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Fine-scale Genetic Structure in Western France

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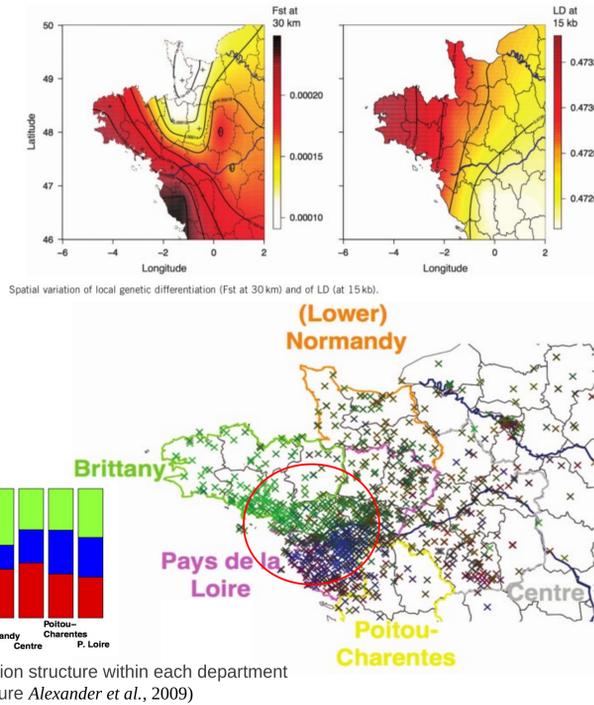
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Rare Variants / Common Disease?

The 'Common Variant - Common Disease' hypothesis was only partly verified through effective discovery of statistical associations. This empirical observation led the research community to reconsider the involvement of rare genetic variation in predisposition to common disease. Rare alleles of recent origin are likely to cluster geographically in communities with limited migration rates, such as the **French rural populations** before the 20th Century. Should these rare alleles strongly increase disease risk, one would expect **outbreaks of disease prevalence** and enhanced power to establish the variant-phenotype relationship (Probst et al. 2006). Recently, we demonstrated genetic structure at the level of Brittany and Anjou (Karakachoff et al. 2014). We aim to test whether this structure is observed at finer **geographical scale**.

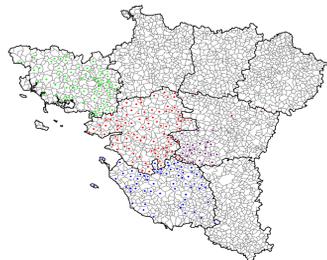
Fine scale structure (Karakachoff et al.)



1,684 individuals from western France were genotyped on Axiom CEU-1 array plates. Fine-scale population differentiation was detected with distinct admixture proportions for individuals originating from Brittany and Pays de la Loire (bottom panel), the RGB color model reports ancestry coefficients obtained with admixture). Genetic differentiation increases with distance at a higher rate in these two areas (middle panel) and linkage disequilibrium is higher in Brittany suggesting a lower effective population size (top panel).

Objectives

Following this work, we aimed at confirming these results and explore a finer-scale genetic structure. We tested correlation between genetic and geographical information in a new data-set selected in a restricted geographical area. As a secondary objective, we wanted to evaluate the respective importance of Isolation by Distance and Clustering in the genetic structure of human populations in this area. The main geographical barrier in this region is the Loire river.



PREGO

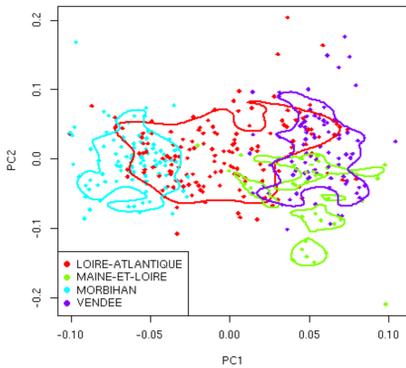
Loire-Atlantique	143
Morbihan	96
Vendée	85
Maine-et-Loire	37
Others	5

Number of individuals per department

The PREGO subset used in this study is composed of 366 individuals whose 4 grand-parents are born in the same village from Vendée, Maine-et-Loire, Loire-Atlantique and Morbihan.

The data-set is genotyped on Axiom Genome Wide CEU 1 Array We selected 78,169 independent frequent SNPs (MAF > 0.1), pruning for LD ($r^2 < 0.2$) and call rate for individuals > 0.97.

