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Detecting imprinting effects in general pedigrees: a cautionary tale

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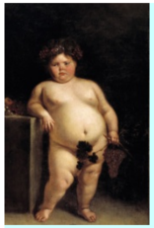
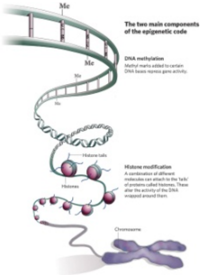
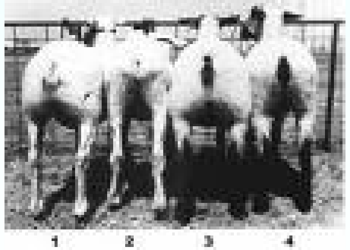


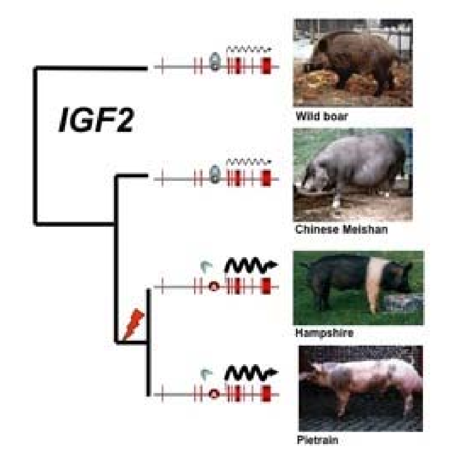


Genomic Imprinting

differential expression depending on whether a gene is inherited from mother or father

- •Prader-Willi/Angelman syndrome in humans
- •IGF2 in pigs
- •Callipyge in sheep





Detecting QTL in general pedigrees Variance component method

- Utilises information from all pedigree relationships
- Linear model to partition variance
- IBD matrix to model relationship between individuals at markers (to infer QTL)

Test

- Based on Shete and Amos/Hanson method in human literature
  - Shete and Yu – alcoholism 2005
  - Heuven pigs 2007

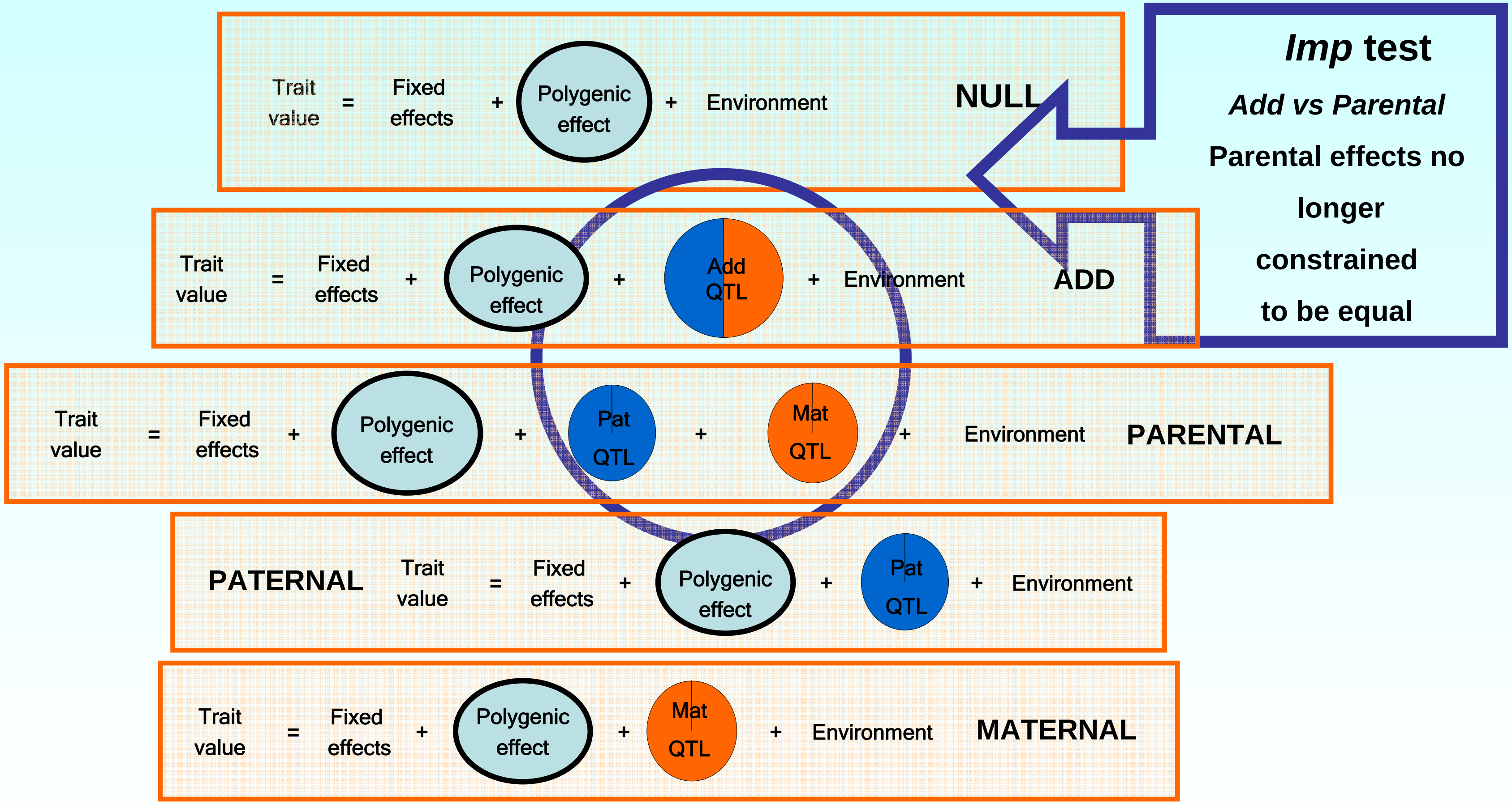
- Under assumption that in the additive model parental contribution is equal

