From the 50K chip to the HD: Imputation efficiency in 9 dairy cattle breeds

Chris HOZÉ

INRA, GABI

UNCEIA

le réseau de la génétique animale

Genomic evaluations

- Require large reference population
- Implemented in the three French main dairy breeds
  - Holstein, Normande, Montbéliarde
  - Since 2008
  - Based on a 50K chip
- For other breeds ?
  - Problem : constitution of reference population
  - Solution : sharing reference population
    - Across countries? e.g. : Intergenomics for Brown Swiss
    - Across breeds ? e.g. : Gembal project

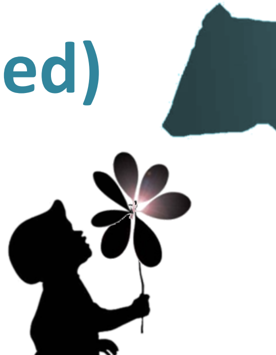
The GEMBAL project
Multibreed Genomics of Beef and Dairy Cattle

- **Develop multi-breed genomic selection**
  - **Share reference population across breeds**
  - **Develop genomic selection in all French cattle breeds**

- **Detect conserved chromosome segments accross breeds**
  - **Distance between markers < 10 Kb to maintain LD**
    - **50K chip : 54.609 SNP -> 1 SNP every 70 Kb** (BovineSNP50 BeadChip®)
    - **HD chip : 777.962 SNP -> 1 SNP every 4 Kb** (BovineHD BeadChip®)
  - **Possible on the high density chip ?**

The GEMBAL project
Multibreed Genomics of Beef and Dairy Cattle

- **Genotype animals on the HD chip**
- **Study imputation efficiency from the 50K chip to the HD chip**
- **Impute 50K genotypes from national databases**
- **Study multi-breed GS using a large reference population with HD-genotypes (true and imputed)**



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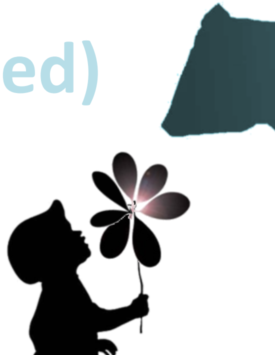
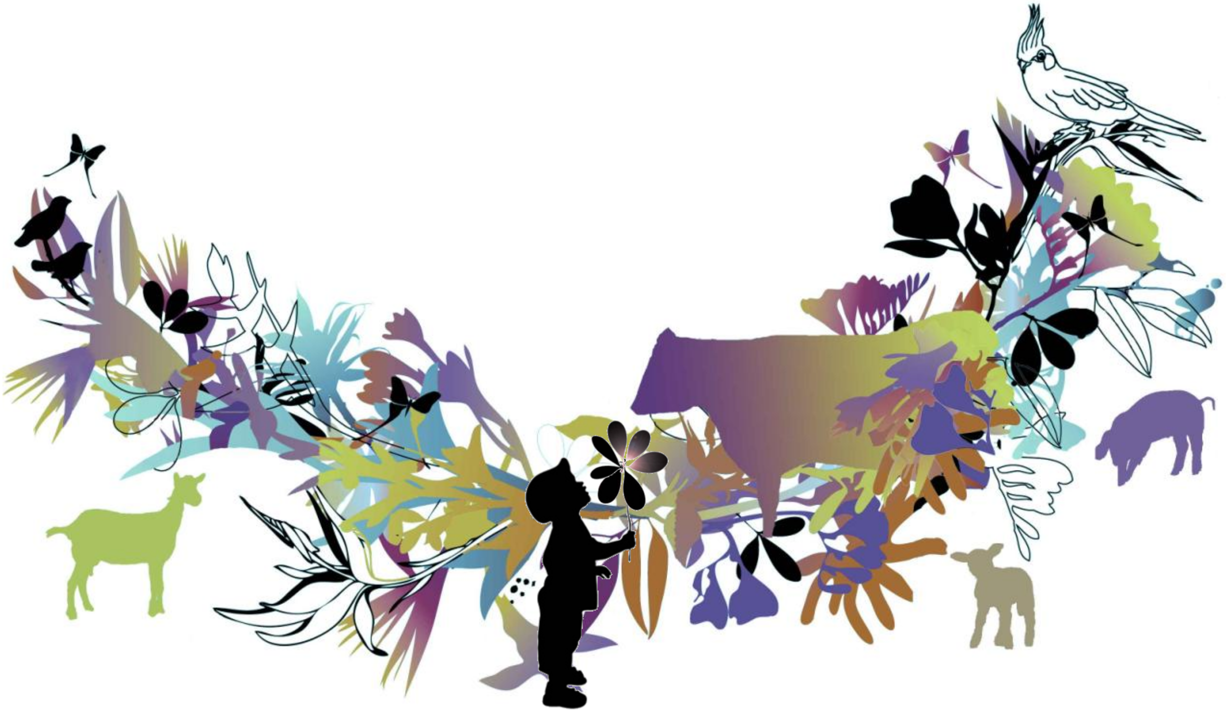