PCA

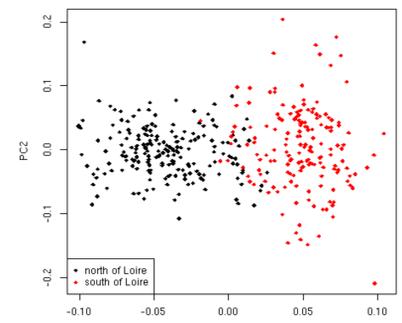


PCA plot of PREGO grand-parents' birth place.

We remove individuals that would otherwise have formed a single cluster (2 from Mayenne, 2 from Deux-Sèvres and 1 from Sarthe).

	PC 1	PC 2
x (longitude)	0.733 ($< 1e-100$)	-0.126 (1.61e-02)
y (latitude)	-0.820 (1.76e-90)	-0.088 (9.28e-02)

Correlation between grand-parents birth place position and the first components.



PCA plot of PREGO grand-parents' birth place. Colors indicating south and north of Loire for birth place.

	PC 1	PC 2
x (longitude)	0.583 (8.07e-45)	-0.200 (9.8e-05)
y (latitude)	-0.330 (2.62e-11)	-0.055 (0.293)

Partial correlation between grand-parents birth place position and the first components with variable indicating south of Loire.

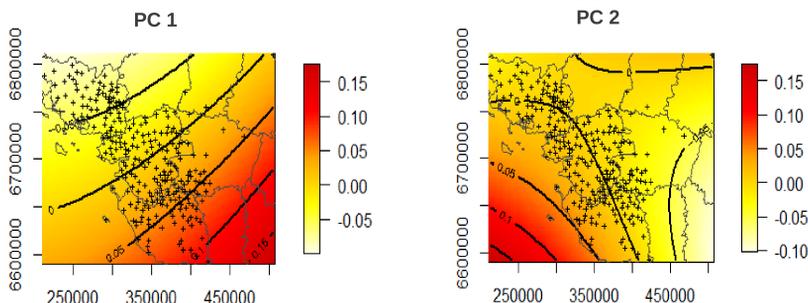
	Loire-Atlantique		Morbihan		Vendée	
	PC 1	PC 2	PC 1	PC 2	PC 1	PC 2
x (longitude)	0.478 (1.32e-09)	0.017 (8.37e-01)	-0.067 (0.52)	-0.070 (0.01)	0.289 (0.008)	-0.282 (0.009)
y (latitude)	-0.662 (1.43e-19)	-0.343 (2.60e-05)	0.084 (0.42)	0.008 (0.93)	0.263 (0.016)	0.140 (0.935)

Correlation between grand-parents birth place position and the first components.

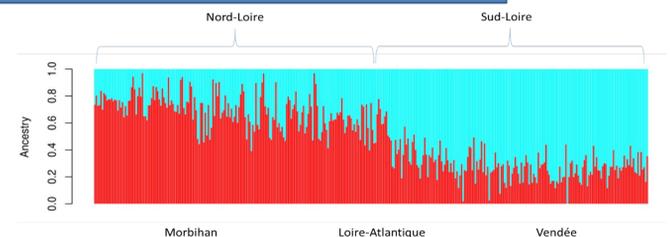
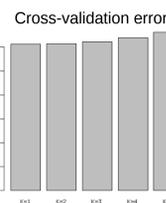
IBD sharing

	Loire-Atlantique	Maine-et-Loire	Morbihan	Vendée
Loire-Atlantique	0.854	0.806	0.870	0.808
Maine-et-Loire		0.892	0.807	0.828
Morbihan			0.939	0.804
Vendée				0.858

Spatial kriging plots



Spatial kriging gives components geographical values by interpolation.



We completed our exploration of fine-scale genetic structure using a model-based ancestry estimation model. This model, implemented in the software ADMIXTURE, is simultaneously modeling the genotype frequencies of all genetic markers as a mixture K populations. The most likely value of K is generating the lower error rate.

Conclusions

- We observe strong correlation between genetic and geography at a finer scale, confirming and strengthening our previous results.
- The Loire river seems to be a genetic barrier
- We observe residual correlation after removing the North-South Loire river (but with low significance, like in Morbihan).

Perspectives

- Apply haplotype-based methods which should reveal more subtle structure.
- Investigate possible batch-effect due to difference of ascertainment by plate.

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