- Extend model to allow parental components to vary

Linear Model - Flexible and easy to extend

Compare linear models

LRT = -2 X log(likelihood)H0 – log (likelihood) H1



Trait value = Fixed effects + Polygenic effect + Environment **NULL**

Imp test

Add vs Parental

Parental effects no longer constrained to be equal

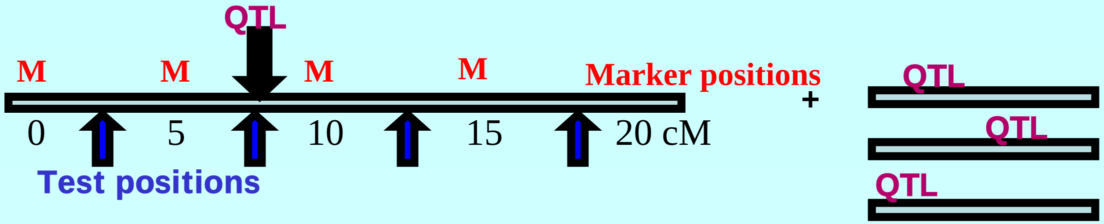
Trait value = Fixed effects + Polygenic effect + Add QTL + Environment **ADD**

Trait value = Fixed effects + Polygenic effect + Pat QTL + Mat QTL + Environment **PARENTAL**

PATERNAL Trait value = Fixed effects + Polygenic effect + Pat QTL + Environment

Trait value = Fixed effects + Polygenic effect + Mat QTL + Environment **MATERNAL**

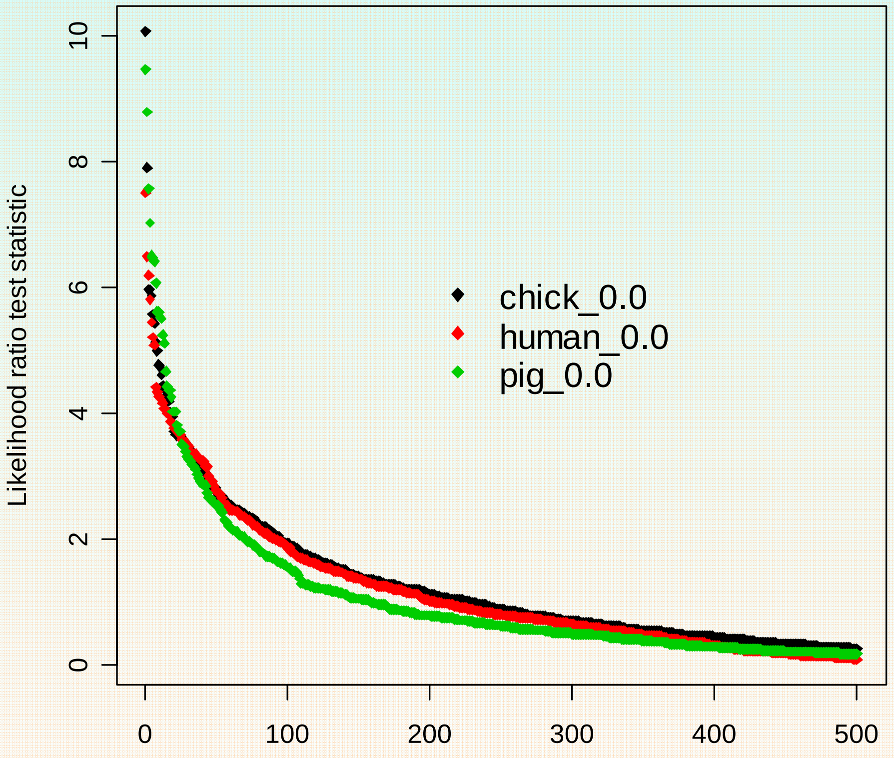
Method



- Simulate chicken, pig and human populations
- Range of additive, dominant and imprinted QTL
- Estimate IBD coefficients to solve Linear Models
- Compare Models using LRT
- Derive empirical null for IMP test
- 1000 replicates (500 shown) QTL effects = 0