MATERIALS AND METHODS

Number of animals genotyped on the HD chip

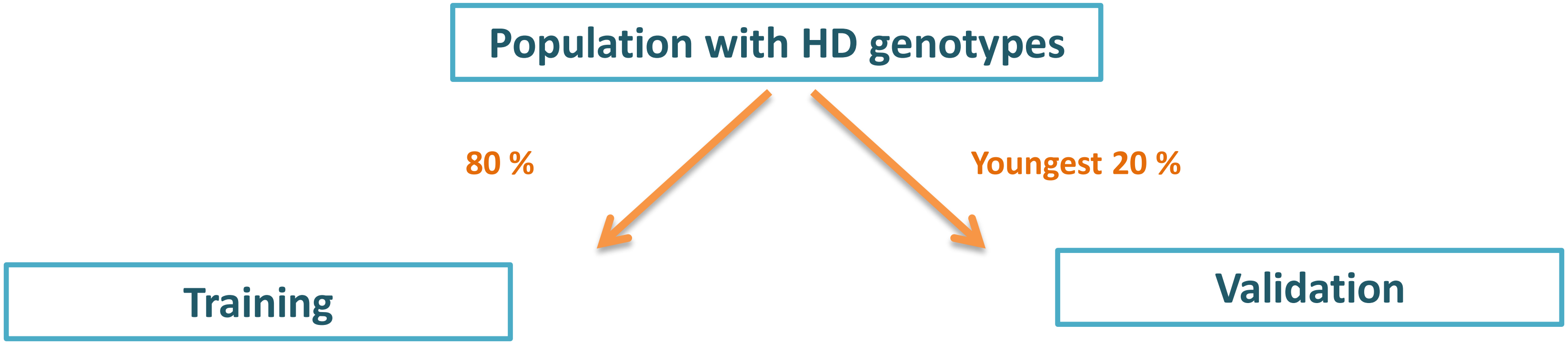
Breed Project / Consortium	Abondance	Brown Swiss	Tarentaise	Simmental	Montbéliarde	Normande	Vosgienne	Holstein	Pie Rouge (Red Pied cattle)
GEMBAL	209	99	184	124	522	546	52	236	41
EUROGENOMICS								540	9
Total	**209**	**99**	**184**	**124**	**522**	**546**	**52**	**776**	**50**

- **2,562 animals from 9 breeds**
- **From 50 to 776 animals per breed**

Quality control

- **Animals :**
  - Call rate above 0.95
  - Consistency between pedigree and SNP-based relationships
- **SNP :**
  - Criteria
    - Located on the 29 autosomes with UMD3 position
    - Call rate > 90%
    - p Hardy Weinberg > 10^{-4}
    - Consistent between the two chips
  - HD chip 777.962 SNP -> 664.808 SNP
  - 50K chip 54.609 -> 43.801 SNP

