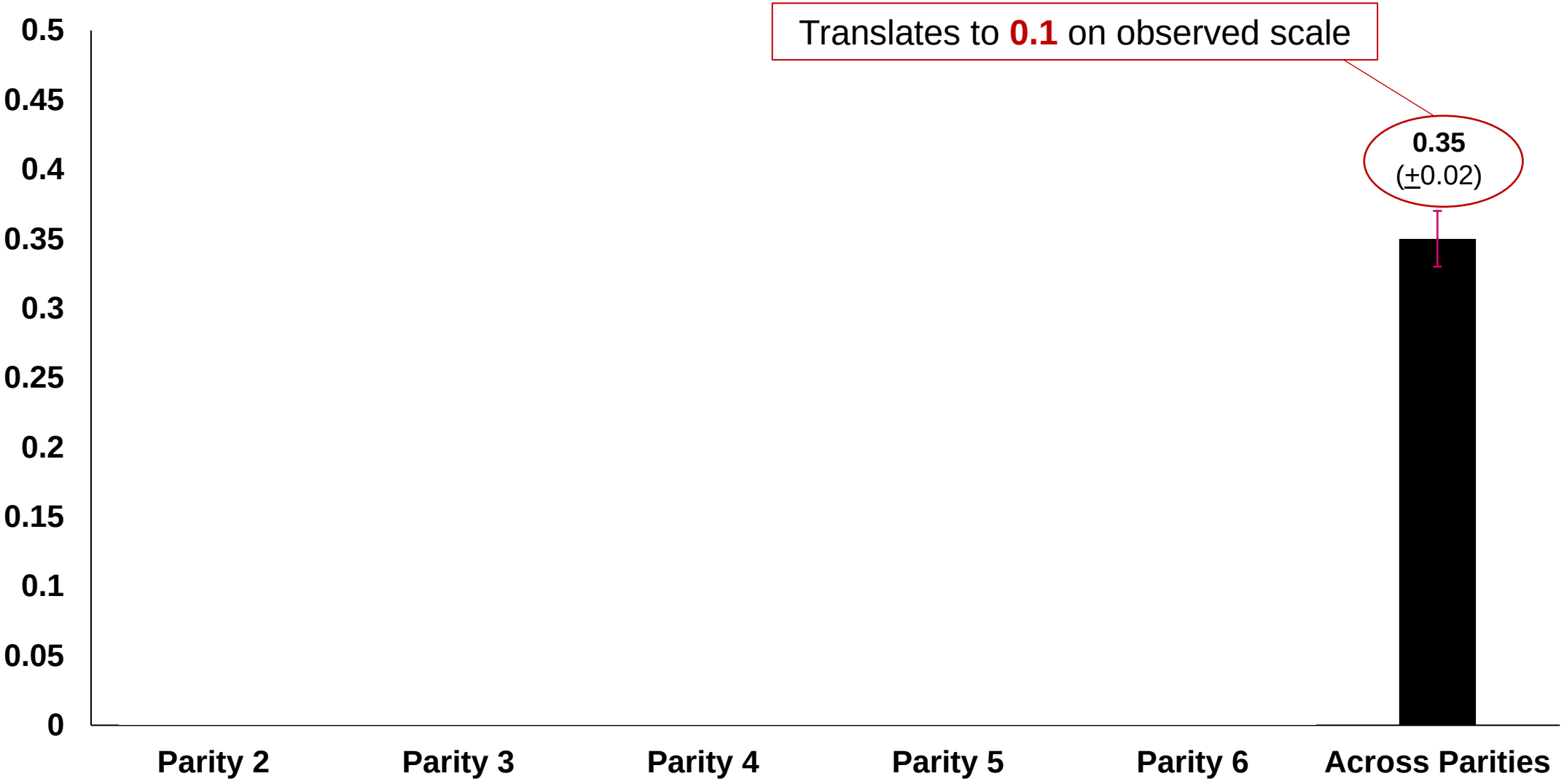
Materials and Methods: Statistical Analyses

- A logit model was used to analyze each binary trait using AsReml 4.1 (Gilmour et al., 2015)

$$\text{Logit (POP)} = \mu + \underbrace{\text{Parity + HYS\_Insemination}}_{\textit{fixed effects}} + \underbrace{\text{Animal Genetics + e}}_{\textit{random effects}}$$

- Genetic Correlations were estimated using bivariate linear models using Bayes-C0 in JWAS (Hao et al., 2018)