	Sires	Dams	Progeny
Pig	10	X 19	X 10
Chicken	19	X 5	X 20
Human	633	X 1	X 3

Empirical distribution *imp* test statistic

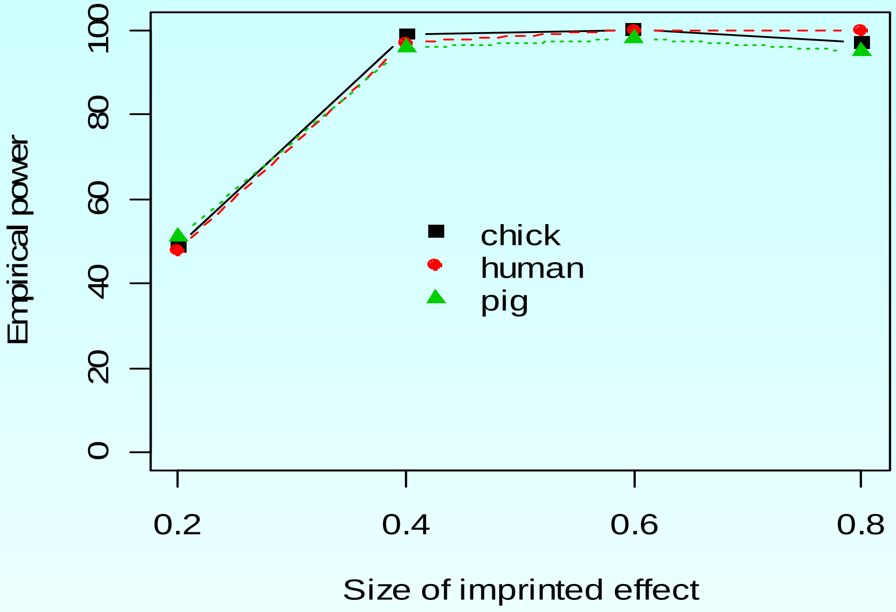


	Sires	Dams	Progeny
Pig	10	X 19	X 10
Chicken	19	X 5	X 20
Human	633	X 1	X 3

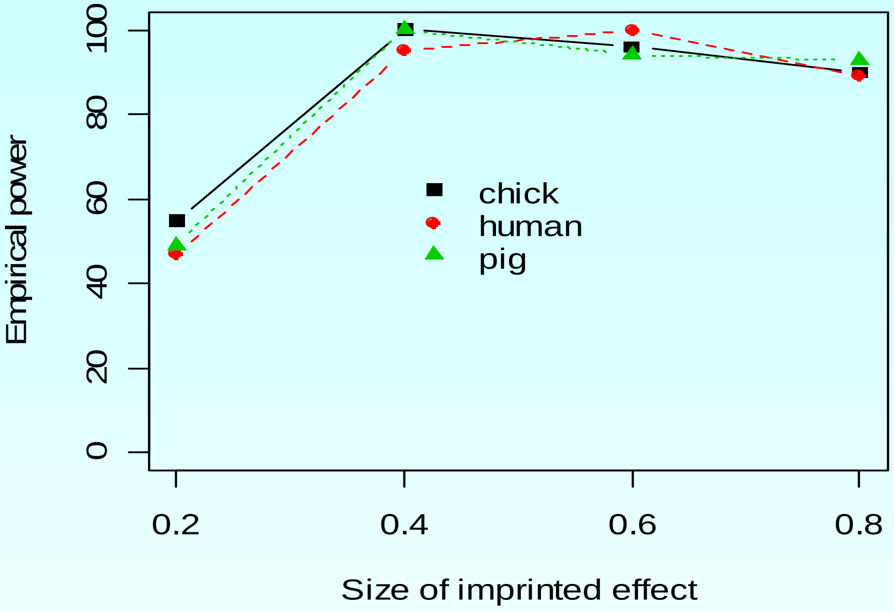
Objectives

- Power
  - QTL fully imprinted
- Accuracy VC estimates
- False positive rates
  - common environment
  - additive and dominant QTL effects

Power



Maternal expression



Paternal expression

	Effect	Variance (prop phenotypic)
Polygenic		**0.10**
Residual		**0.75**
Additive QTL	**0.0 – 0.8**	**0.02 – 0.32**
Dominant QTL	**0.0 – 0.8**	**0.02 – 0.16**
Mat expressed QTL	**0.2 – 0.8**	**0.04 – 0.64**
Pat expressed QTL	**0.2 – 0.8**	**0.04 – 0.64**

	Sires	Dams	Progeny
Pig	**10**	**X 19**	**X 10**
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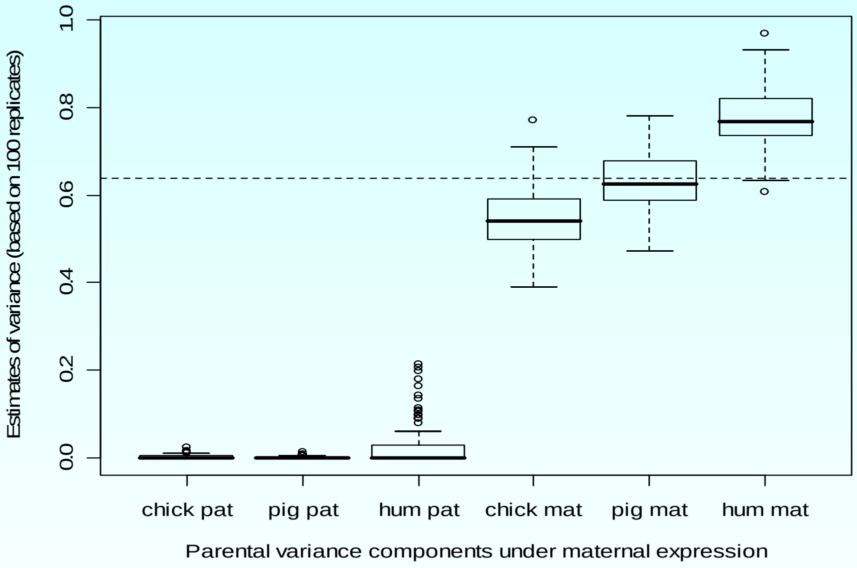
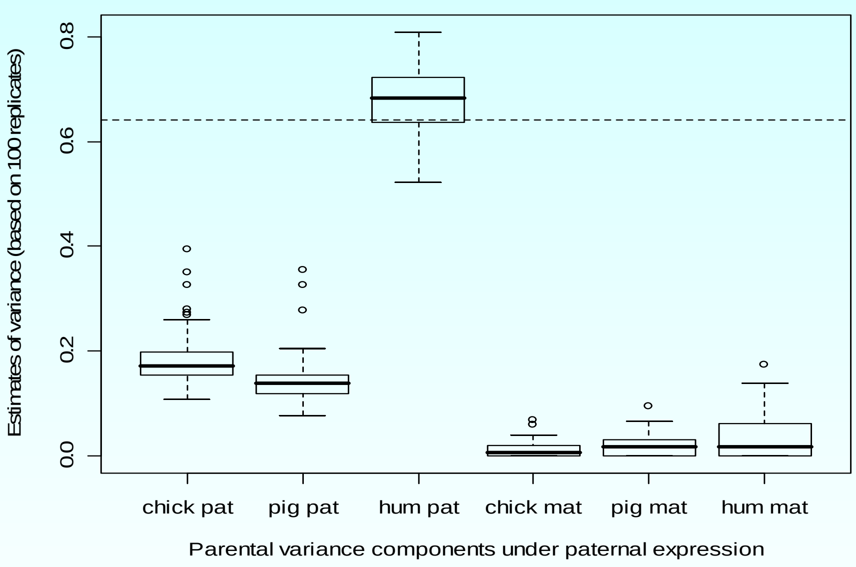
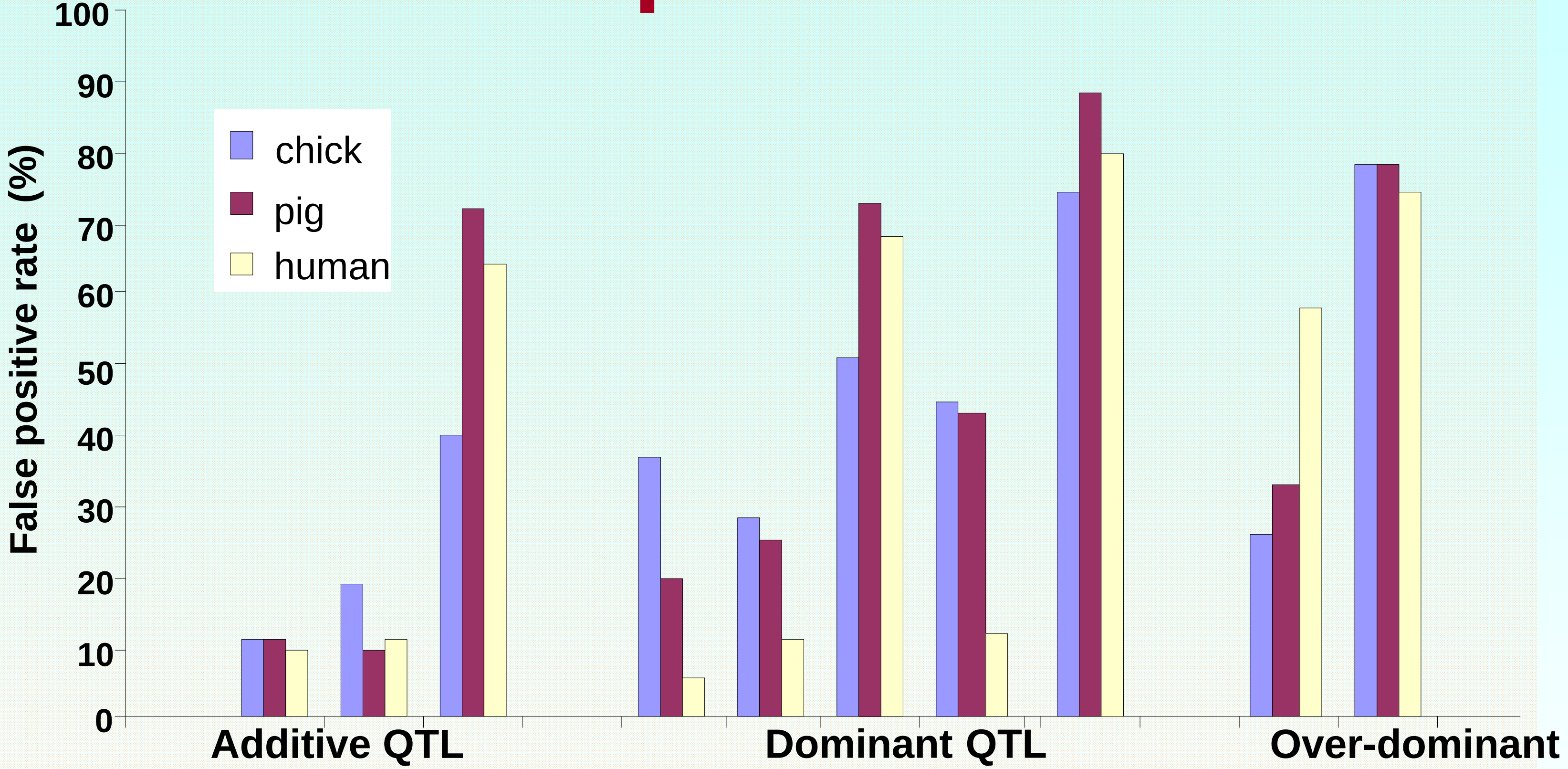
Human	**633**	**X 1**	**X 3**