Computation of imputation efficiency



Population with HD genotypes

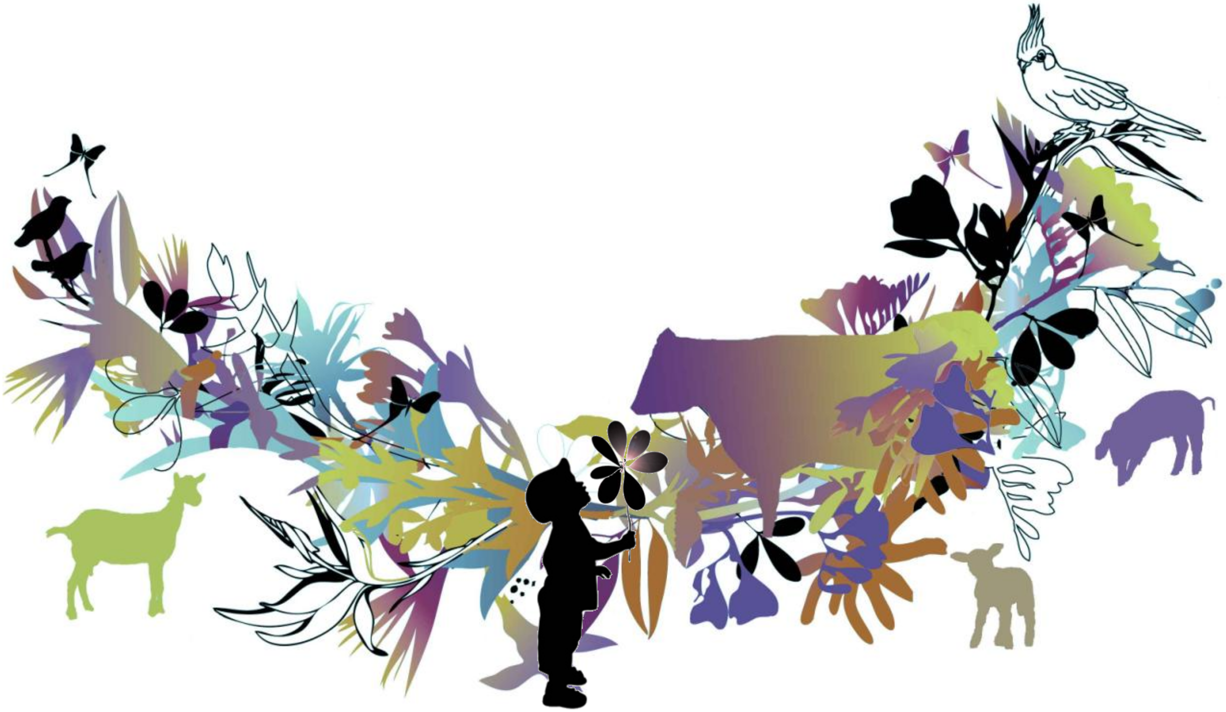
80 %

Youngest 20 %

Training

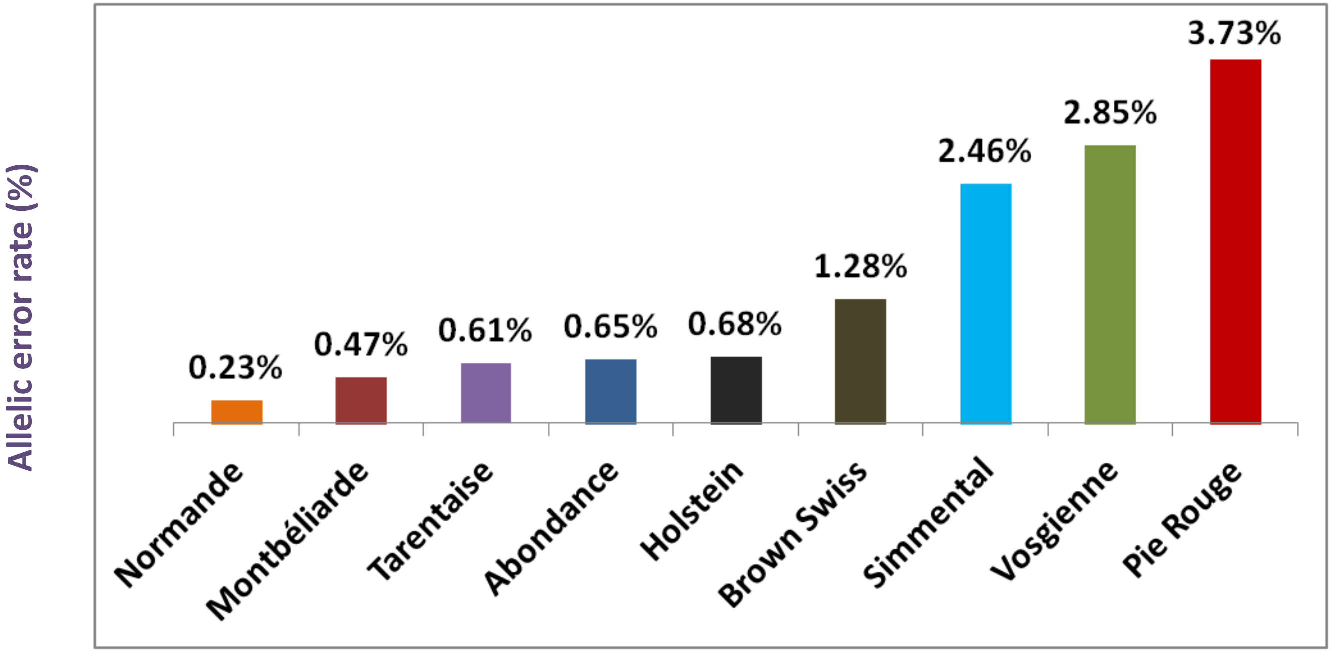
Validation

- For validation population
  - Erase markers specific to the HD chip
  - Impute them using Beagle 3.3.0 software
  - Compare true and imputed genotypes
  - Compute allelic imputation error rate



