Whole-genome sequence quest targeting parent-of-origin effects in pigs

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Introduction

- Imprinting > parent of origin effects

- Genes are expressed in a parent of origin specific manner

- Phenotypic differences between the heterozygous genotypes

- Examples:

  - Callipyge mutation in sheeps – polar overdominance (Cockett et al., 1996)

  - Imprinted QTL with paternal expression on SSC2 (Jeon et al., 1999; Nezer et al., 1999), causative mutation of the paternally expressed QTL > IGF2 gene (Van Laere et al., 2003)

- Additivity and non-additivity

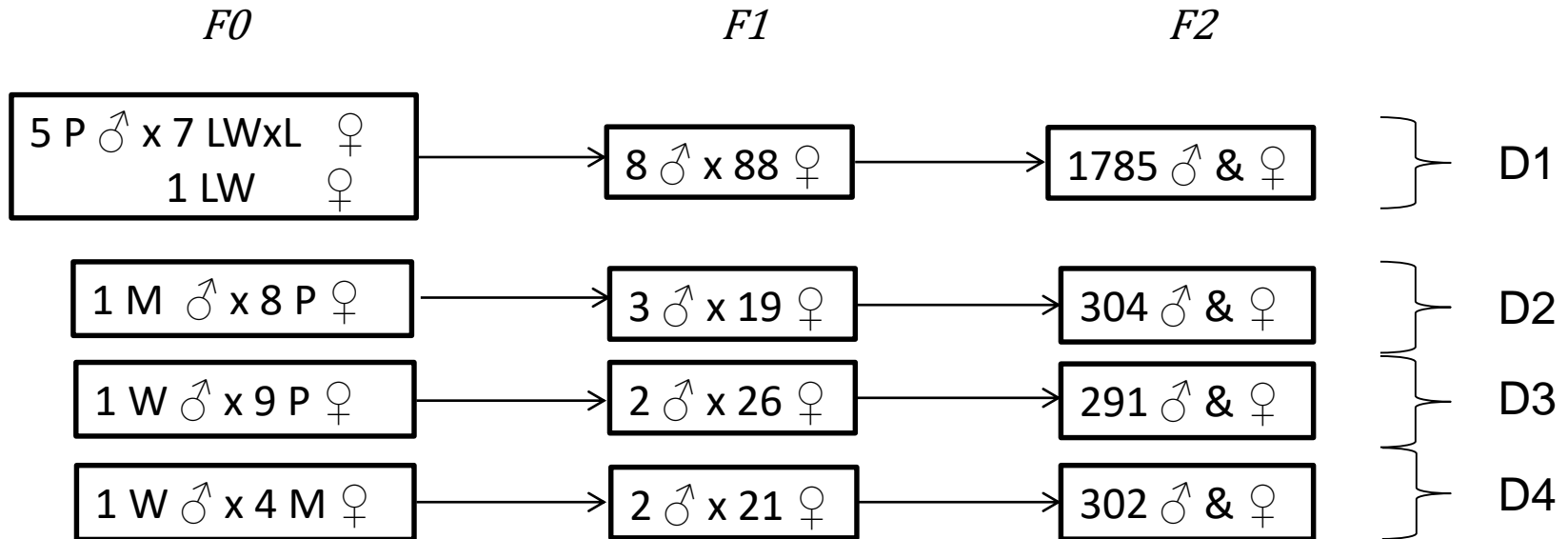 - Nishio and Satoh, 2015, Jiang et al., 2017, Varona et al., 2018

Target parent-of-origin effects for growth and fatness related traits in pig F2

crosses stemming from different founder breeds

Three-generation experimental populations

F0	F1	F2	
5 P ♂ x 7 LWxL ♀ 1 LW ♀	8 ♂ x 88 ♀	1785 ♂ & ♀	D1
1 M ♂ x 8 P ♀	3 ♂ x 19 ♀	304 ♂ & ♀	D2
1 W ♂ x 9 P ♀	2 ♂ x 26 ♀	291 ♂ & ♀	D3
1 W ♂ x 4 M ♀	2 ♂ x 21 ♀	302 ♂ & ♀	D4

Piétrain (**P**), Large White (**LW**), Landrace (**L**) , Meishan (**M**) and Wild Boar (**W**)
♂ - male and ♀ - female