Results: Estimates of Heritability (logit scale)



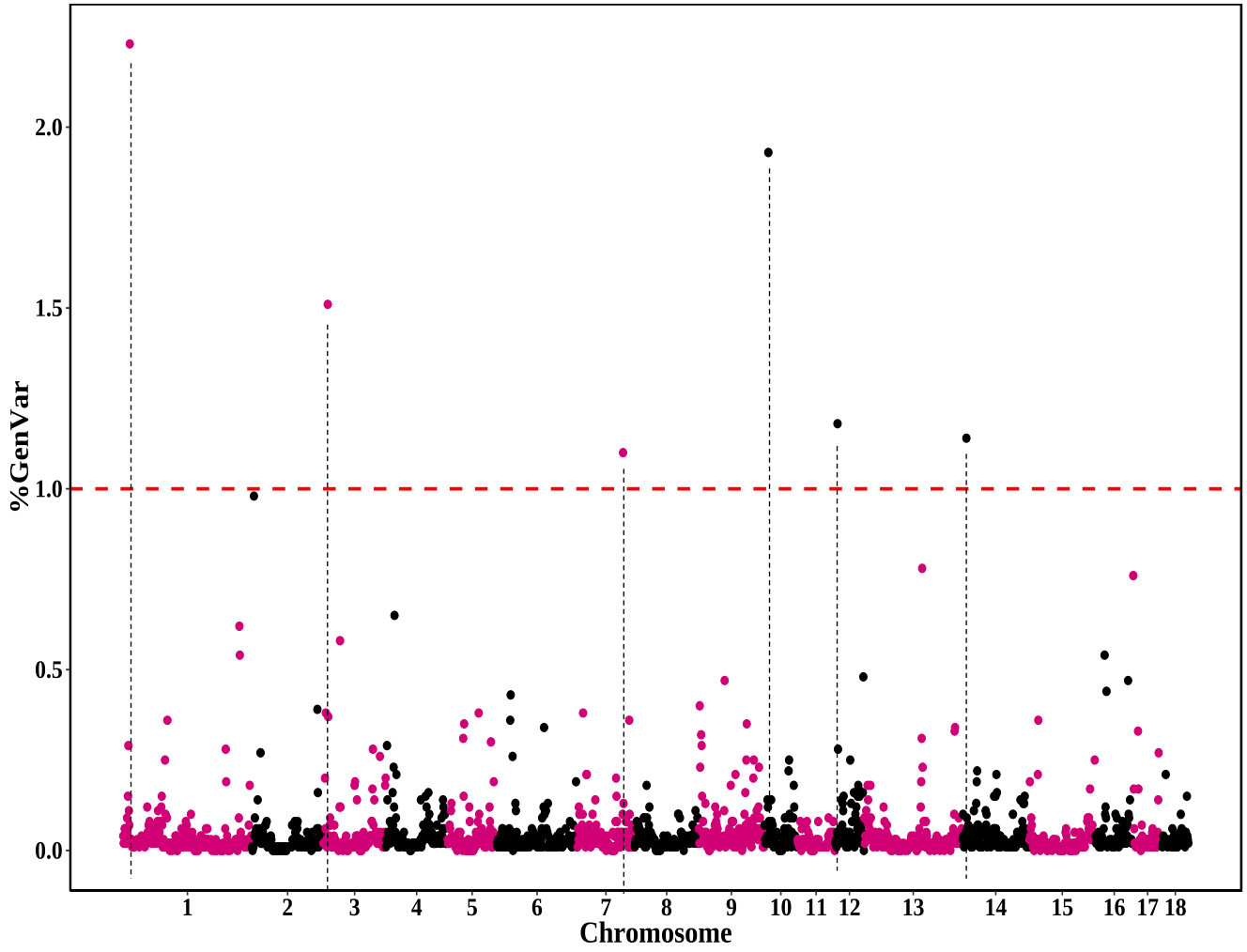
Estimates of Genetic Correlations

Mean \ HPD (Lower – Upper)	Parity 2	Parity 3	Parity 4	Parity 5	Parity 6
Parity 2		0.50 – 0.85	-0.01 – 0.83	0.15 – 0.83	-0.05 – 0.85
Parity 3	0.71		0.37 – 0.85	0.14 – 0.82	-0.36 – 0.70
Parity 4	0.54	0.65		0.48 – 0.87	-0.23 – 0.78
Parity 5	0.50	0.56	0.69		-0.31 – 0.76
Parity 6	0.45	0.20	0.35	0.28	