RESULTS

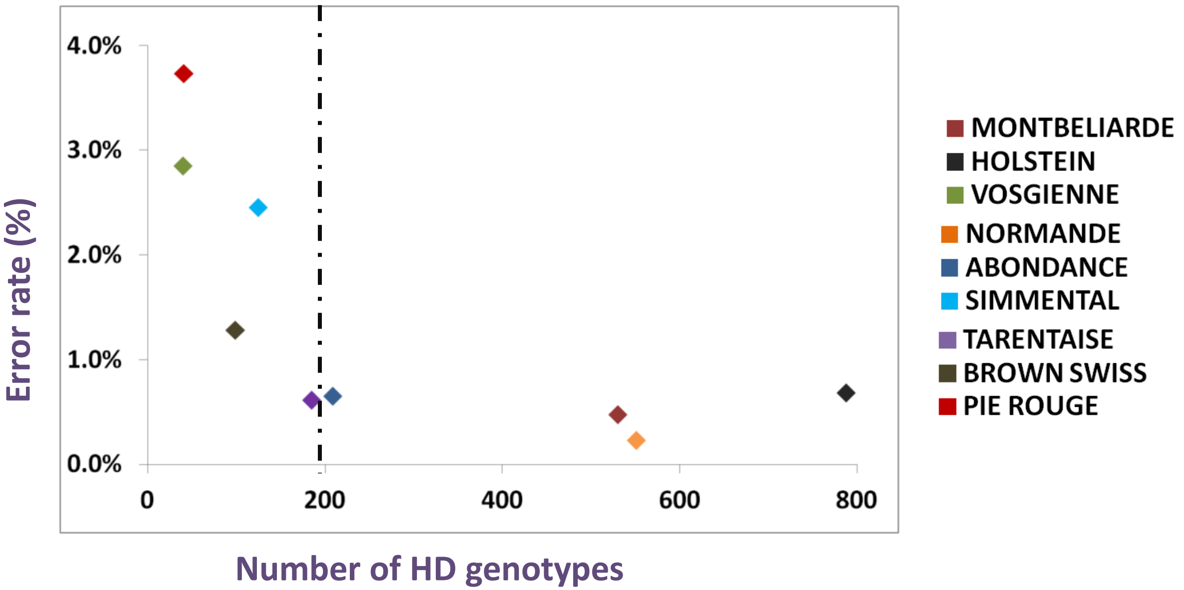
Imputation error rate per breed



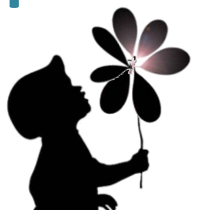
- **Efficient in large and medium size dairy breeds**
- **Higher error rates in foreign breeds and in small French cattle breeds**

