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Abstract — We implemented a brain-wise genome-wide association tool and ran a study on gray matter in neuroimaging. It reveals an association between Pallidum/Putamen regions and a SNP; both may be related to existing neuroimaging and genetics findings.

Index terms - Imaging Genetics, MRI, SNPs.

I. INTRODUCTION

Structures of the brain have been shown to be highly heritable either globally or locally. We chose to study the gray matter (GM) tissue in the subjects of the IMAGEN cohort [1]. We present here the results from a method based on the agnostic approach that screens the whole genotype measured in a set of single nucleotide polymorphisms (SNPs) to find potential association with a trait. Basically, we conducted the study for each voxel of GM leading to a voxel-wise genome wide association study (vGWAS, with as many phenotypes as GM voxels in one image) [2]. vGWAS consists in adjusting across subjects an additive model between the variant configurations – a SNP takes the value 0, 1 or 2 that counts the number of mutated alleles at the SNP position– and the GM volume in each voxel within the image. This involves fitting numerous linear models and is referred to as mass univariate linear models (MULM).
Our study reveals two significant associations. Since this work is still ongoing, we will specifically focus on the first one. The links between our findings and existing results are outlined.

II. MATERIALS AND METHODS

MR images, SNPs and demographics originated from the multicentric IMAGEN project designed to identify biological and environmental factors that might alter behavior in teenagers (~2,000 subjects). Anatomical MR images were obtained using the ADNI 3D T1-MPRAGE. We considered GM volume as phenotype of interest. Using SPM8 and Voxel Based Morphometry [3], the T1-images were segmented and spatially normalized using a customized adolescent brain template; then the images were modulated with the Jacobian determinants of the nonlinear deformation yielding volumes with matrix size 121x145x121 and voxel size 1.5x1.5x1.5 mm.
Genome-wide genotyping was performed using Illumina 610 and 660 arrays. Quality control comprised a check for the genotyping call rate and the population homogeneity in European ancestry. Finally, we selected SNPs with Minor Allele Frequency >5%, Hardy Weinberg Equilibrium p<1e-4 from the autosomal chromosomes.
For one (SNP, voxel) pair, let consider y be a vector of observations (GM) in the voxel, and x a vector of mutated allele counts for the SNP across the subjects. We fit the model: $y = x\beta + Z\gamma + \varepsilon$, where Z is the matrix of confounding variable and ε is an error term. The Family Wise Error Rate is controlled using permutations performed on the y. We used the algorithm presented in [4]. Briefly, this algorithm first extracts the residuals $R_{y|Z}$ and $R_{x|Z}$, replaces the costly pseudo inverse of the design matrix by a correlation to yield the usual *F-score* and uses a corrective term to compute exact *F-score* on permuted $R_{y|Z}$ data. This algorithm was adapted to work on GPUs [5]. Considering only the subjects with good quality and complete data, the vGWAS was applied on n=1,292 subjects, 466,125 SNP variables, 336,188 GM voxels and 3 covariables (sex, centre, pubertal status) with 10,000 permutation, which represents 1.56e+15 statistical scores. To manage this flood of statistical scores, only those above a threshold F_T were kept. Post processing analyzer scripts computed the permutation distribution of the *max-F* under the null to obtain the corrected p_{corr} *values*.
A post-hoc analysis was performed in the same sample in anatomical ROIs that contained the voxels maximally associated to the SNP; in this post-hoc we studied the mean GM value within an anatomical region as phenotype and we fitted a dominant genetic model. We considered the Putamen, Pallidum, Accumbens and Thalamus from the subcortical HarvardOxford atlas.

III. RESULTS

The MULM run involved 200 GPUs of Curie French supercomputer running for 4 days (~12.000 hGPU). Two pairs of (voxel, SNP) got an association that passed p_{corr}<1.e-4 ; the other associations were not significant p_{cor}>0.5. The first hit relates SNP rs13107325 (rs13x) with one voxel (X=78, Y=84, Z=52) in the Pallidum/Putamen area (see Figures 1and 2).

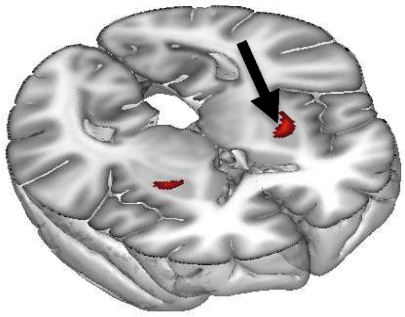

Figure 1. The first pair of (Voxel, SNP) detected as significant in the vGWAS study. The associated voxel (X=78, Y=84, Z=52) we report in this abstract is shown here with the cluster (CLU) of connected voxels in red with a score that passes F_T.

