# Gene-Environment interactions in childhood type 1 diabetes. A case-only geographical approach in the Isis-Diab cohort.

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## BACKGROUND

The « hygiene hypothesis » postulates that the reduced exposure to infections favours the development of autoimmunity and childhood type 1 diabetes (T1D). The assessment of the possible relationships between infections and T1D still defies the classical tools of epidemiology. T1D is caused by complex, and possibly heterogeneous interactions between genetic variants (G) and environmental factors (E). There has been however a limited number of GxE studies.

## OBJECTIVES

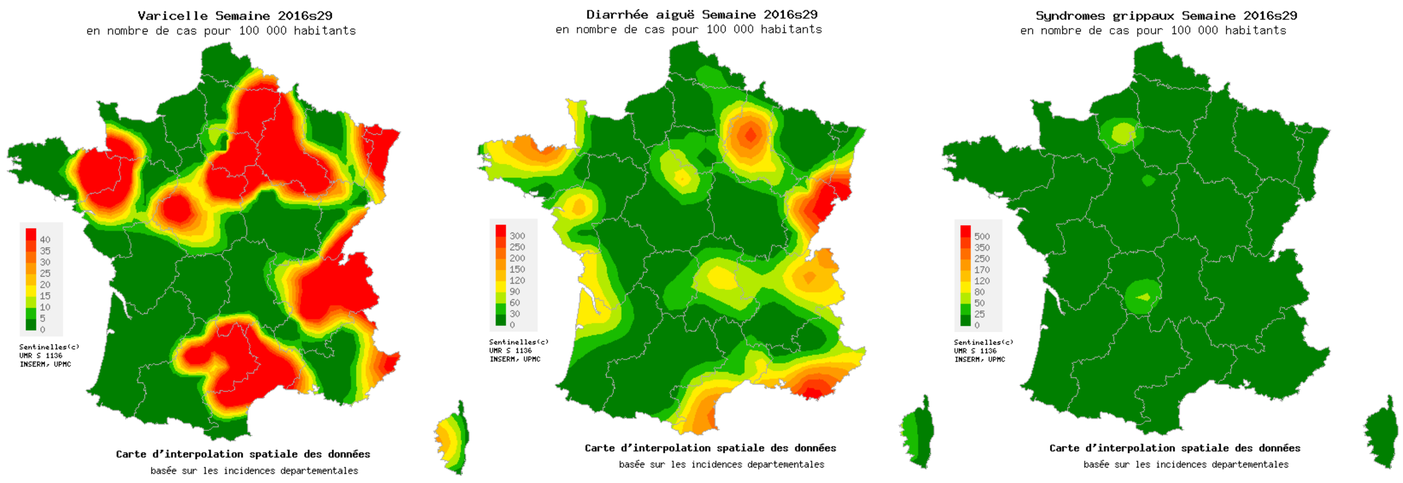
To explore GxE interactions with a « case-only » approach and obtain proof-of-concept results. This method can be used since geographical infectious exposures are independent of genotypes.

## METHODS

1956 patients, who developed autoimmune T1D at age 7.1 ± 3.4 yrs after 1984, were genome-wide genotyped with Illumina microarrays.