Factors affecting imputation error rate

REFERENCE POPULATION SIZE

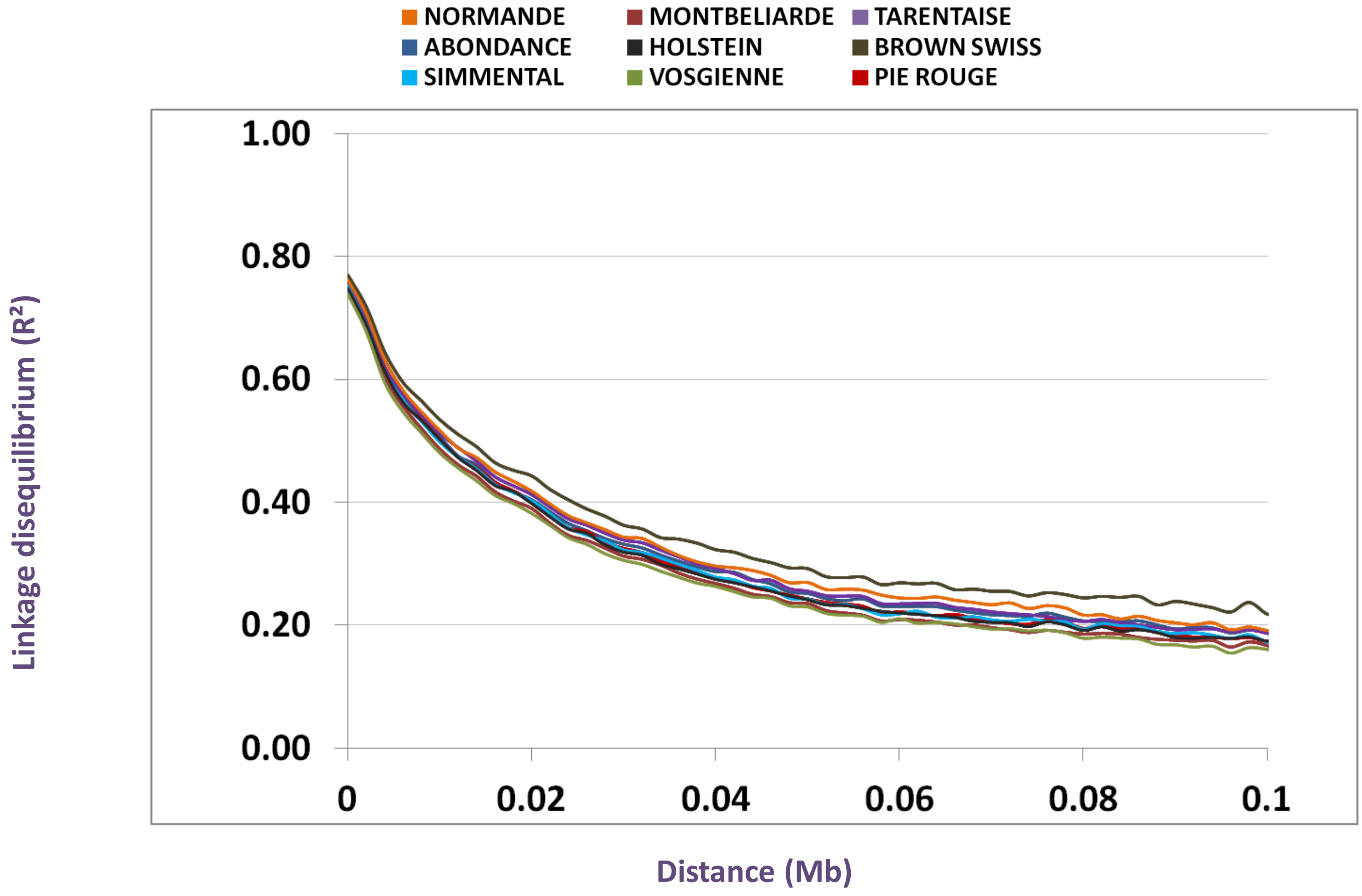


- **Strongly related to reference population size**
- **Efficient when more than 200 animals are genotyped**