Accuracy


Estimates of variance (based on 100 replicates)
0.0
0.2
0.4
0.6
0.8
1.0
chick pat
pig pat
hum pat
chick mat
pig mat
hum mat
Parental variance components under maternal expression

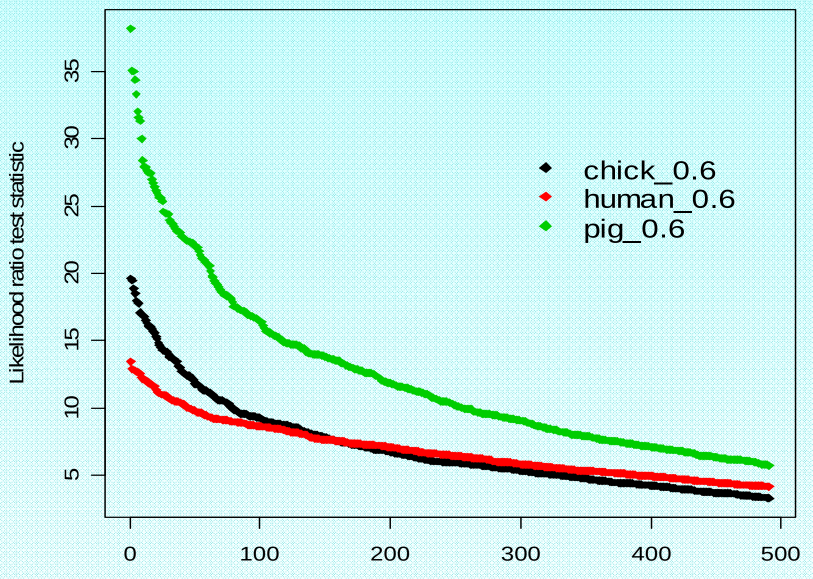

Estimates of variance (based on 100 replicates)
0.0
0.2
0.4
0.6
0.8
chick pat
pig pat
hum pat
chick mat
pig mat
hum mat
Parental variance components under paternal expression