95% HPD
Genetic correlations

GWAS using Bayes-B Threshold model in JWAS

Across parity analysis



SSC[1]	Mb window	Across parity analysis % of genetic variance
1	14	2.23
3	9	1.51
7	97	1.10
10	8	1.93
12	5	1.18
14	8	1.14

GWAS across and by-parity analyses

Across parities

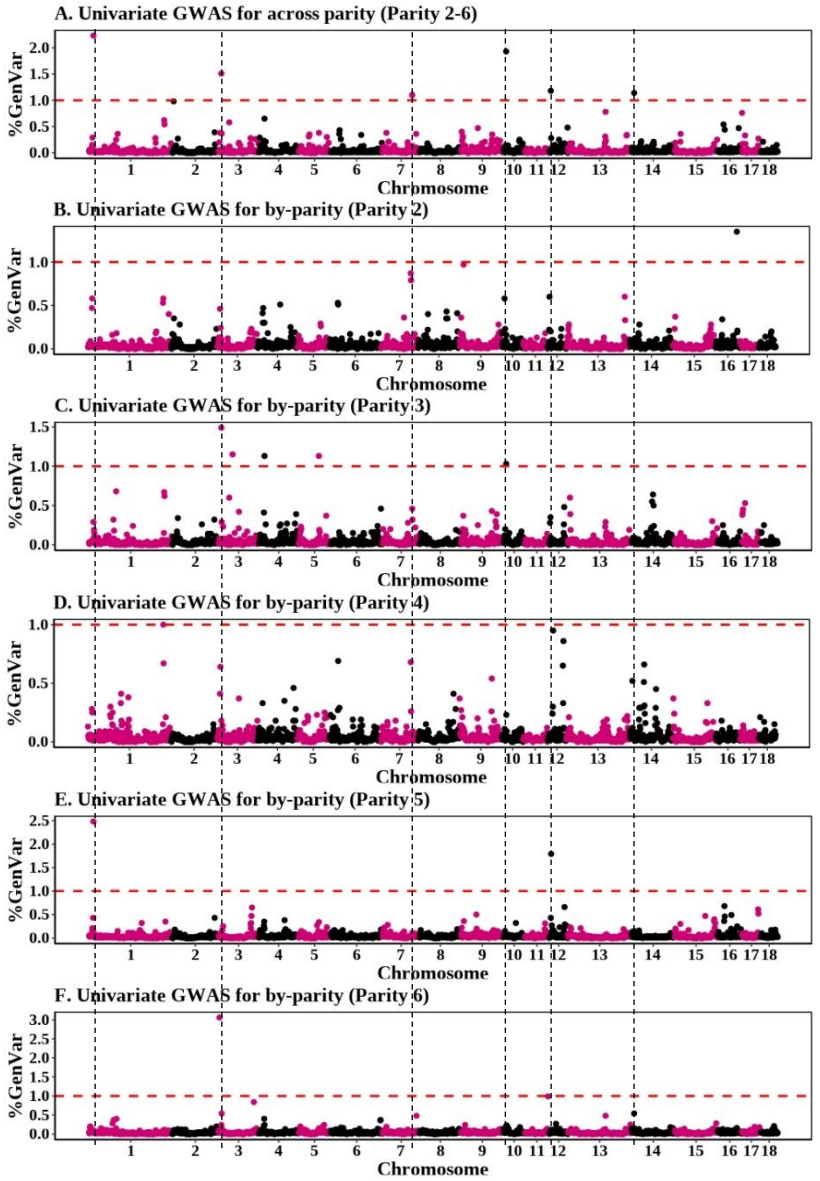
Parity 2

Parity 3