Three-generation experimental populations

➤ Genotyping with PorcineSNP60 BeadChip (Illumina) for F0, F1 and F2

➤ Sequence data: F0 ~ 22x coverage and F1 ~ 1x coverage

➤ Imputation step - Beagle 4.0

➤ Reference genome: SusScrofa11.1

Common all designs	Additionally for D1
Average daily gain (ADG)	Fat thickness neck (SCF)
Backfat thickness (BFT)	Fat thickness middle of the back (BFM)
Meat to fat ratio (MFR)	Fat thickness end of the back (BFTR)
Carcass length (CRCL)	Fat thickness at latissimus dorsi muscle (SCFLD)
	Fat thickness over the loin muscle (SCFLM)
	Belly fatness score (BFS)

Table 1. Phenotypic traits

Variance component

$$y=\mu+g_A+e \tag{Eq. 1}$$
$$y=\mu+g_A+g_D+e \tag{Eq. 2}$$
$$y=\mu+g_A+g_D+g_{imp}+e \tag{Eq. 3}$$

Additive GWAS

{-1,0,0,1}

$$y=\mu+x_{add}b_{add}+g_A+g_D+g_{imp}+e \tag{Eq. 4}$$

Imprinting GWAS

{0,-1,1,0}

$$y=\mu+x_{imp}b_{imp}+g_A+g_D+g_{imp}+e \tag{Eq. 5}$$

Maternal and paternal GWAS

{0,1}

$$y=\mu+x_{mat}b_{mat}+g_A+g_D+g_{imp}+e \tag{Eq. 6}$$

$$y=\mu+x_{pat}b_{pat}+g_A+g_D+g_{imp}+e \tag{Eq. 7}$$

SHAPEIT2 (*O'Connell, Jared, et al. 2014*)
R package 'sommer' (*Covarrubias-Pazaran G. 2016*)

Variance component

$$y = \mu + g_A + e \qquad \text{(Eq. 1)}$$
$$y = \mu + g_A + g_D + e \qquad \text{(Eq. 2)}$$
$$y = \mu + g_A + g_D + g_{imp} + e \qquad \text{(Eq. 3)}$$

Additive GWAS

$\{-1,0,0,1\}$

$$y = \mu + x_{add}b_{add} + g_A + g_D + g_{imp} + e \qquad \text{(Eq. 4)}$$

Imprinting GWAS

$\{0,-1,1,0\}$

$$y = \mu + x_{imp}b_{imp} + g_A + g_D + g_{imp} + e \qquad \text{(Eq. 5)}$$

Maternal and paternal GWAS

$\{0,1\}$

$$y = \mu + x_{mat}b_{mat} + g_A + g_D + g_{imp} + e \qquad \text{(Eq. 6)}$$
$$y = \mu + x_{pat}b_{pat} + g_A + g_D + g_{imp} + e \qquad \text{(Eq. 7)}$$