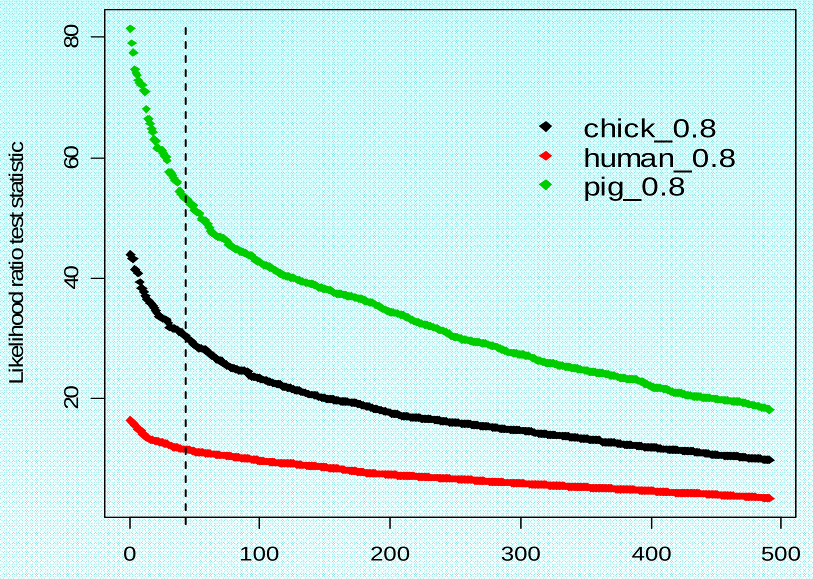
False positive rate



	Additive QTL			Dominant QTL					Over-dominant	
a	0.4	0.6	0.8	0.6	0.4	0.8	0.6	0.8	0.4	0
d	0	0	0	0.3	0.4	0.4	0.6	0.8	0.8	0.8
QTL h2	0.07	0.15	0.23	0.16	0.1	0.26	0.20	0.33	0.36	0.13

Distribution imp statistic with complete dominance





Conclusions (1)

- **Can look for imprinted effects in general pedigrees**
  - **power, accuracy and distribution of the test statistic dependent on population structure and genetic background**
  - **Proposed empirical thresholds sufficient if h^2 QTL < 7%**

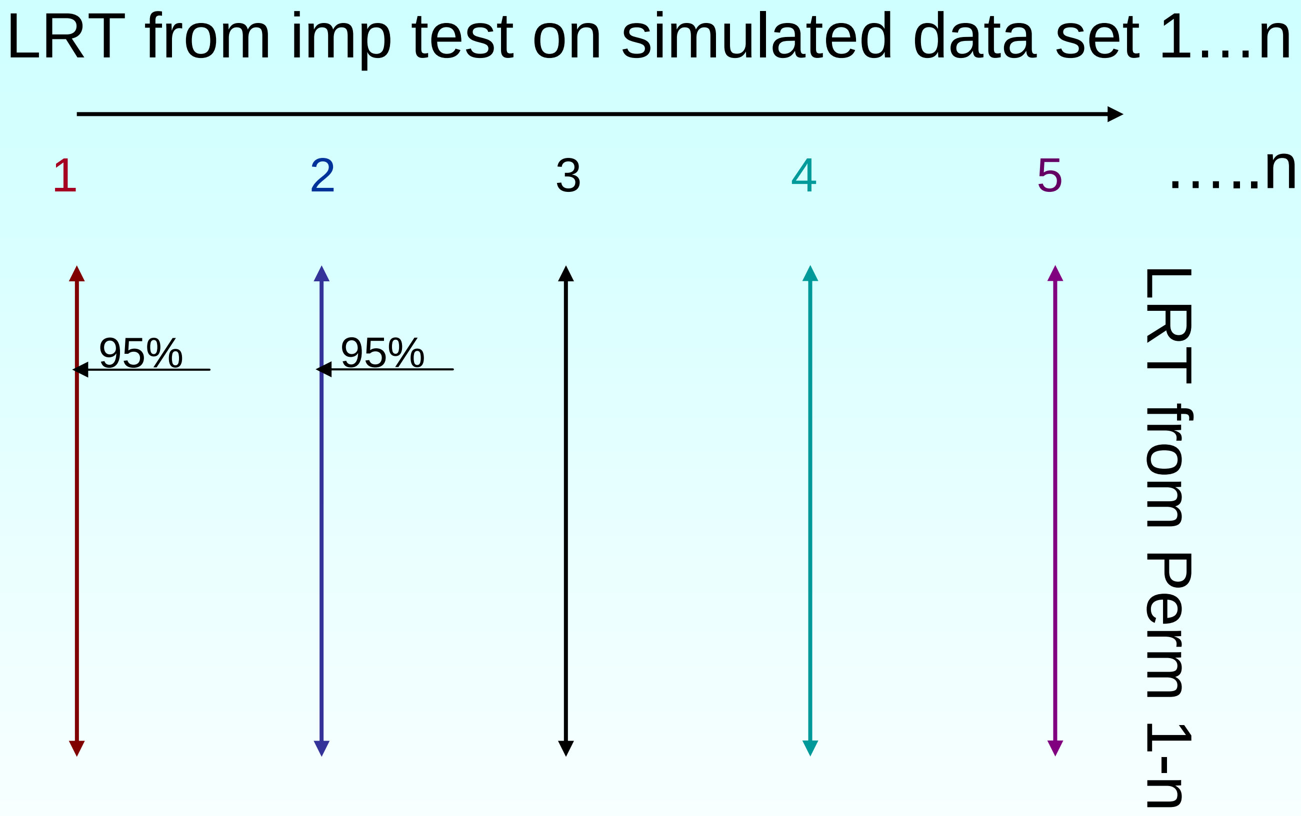
- **Appropriate test? Not truly nested**

- **Important for small effects ?**

- **Could use permutation analysis**
  - **Permute phenotypes with genotypes within dam**
  - **Permute parental IBD within full sib families**

Permutation (Human – FS families)

- Simulate 100 data sets – large dominant QTL
  - Test for imprinting
- Permute each data set 100 times swapping maternal and paternal alleles at random
  - Test for imprinting
- Take 95th value for type 1 error threshold for each data set