Parity 4

Parity 5

Parity 6

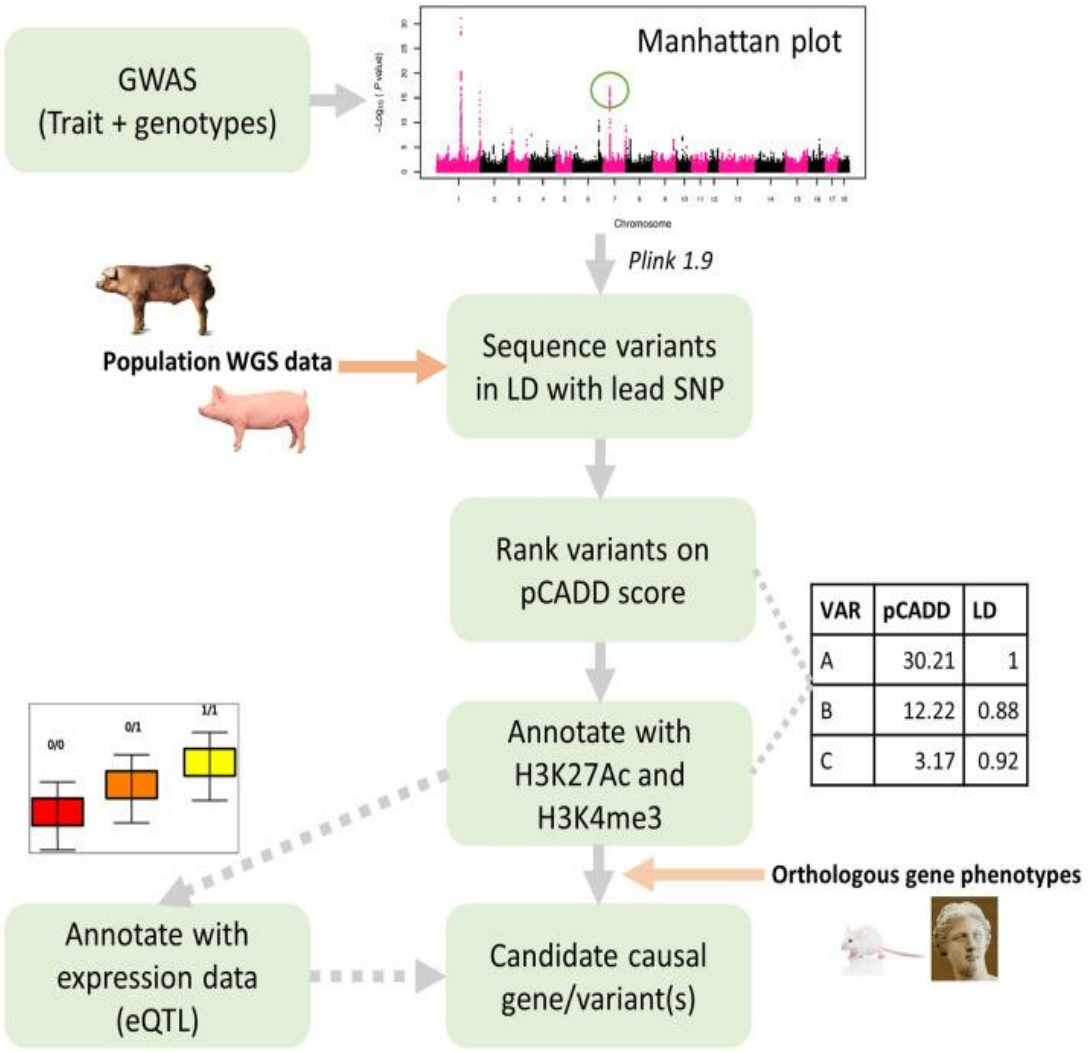


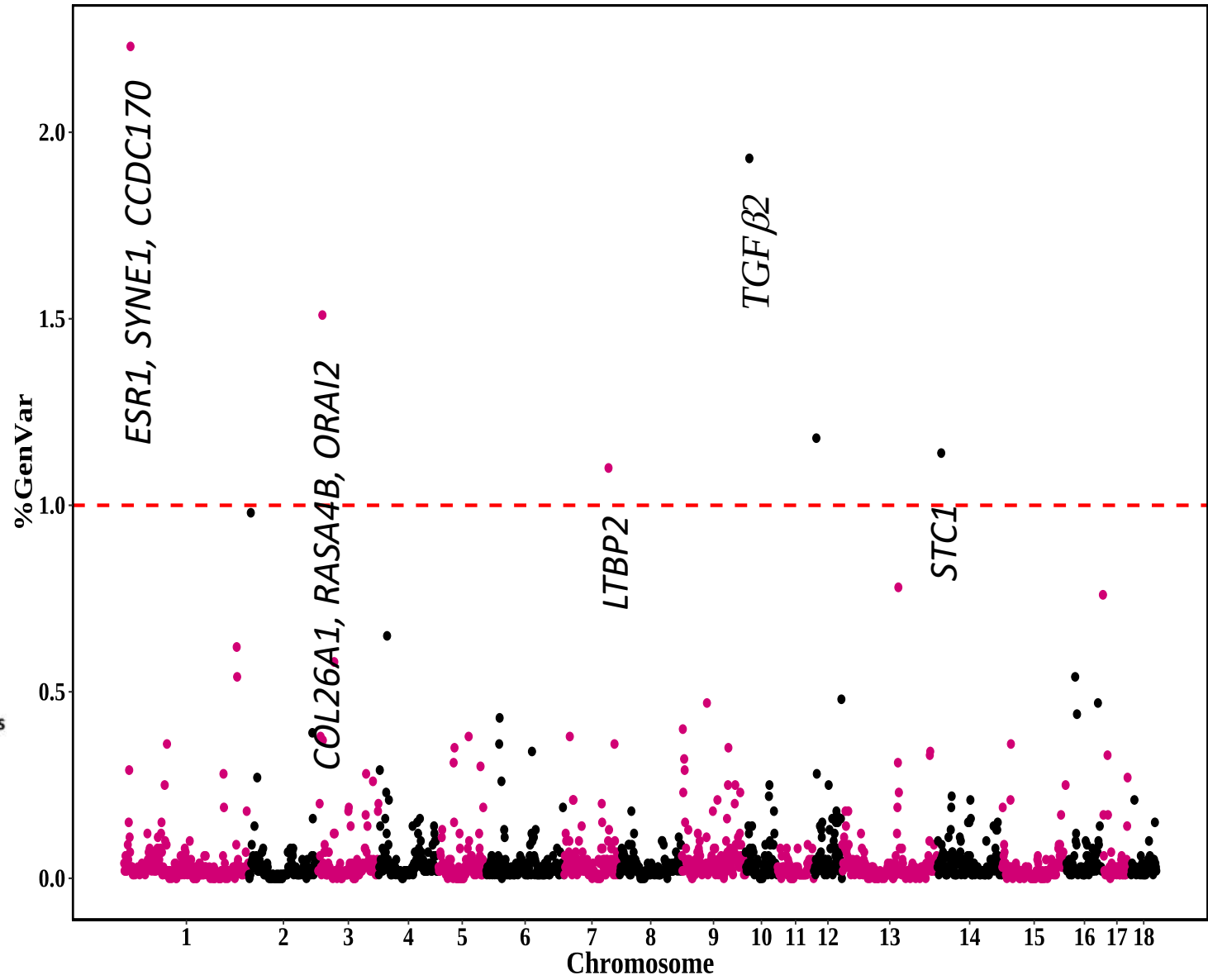
Most genomics regions identified in the across parity analysis also explained explained >0.5% of genetic variance in multiple by-parity analyses.

SSC	Mb window	Across parity analysis % of genetic variance	By parity analyses % variance in window +2 Mb				
			2	3	4	5	6
1	14	2.23	1.15	0.65	0.63	3.23	0.31
3	9	1.51	0.86	1.84	1.14	0.20	1.01
7	97	1.10	1.83	0.88	1.09	0.20	0.18
10	8	1.93	0.99	1.16	0.25	0.21	0.61
12	5	1.18	0.96	0.6	0.27	2.41	0.31
14	8	1.14	0.32	0.27	0.81	0.30	0.91

Functional analyses of identified regions using PCADD

(Derks et al., 2021)