Using genotype data

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Using sequence data

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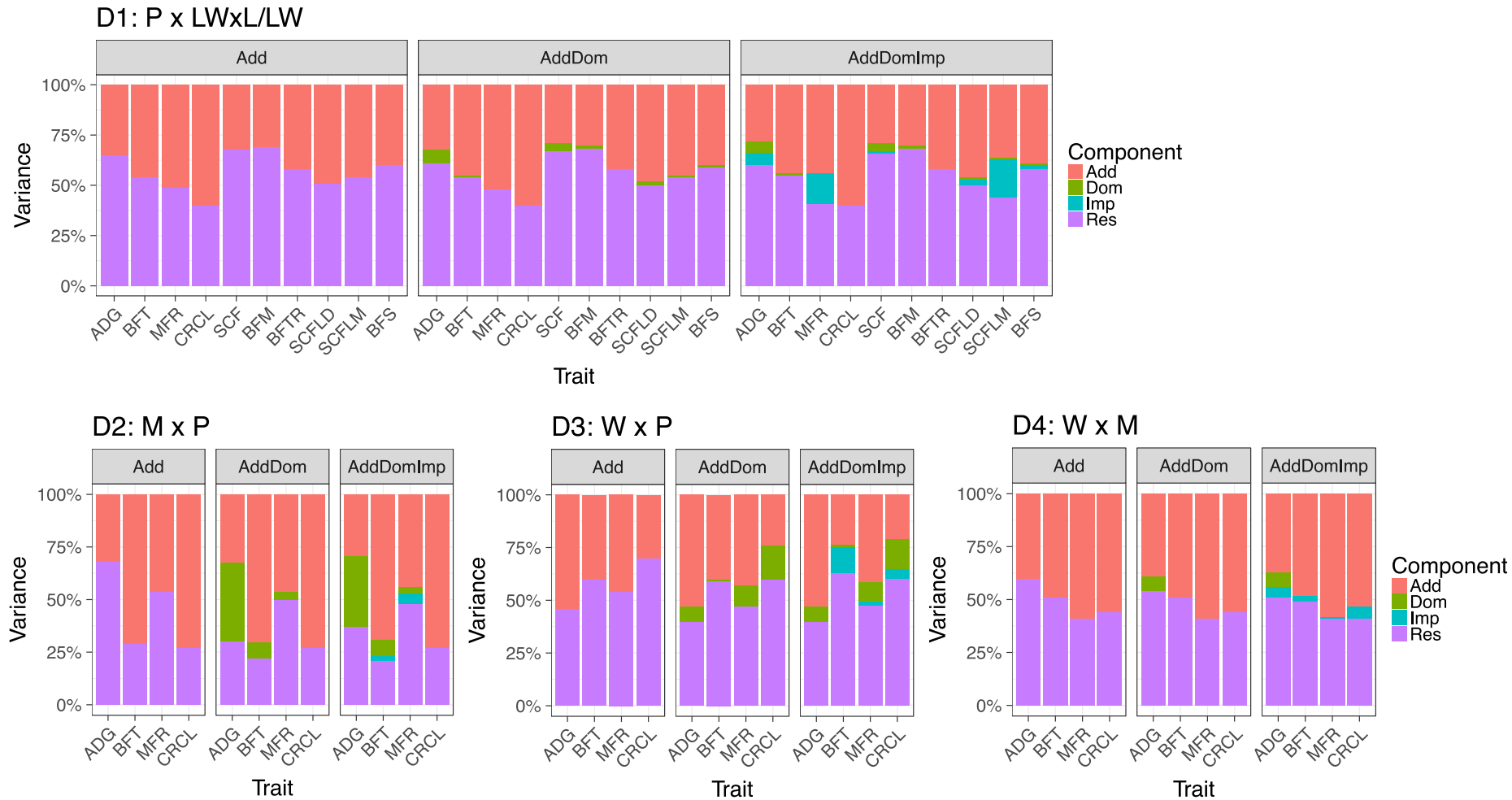
Fig 1. Variance component estimation (genotype data)

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Table 2. Associated regions above genome-wide significance levels for the GWAS models (genotype data)

Cross	Trait	Additive		Imprinting		Maternal		Paternal	
D1	ADG	x	2, 7	-	-	-	-	x	2
	BFT, SCF, BFTR, SCFLD, SCFLM, BFS	x	2	x	2	-	-	x	2
	MFR	x	1, 2	x	2	-	-	x	2
	CRCL	x	7, 17	x	17	x	17	x	17
	BFM	-	-	x	2	-	-	x	2
D2	BFT	x	7	-	-	-	-	x	2
	MFR	-	-	x	2	-	-	x	2
	CRCL	x	7	-	-	x	7	-	-
D3	BFT, MFR	-	-	x	2	-	-	x	2
	CRCL	x	1	-	-	-	-	-	-
D4	ADG, BFT, CRCL	x	7	-	-	x	7	-	-

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D1	ADG	x	2, 7	-	-	-	-	x	2
	BFT, SCF, BFTR, SCFLD, SCFLM, BFS	x	2	x	2	-	-	x	2
	MFR	x	1, 2	x	2	-	-	x	2
	CRCL	x	7, 17	x	17	x	17	x	17
	BFM	-	-	x	2	-	-	x	2
D2	BFT	x	7	-	-	-	-	x	2
	MFR	-	-	x	2	-	-	x	2
	CRCL	x	7	-	-	x	7	-	-
D3	BFT, MFR	-	-	x	2	-	-	x	2
	CRCL	x	1	-	-	-	-	-	-
D4	ADG, BFT, CRCL	x	7	-	-	x	7	-	-

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	BFT, SCF, BFTR, SCFLD, SCFLM, BFS	x	2	x	2	-	-	x	2
	MFR	x	1, 2	x	2	-	-	x	2
	CRCL	x	7, 17	x	17	x	17	x	17
	BFM	-	-	x	2	-	-	x	2
D2	BFT	x	7	-	-	-	-	x	2
	MFR	-	-	x	2	-	-	x	2
	CRCL	x	7	-	-	x	7	-	-
D3	BFT, MFR	-	-	x	2	-	-	x	2
	CRCL	x	1	-	-	-	-	-	-
D4	ADG, BFT, CRCL	x	7	-	-	x	7	-	-