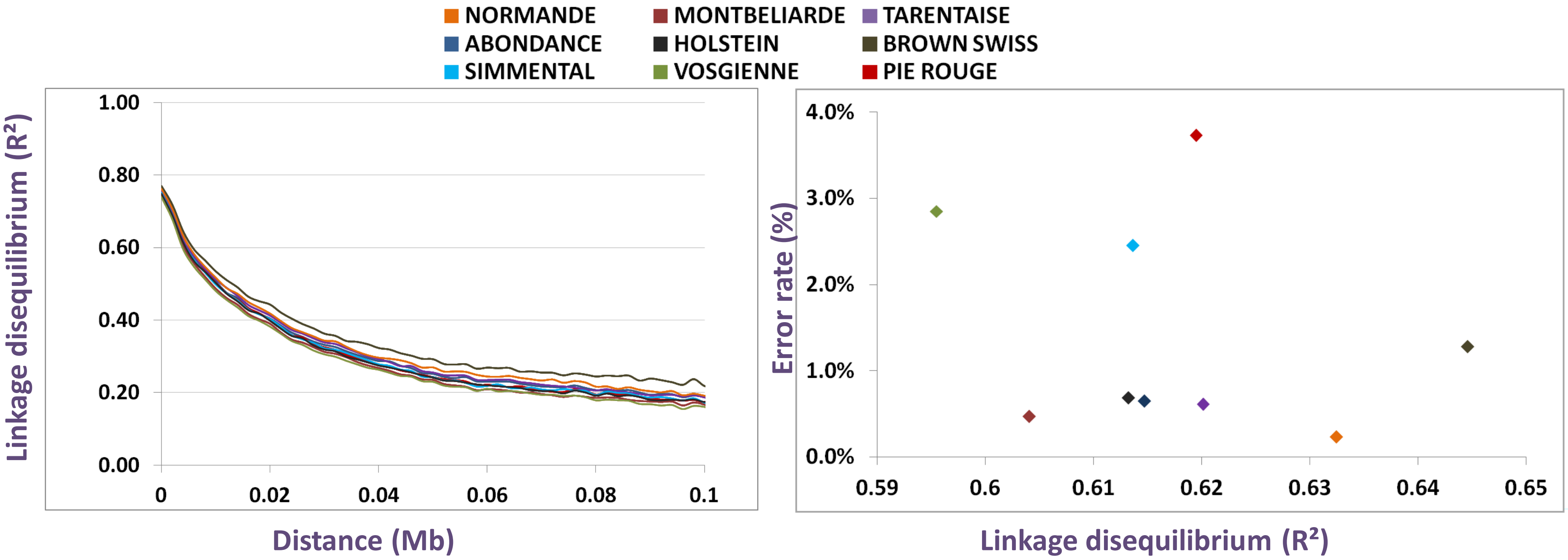
Factors affecting imputation error rate

LINKAGE DISEQUILIBRIUM DECAY



Factors affecting imputation error rate

LINKAGE DISEQUILIBRIUM DECAY **ERROR RATE AND LD LEVEL AT 4Kb**



- **No clear impact of LD level on imputation error rate**

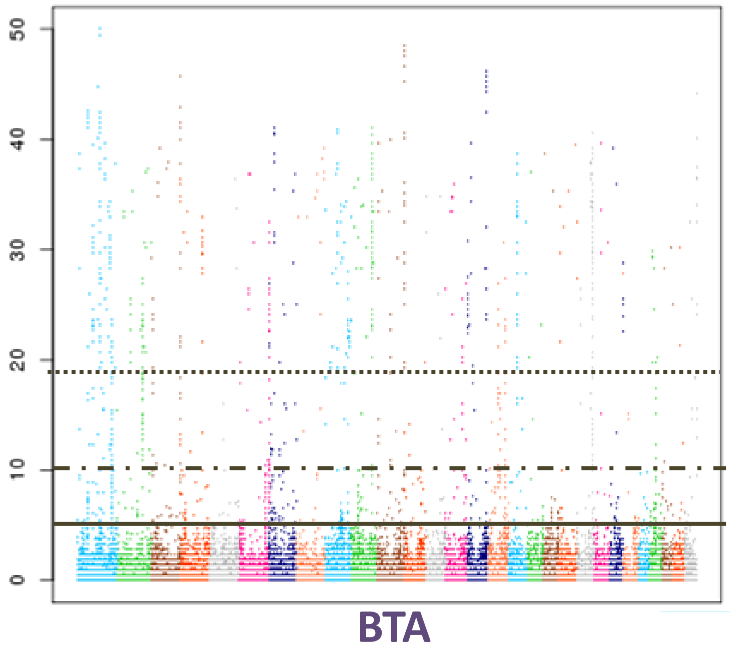
Imputation error rate in Montbéliarde

- **522 animals (416 T + 106 V)**
- **Mean error rate = 0.47%**