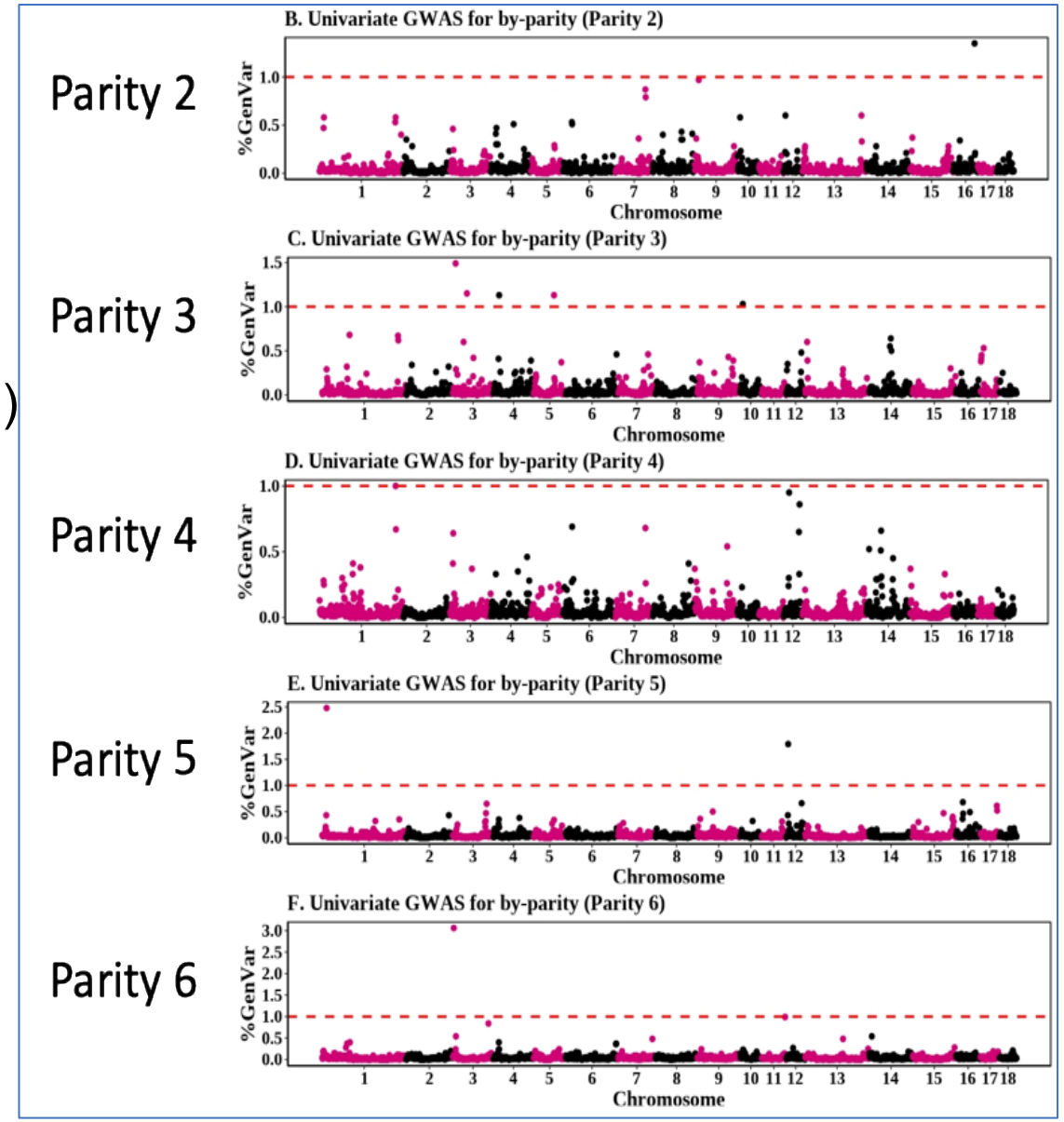


Gene Set Enrichment Analysis (GSEA) (Subramanian et al., 2005)

- 1 Mb windows from the by-parity GWAS combined and ranked on % genetic variance.
- Enriched features identified using pre-ranked GSEA based on 2 libraries:

- **Pig Transcriptome Database** (FDR ≤ 0.05)
  - Upregulation of ovarian tissue in high vs low prolific sows.
  - Downregulation of dedifferentiation in mature adipocytes.

- **GO Database** (FDR ≤ 0.2)
  - Estrogen Receptor Activity
  - IL-1 Receptor Binding
  - Involvement of Mammary Gland Branching in Pregnancy



Conclusions

- Susceptibility to POP is **moderately heritable** in these data
- Moderate to high genetic correlations between parities indicate a **similar genetic basis of POP between parities**
- GWAS revealed several genomic regions to be associated with susceptibility to POP
- By-parity GWAS provided further validation for these genomic regions
- Several **candidate genes** and various **biological processes** and pathways were identified that may contribute to the genetics of susceptibility to POP

Acknowledgements

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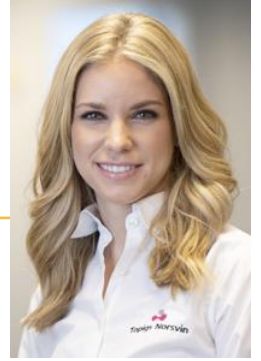

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