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D1	ADG	x	2, 7	-	-	-	-	x	2
	BFT, SCF, BFTR, SCFLD, SCFLM, BFS	x	2	x	2	-	-	x	2
	MFR	x	1, 2	x	2	-	-	x	2
	CRCL	x	7, 17	x	17	x	17	x	17
	BFM	-	-	x	2	-	-	x	2
D2	BFT	x	7	-	-	-	-	x	2
	MFR	-	-	x	2	-	-	x	2
	CRCL	x	7	-	-	x	7	-	-
D3	BFT, MFR	-	-	x	2	-	-	x	2
	CRCL	x	1	-	-	-	-	-	-
D4	ADG, BFT, CRCL	x	7	-	-	x	7	-	-

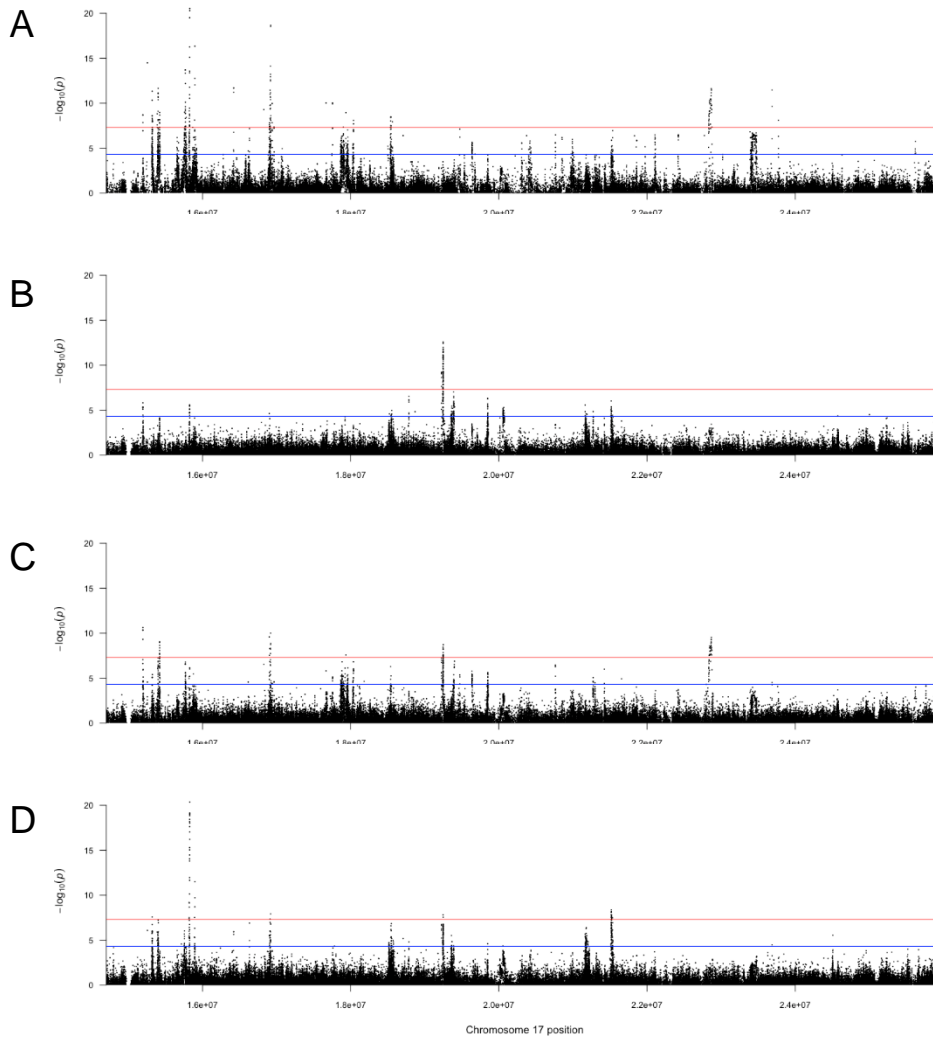**Table 3**. Associated regions above genome-wide significance levels for the GWAS models (sequence data)