Imputation error rate in Montbéliarde

- **522 animals (416 T + 106 V)**
- **Mean error rate = 0.47%**
  - **Strong differences between SNP**
    - **13,104 SNPs with error rate > 5 %**
    - **8,214 SNPs with error rate > 10 %**
    - **6,030 SNPs with error rate > 20 %**

IMPUTATION ERROR RATE ALONG GENOME



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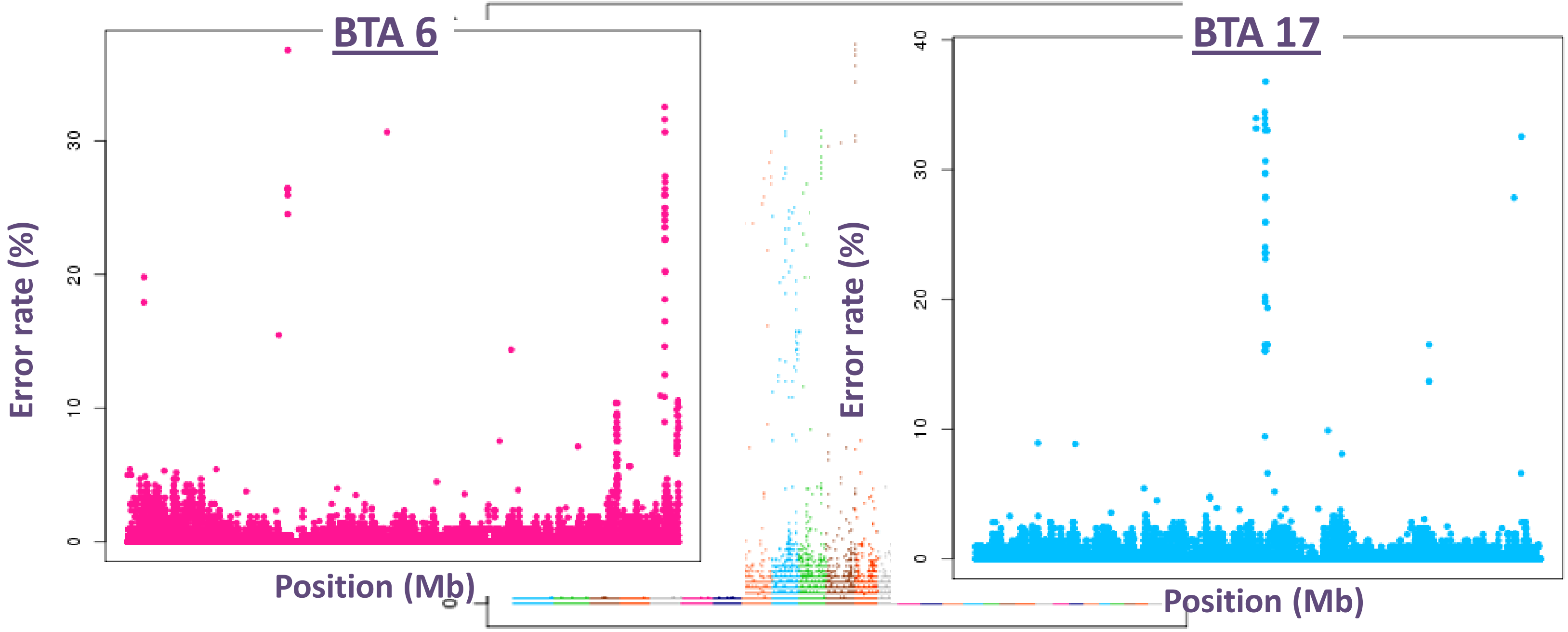
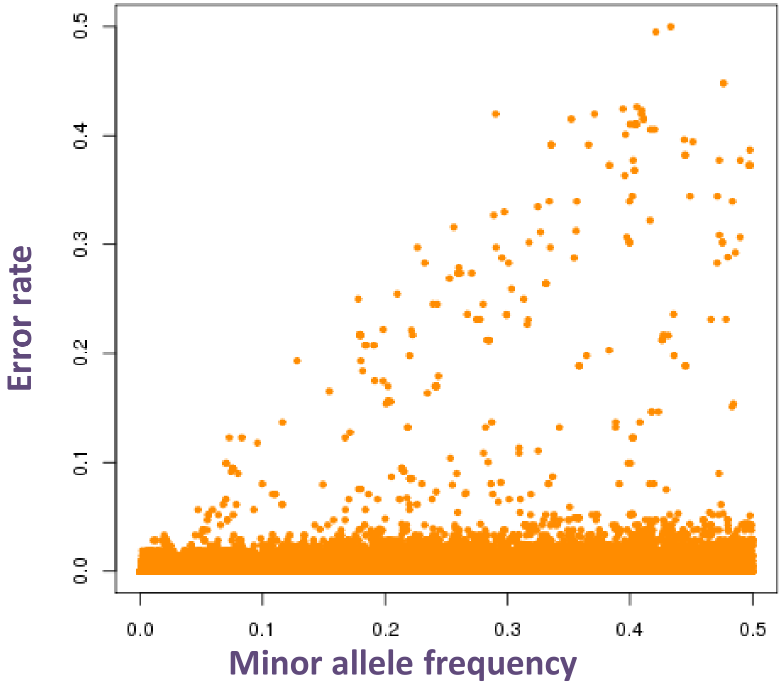