LRT from imp test on simulated data set 1…n

1

2

3

4

5

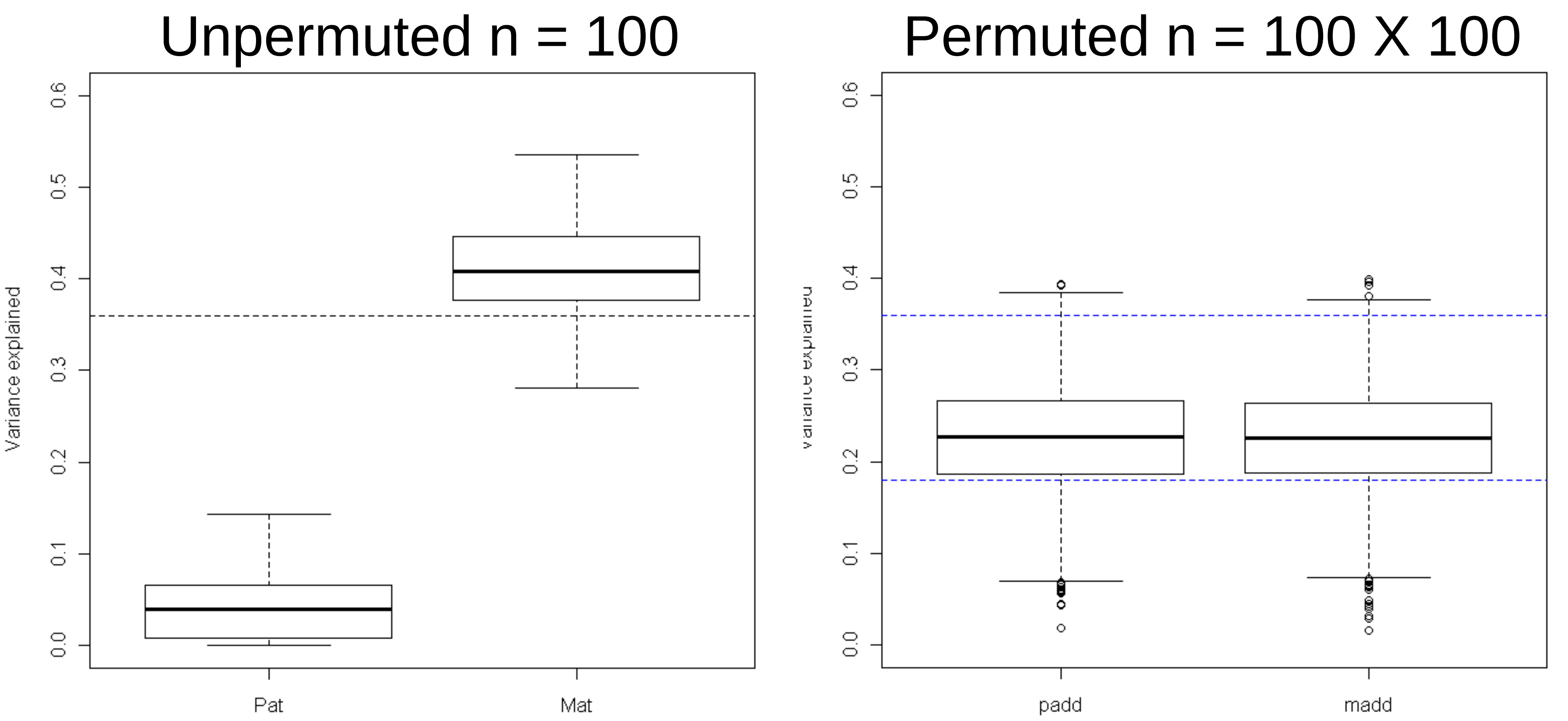
…..n

95%

95%

LRT from Perm 1-n

Effect of Permutation on simulated maternal and paternal variance components (Maternal imprinting)