Cross	Trait	Imprinting		Maternal		Paternal	
D1	ADG	-	-	-	-	x	2
	BFT, SCF, BFTR, SCFLD, SCFLM, BFS	x	2	-	-	x	2
	MFR	x	2	-	-	x	2
	CRCL	x	17	x	17	x	17
	BFM	x	2	-	-	x	2
D2	BFT	-	-	-	-	x	2
	MFR	x	2	-	-	x	2
	CRCL	-	-	x	7	-	-
D3	BFT, MFR	x	2	-	-	x	2
	CRCL	-	-	-	-	-	-
D4	ADG, BFT, CRCL	-	-	x	7	-	-

SSC17: 14.7- 26 Mb

Fig 2. Manhattan plot for CRCL in D1 (sequence data). A. Additive. B. Imprinting. C. Maternal. D. Paternal

SSC2: 0 – 13 Mb
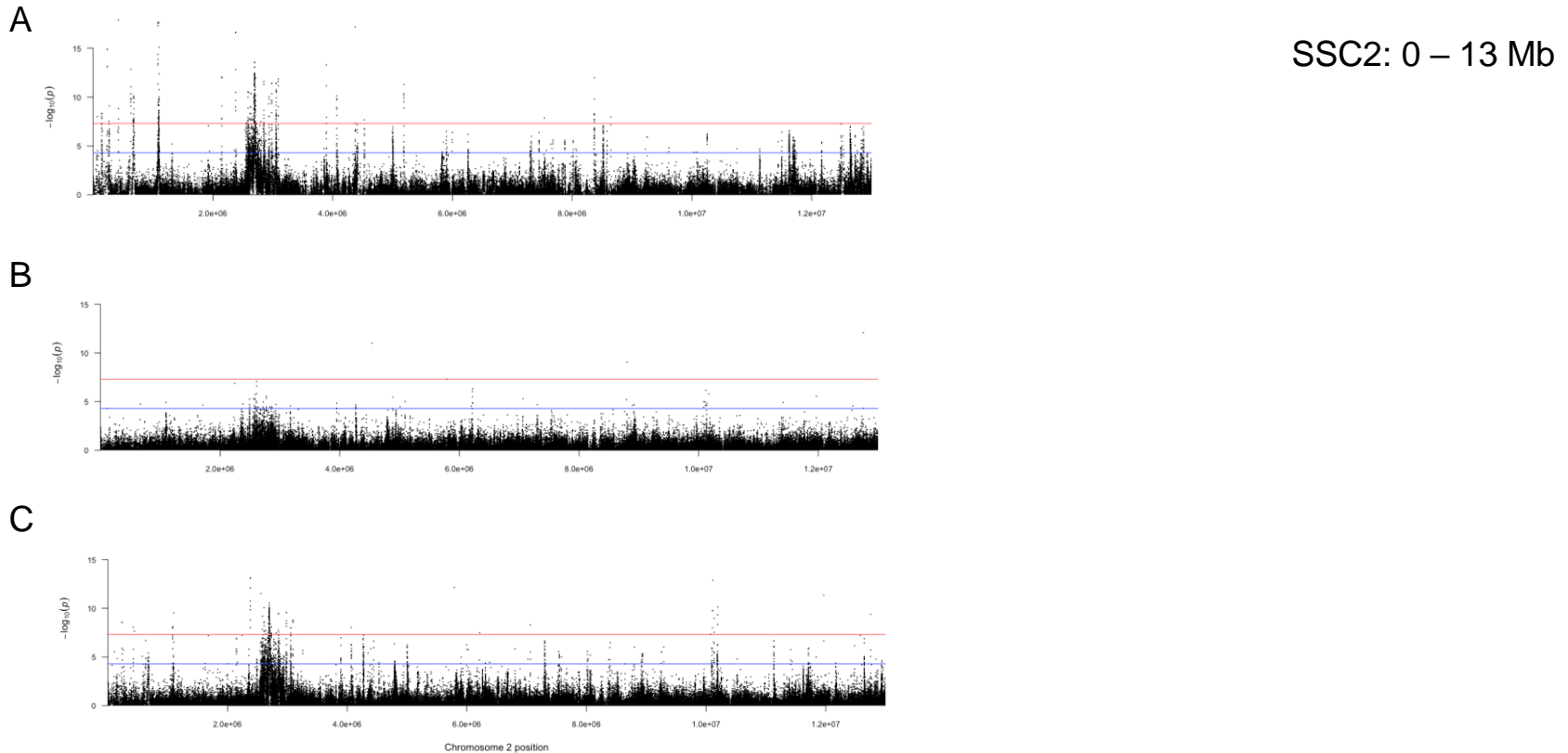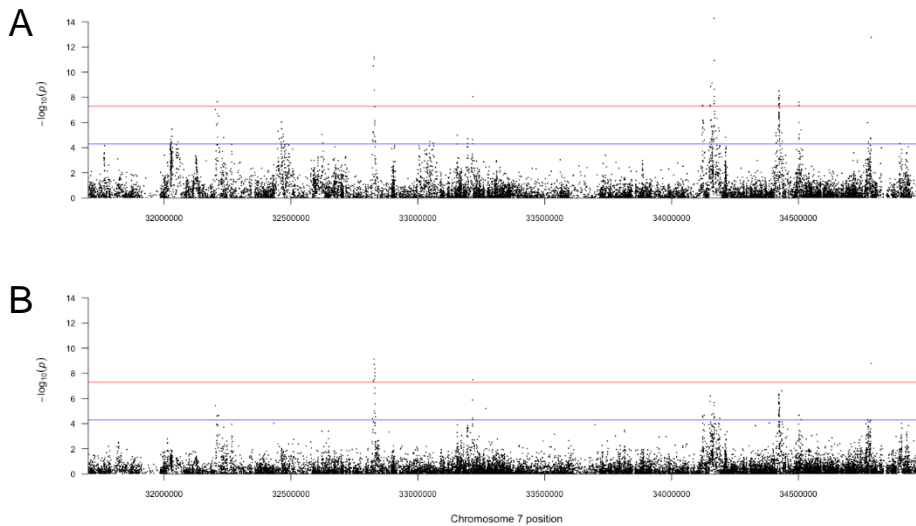
Fig 3. Manhattan plot for SCFLM in D1 (sequence data). A. Additive. B. Imprinting. C. Paternal