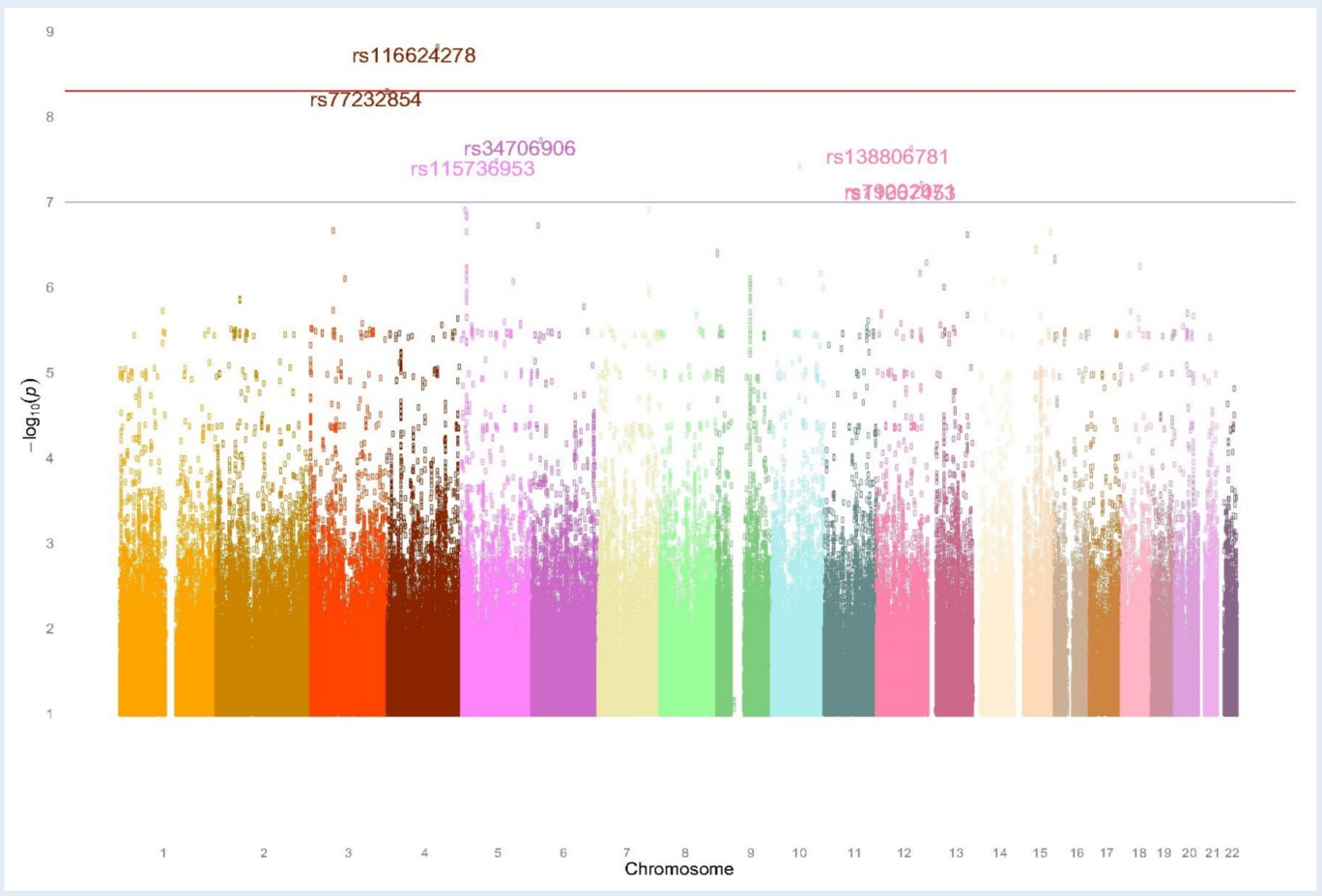
Infectious exposures were determined using the French Sentinel System (FSS) mapped at the geolocalized address of the child between 1 and 3 yrs of age and before diagnosis. The FSS provides weekly regional incidence data : http://www.sentiweb.org.

Levels of infectious exposures were compared across genotypic groups at each SNP position of the genome-wide scan (GWAS).




## RESULTS

GxE interactions of 1,2 and 11 SNPs were detected with exposures to influenza-like illnesses (ILI), diarrhea and varicella, respectively. Interactions between varicella exposure and 2 SNPs (rs116624278 and rs77232854) survived the Bonferroni correction. None of the SNPs was within a region known to predict T1D susceptibility. Their interaction with the exposure to varicella exposure escapes understanding, but might be thought within a protective context for varicella towards T1D. Our lack of biological understanding of the GxE interactions should not be felt as too deceiving since it is common to the vast majority of genomic studies in multifactorial diseases.




**Manhattan Plot showing the SNPs associated with an environmental exposure to chickenpox.** The exposure is the cumulated incidence of chickenpox before age 3yrs computed at the place of birth. The grey line indicates the significance level ($p=1.4/10^{-8}$) considered as possibly indicating an association at birth. The two SNPs above the red line (located in Chromosome 4) passed the Bonferroni correction ($p<7.1 \times 10^{-9}$). rs116624278 is an intergenic SNP located between *PGRMC2* and *JADE1* genes, in a QTL for chronic obstructive pulmonary disease, heart rate and osteoarthritis. rs77232854 is an intergenic SNP located between *PIGG* and *PDE6B*. The two SNPs seem to be in inactive chromatin regions.

## CONCLUSIONS

Space-time GxE interactions can be modeled to explore T1D epidemiology. As for most GWAS-based research, statistical associations are not directly indicative of biological mechanisms. The combination of next generation sequencing and numerous environmental databases will deserve a big data approach of T1D causality.

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Diabetes

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