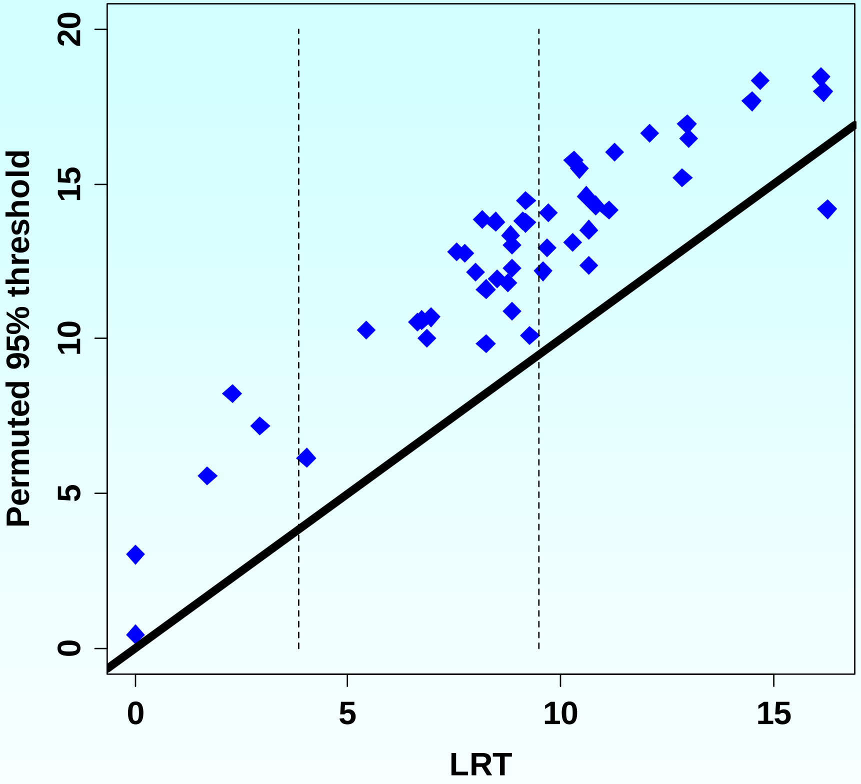

Unpermuted n = 100

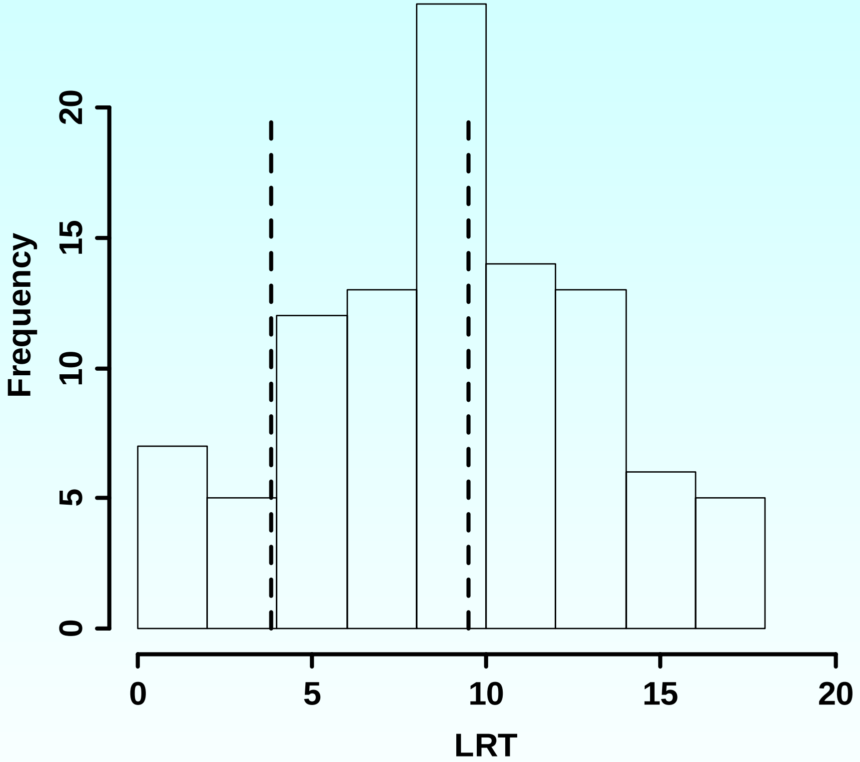
Permuted n = 100 X 100

Simulated paternal variance = 0, maternal variance = 0.36

Permuted threshold

fully dominant QTL explaining 33% variance

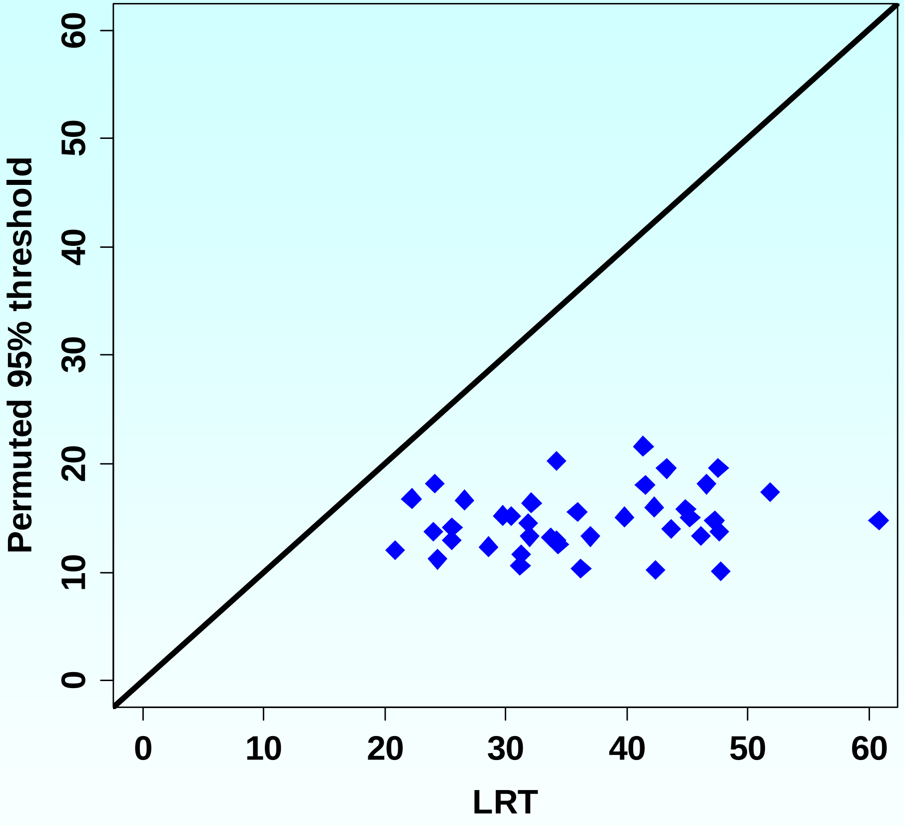




Threshold	Type 1 error
Permuted threshold	2%
Tabulated chi square 1df (3.84)	86%
Empirical based on no QTL (9.48)	42%

Power to detect imprinting

- Simulate 100 data sets with Mat imp QTL
- Permute 100 times
- Test for imprinting
- Permuted threshold 95th percentile



Conclusions (2)

- LRT for imprinting test varies across data sets
  - Tabulated chi^2 and empirical thresholds under a null model are inappropriate
- Permutation analysis gives appropriate ‘data specific’ threshold
- Type 1 error rate is conservative even for large dominant effects
- Power remains high using permuted threshold

Acknowledgements

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Threshold	Type 1 error
Tabulated chi square 1df (3.84)	86%
Empirical based on no QTL (9.48)	42%
Permuted threshold	2%