SSC7: 31.7 – 35 Mb

Fig 4. Manhattan plot for CRCL in D2 (sequence data). A. Additive. B. Maternal

- ➢ D1: P x LwxL/L - parent-of-origin

- ➢ D2: MxP and D3: WxP - dominance

- ➢ *IGF2*

- ➢ varying expression patterns

- ➢ grandparent-of-origin effect > D1 suitable

Outlook:

- ➢ extend genome-wide

- ➢ validate findings

Thank you for your attention!

Cross	Trait	Var A	Var AD	Var ADI
D1	ADG	0.35 (0.04)	0.39 (0.04)	0.41 (0.04)
	BFT	0.46 (0.04)	0.46 (0.04)	0.46 (0.04)
	MFR	0.51 (0.03)	0.52 (0.03)	0.59 (0.03)
	CRCL	0.60 (0.03)	0.60 (0.03)	0.60 (0.03)
	SCF	0.32 (0.04)	0.34 (0.04)	0.34 (0.04)
	BFM	0.31 (0.04)	0.32 (0.04)	0.32 (0.04)
	BFTR	0.42 (0.04)	0.42 (0.04)	0.42 (0.04)
	SCFLD	0.49 (0.03)	0.50 (0.04)	0.51 (0.04)
	SCFLM	0.46 (0.04)	0.47 (0.04)	0.56 (0.03)
	BFS	0.40 (0.04)	0.41 (0.04)	0.42 (0.04)

Cross	Trait	Var A	Var AD	Var ADI
D2	ADG	0.32 (0.09)	0.63 (0.11)	0.63 (0.11)
	BFT	0.71 (0.07)	0.79 (0.08)	0.79 (0.08)
	MFR	0.46 (0.09)	0.50 (0.11)	0.52 (0.11)
	CRCL	0.73 (0.07)	0.73 (0.08)	0.73 (0.08)
D3	ADG	0.54 (0.09)	0.60 (0.12)	0.60 (0.12)
	BFT	0.40 (0.10)	0.41 (0.14)	0.44 (0.14)
	MFR	0.46 (0.09)	0.53 (0.13)	0.53 (0.13)
	CRCL	0.30 (0.09)	0.40 (0.14)	0.41 (0.15)
D4	ADG	0.40 (0.08)	0.46 (0.10)	0.50 (0.10)
	BFT	0.49 (0.08)	0.49 (0.09)	0.51 (0.10)
	MFR	0.59 (0.08)	0.59 (0.09)	0.59 (0.09)
	CRCL	0.56 (0.08)	0.56 (0.09)	0.59 (0.09)

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