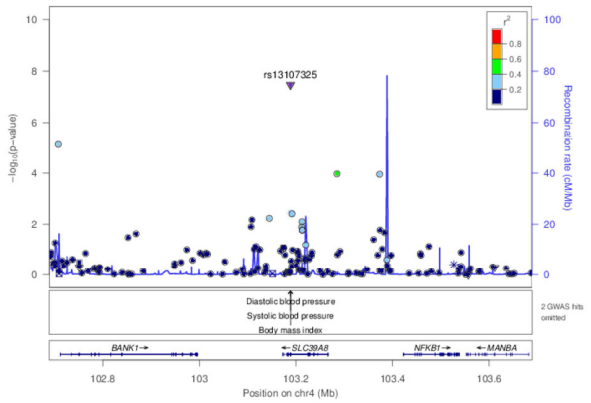

Figure 2. rs13107325 in its genomic context, variant of gene SLC39A8; mean GM in the CLU regions is used as phenotype to generate this plot (from LocusZoom).

The mean GM value of 5 regions was studied and a post-hoc dominant model including sex, centre, and pubertal status was fitted. P-values of the score of the model terms in the anova study are reported in Table 1.

ROI	rs13x	gender	pds	centre
R Pallidum	2,0e-10	1,1e-46	3,6e-02	1,1e-34
L Pallidum	1,1e-09	8,1e-49	8,2e-02	8,3e-08
R Putamen	1,1e-07	4,2e-54	1,4e-01	7,7e-35
L Putamen	1,7e-07	7,4e-53	1,3e-01	2,9e-12
R Accumb	8,1e-03	3,4e-48	6,0e-02	2,8e-03
L Accumb.	1,7e-02	1,5e-53	2,2e-01	1,2e-03
R Caudate	6,3e-02	2,3e-27	4,6e-02	1,7e-02
L Caudate	1,1e-01	2,6e-28	8,5e-02	1,5e-02
R Thalamus.	8,1e-01	1,9e-58	7,7e-02	6,6e-06
L Thalamus	8,8e-01	1,2e-59	1,1e-01	8,9e-11

Table 1:.Uncorrected p-values for the terms of the model to predict ROI mean GM volume.

IV. DISCUSSION – CONCLUSION

A vGWAS reveals a significant association (FWER p-val < 10e-4) between rs13x and GM volume in (X=78, Y=84,Z=52); post-hoc analysis shows a significant positive association with mean GM volume in Putamen and Pallidum regions.

The single nucleotide polymorphism rs13x (fwd: C→T) is a missense coding SNP (Ala→Thr at pos. 391) located on chromosome 4q22 in exon 8 of the metal-ion transporter gene SLC39A8. Existing GWAS of large datasets in human already revealed robust associations between rs13x and body mass index or obesity [6], and schizophrenia [7]. SLC39A8 is a transmembrane protein that mediates the cellular uptake of divalent metal-ions including zinc and manganese which are essential in brain biology. Located in synaptic vesicles, Zn acts as a neuromodulator of synaptic transmission and plasticity in limbic/cortical structures; Mn is an essential cofactor for the astrocyte-specific enzyme glutamine synthetase, which catalyzes the conversion of glutamate to glutamine [7]. Since SLC39A8 is highly expressed in Placenta, Putamen, Pallidum (>x10) and Striata [8], the association suggests an implication of the variant in metal homeostasis mechanisms in the developing brain.

In neuroimaging, two recent multicentric population studies of GM [9], [10] revealed a larger volume of Putamen found in patients with various psychiatric syndrome, suggesting this phenotype is a marker of interest.

Our study confirms the sex differences in Putamen and Pallidum volume [11] and the effect of the scanner on the VBM method. Nevertheless the effect of rs13x mutated allele remains significant. The effect appears to be located in two main structures out of the different subcortical ROIs assessed in the post-hoc analysis.

We implemented and ran a vGWAS to investigate potential links between voxel-based gray matter density and SNPs. We reported here one hit with rs13x that was independently found in other recent works. The result would need replication, but together with genomic meta information and neuroimaging results it provides clues to hypothesize some biological mechanisms in brain and to design future studies.

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