Real Data

Permuted phenotypes and genotypes within FS dam families

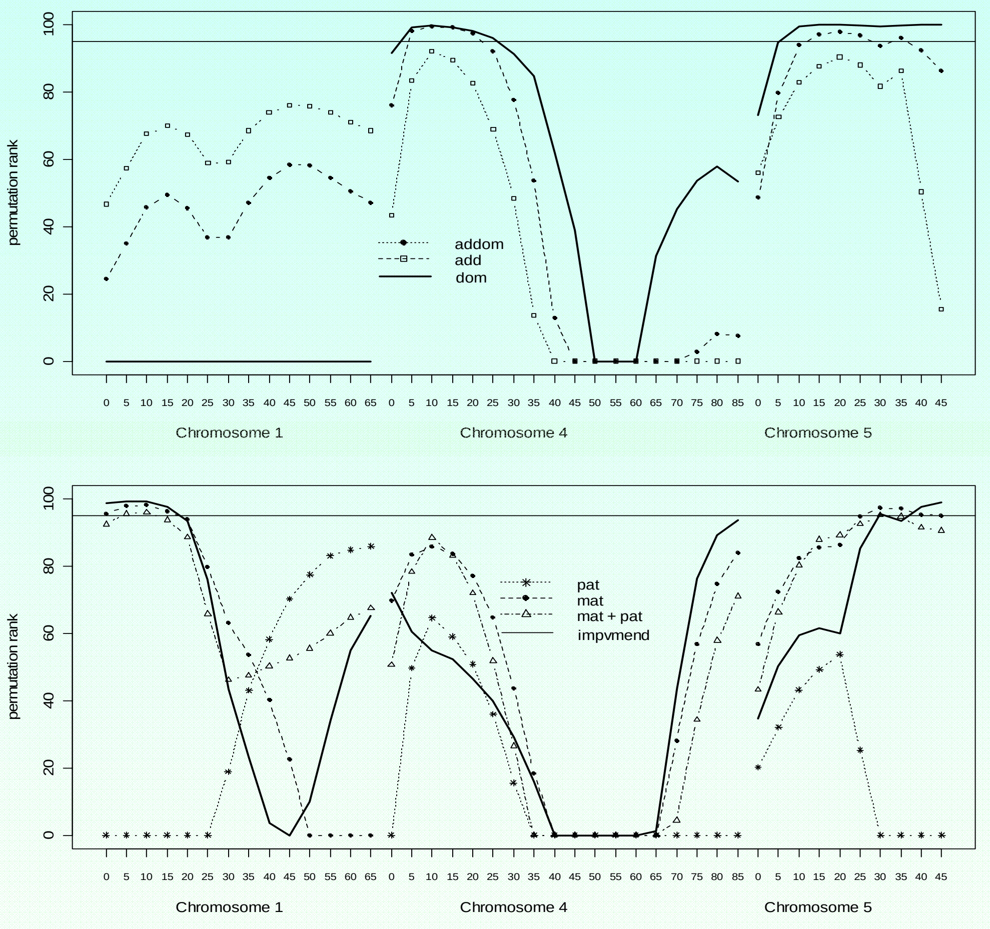
Evidence for imprinted QTL affecting conformation score on chicken chromosome 1

No evidence for add/dom effects on GGA1

GGA1 orthologous with imprinted regions

There is a dom QTL (6% phen var) on GGA4 but no evidence for imprinting

Evidence for dom and imprinting on GGA5



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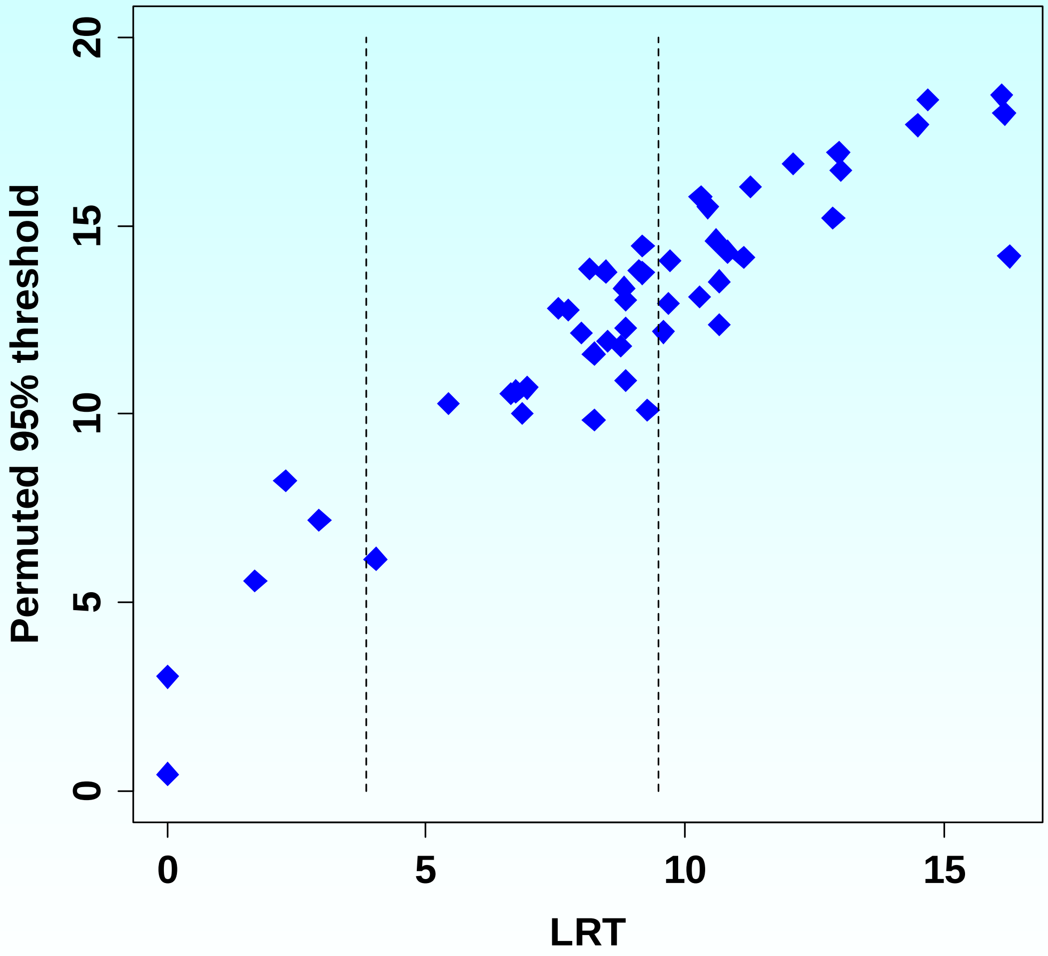
Permuted 95% threshold
0
5
10
15
20
0
5
10
15
LRT

Permutation analysis

- Permute sire and dam alleles within full sib human families prob 0.5
- Polygenic and additive component remain
- Estimate empirical threshold for imp test
- Conservative when dam is fitted
- Power to detect imprinting affected?