- **Higher error rate in chromosome extremities**
- **Some regions are likely to be mismapped**

Imputation error rate in Montbéliarde

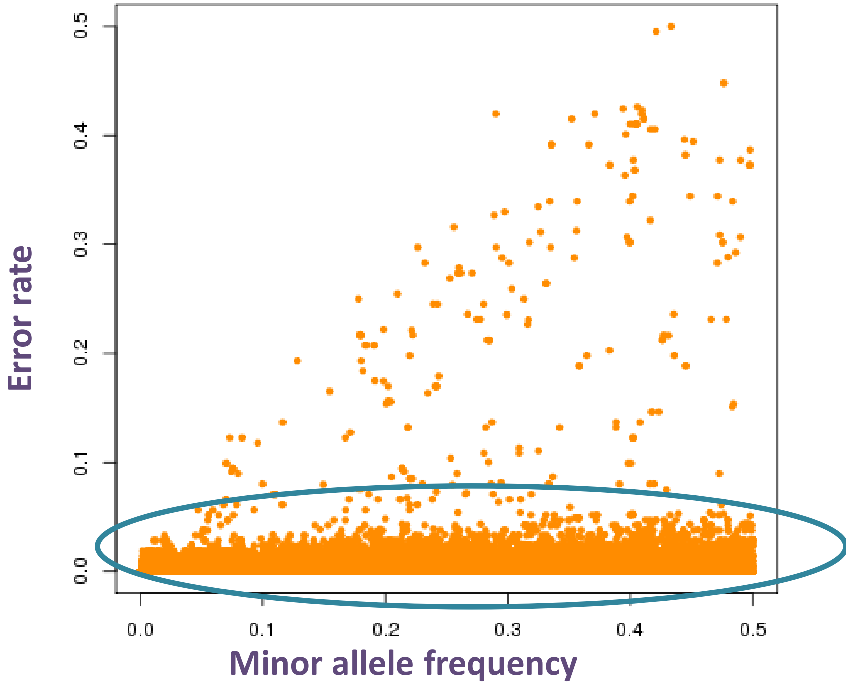
IMPUTATION ERROR RATE AND MAF



Imputation error rate in Montbéliarde

- **Almost no link for low error rate markers**

IMPUTATION ERROR RATE AND MAF

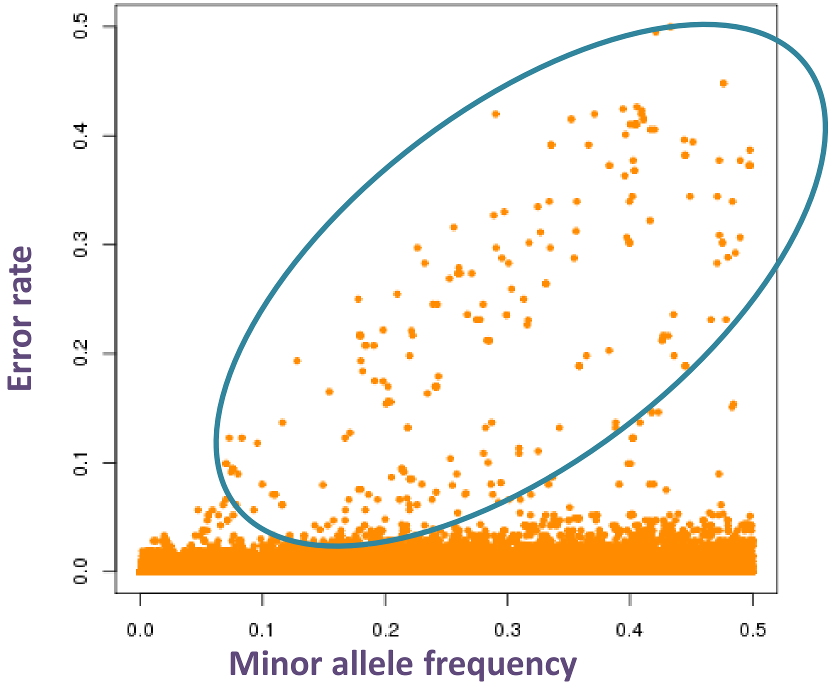


Imputation error rate in Montbéliarde

- **Almost no link for low error rate markers**

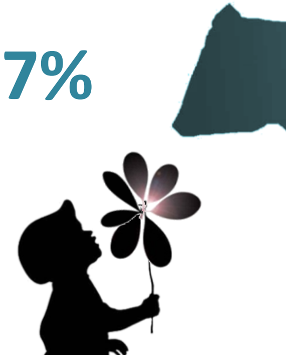
- **Correlation for high error rates markers**
  - **Due to SNP localization?**
  - **No LD between markers**
  - **Imputation = Random with respect to allele frequencies**
  - **Error rate ≈ MAF**

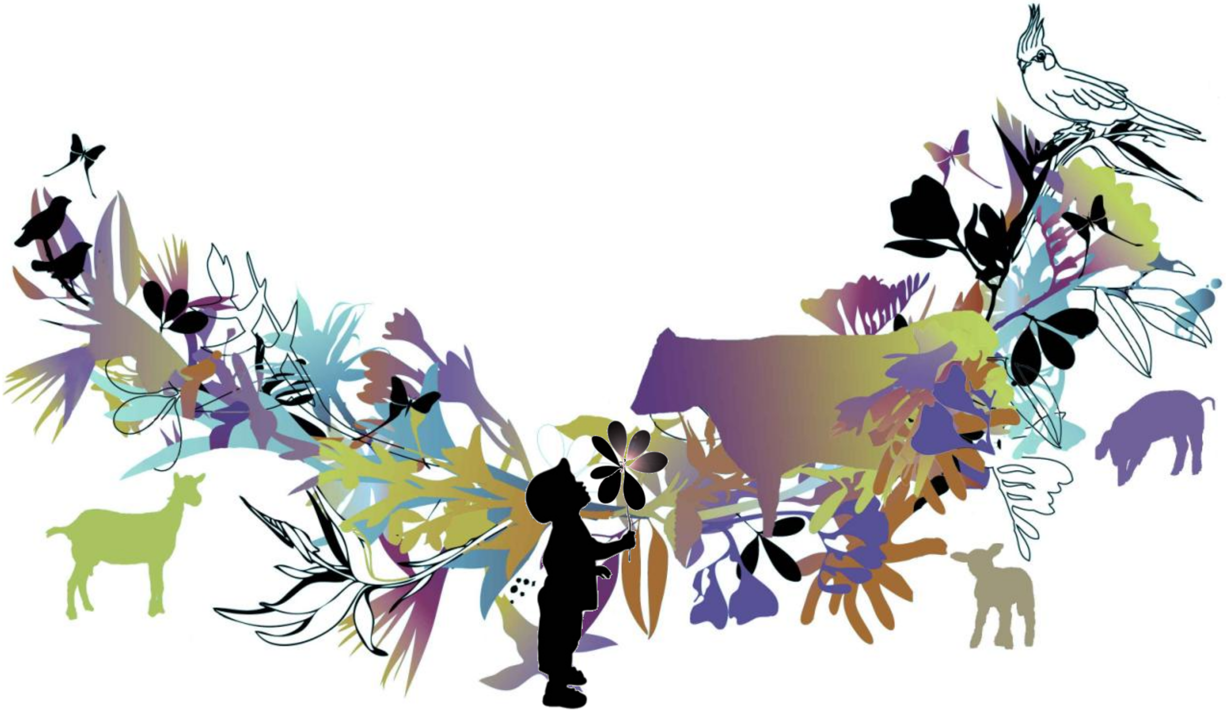
IMPUTATION ERROR RATE AND MAF



Imputation error rate in Montbéliarde

- **Have to remove poorly imputed SNPs for further analysis**
  - **May induce error in QTL detection and GS**
  - **Similar to SNP with high genotyping error rate**
- **Identification may be difficult in multi-breed context**
  - **Have to perform this analysis in all breeds**
  - **High error rate SNP in all breeds are due to mismapping**
- **Error rate in Montbéliarde drop from 0.47% to 0.37% when SNP with error rate > 5% are removed**





CONCLUSION

Conclusions

- **Imputation is efficient in most breeds of the project**
    - **When the number of HD genotype is high enough**
    - **Pay attention to poorly imputed SNP**

- **To improve the situation in other breeds :**
    - **Increase the number of HD genotypes**
    - **Through genotypes exchange in Brown Swiss and Simmental ?**

Perspectives

- **33,274 (2,562 + 30,712 imputed) HD genotypes are available**
  - **In Montbéliarde, Normande and Holstein breeds**
- **Work on this reference population with HD genotypes**
- **Within and between breeds QTL detection**
- **Within and between breeds genomic selection**

Acknowledgements

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