UNIVERSITE DU DROIT ET DE LA SANTE - LILLE 2

FACULTE DE MEDECINE HENRI WAREMBOURG

Année 2018

THÈSE POUR LE DIPLÔME D'ÉTAT
DE DOCTEUR EN MÉDECINE

Polymorphismes des gènes des récepteurs A_1 et A_{2A} de l'adénosine et déclin cognitif lié à âge – Cohorte des 3 cités

Présentée et soutenue publiquement le 30 mai à 16 heures
au Pôle Recherche

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Avant-propos

Cette thèse d'exercice a été réalisée au sein de l'unité mixte de recherche 1167 de l'Institut National de la Santé et de la Recherche Médicale (Inserm, UMR 1167) hébergée au sein de l'Institut Pasteur de Lille et dont le projet de recherche s'intitule "Facteurs de risque et déterminants moléculaires des maladies liées au vieillissement". Ce travail a été conduit sous la direction du Professeur Florence RICHARD.

Nous remercions le LabEx DISTALZ, les participants à l'étude et l'équipe d'étude 3C. La base de données est soutenue par l'ANR (ADORATAU), la Région Hauts-de-France (PARTENAIRR Cognadora), l'Inserm et l'Université Lille 2.

Les résultats obtenus au cours de ce projet ont donné lieu aux publications et communications suivantes :

Article en cours de soumission

- M. Wathelet, C. Bellenguez, D. Blum, J. Dumont, L. Buée, C. Berr, JF. Dartigues, C. Tzourio, P. Amouyel, F. Richard. Genetic polymorphisms of adenosine receptors genes A1 and A2A in association with aging cognitive decline – The Three-city Cohort study. *Neurobiology of disease.*

Communication affichée

- M. Wathelet, C. Bellenguez, D. Blum, J. Dumont, L. Buée, C. Berr, JF. Dartigues, C. Tzourio, P. Amouyel, F. Richard. Genetic polymorphisms of adenosine receptors genes A1 and A2A in association with aging cognitive decline – The Three-city Cohort study. *Longevity, first international symposium research on healthy aging, Lille, France, december 2016.*

Résumé

Polymorphismes des gènes des récepteurs A1 et A2A de l'adénosine et déclin cognitif lié à âge – Cohorte des 3 cités

Introduction

Le "syndrome de fragilité" est un syndrome gériatrique complexe impliquant un déficit cognitif en l'absence de démence. Des études ont suggéré que les récepteurs A_1 et A_{2A} de l'adénosine (ADORA1 et ADORA2A), éléments clés du fonctionnement cognitif, pouvaient être impliqués dans le déclin cognitif lié à l'âge (DCLA). En outre, la caféine, antagoniste des récepteurs de l'adénosine le plus consommé, pourrait avoir un effet protecteur contre le DCLA. L'objectif de cette étude était d'étudier l'association entre les polymorphismes des gènes d'ADORA1 et ADORA2A et le DCLA. En cas d'association, la médiation par la caféine était testée. A noter que la « réserve cognitive » a été prise en compte en raison de la capacité des personnes à haut niveau d'éducation à compenser le DCLA.

Méthodes

5019 participants à la Cohorte des 3 cités ont été analysés. Le DCLA était mesuré par le test d'Isaac en 15 secondes (IST15) à l'inclusion puis à 2, 4 et 7 ans. 70 polymorphismes mononucléotidiques (SNPs) des locus d'ADORA1 et ADORA2A ont été testés. Des modèles linéaires mixtes ont estimé l'association entre ces SNPs et l'IST15 au moyen d'une triple interaction SNP*temps*éducation. En cas de triple interaction significative, les analyses étaient stratifiées sur le niveau d'éducation. Dans le cas contraire, les modèles étaient exécutés sans triple interaction pour tester l'effet des SNPs sur le DCLA dans la population totale. Pour les SNPs associés au DCLA, des analyses de médiation évaluaient le rôle de la caféine.

Résultats

Le SNP rs5760440, situé dans le locus d'ADORA2A, a montré une triple interaction temps*SNP*éducation significative après correction de Bonferroni sur 70 tests ($p < 7{,}1 \times 10^{-4}$). Pour ce SNP, les analyses ont été stratifiées sur le niveau d'éducation. L'allèle mineur était associé à une diminution de l'IST15 (bêta = $-9{,}2 \times 10^{-2}$, ET = $2{,}6 \times 10^{-2}$, $p = 4{,}4 \times 10^{-4}$) chez les sujets à bas niveau d'éducation. Cette association n'était pas médiée par la caféine et aucune association n'a été montrée chez les individus à haut niveau d'éducation. Pour les 69 autres SNPs, les modèles ont été exécutés sans la triple interaction et aucun SNP n'était associé au déclin de l'IST15 dans la population globale.

Conclusion

Le SNP rs5760440, situé dans le locus ADORA2A, était associé au déclin de l'IST15 chez les personnes à bas niveau d'éducation. Aucun SNP n'était associé au déclin de l'IST15 dans la population totale.

Abstract

Genetic polymorphisms of adenosine receptors genes A1 and A2A in association with aging cognitive decline – The Three-city Cohort study

Introduction

"Cognitive fragility" is a complex syndrome involving cognitive impairment after excluding dementia. Some studies suggested that adenosine receptors A_1 and A_{2A} (ADORA1 and ADORA2A), key elements of cognition control, are likely to be implicated in aging cognitive decline (ACD). Besides, caffeine, the most consumed adenosine receptors antagonist, has been suspected to have a protective effect against ACD but the association remains uncertain. Our objective was to study the association between polymorphisms in ADORA1 and ADORA2A locus and ACD evaluated by the Isaac set-test in 15 seconds (IST15). If an association was identified, we then assessed the part mediated by caffeine. As highly educated people are likely to offset ACD, which could hide the association between a risk factor and ACD, we considered “cognitive reserve” in our models.

Methods

Analysis was performed on 5019 participants from the Three-city Cohort study. ACD was evaluated by IST15 and was measured at baseline, 2, 4 and 7 years. 70 genotyped single nucleotide polymorphisms (SNPs) were considered in ADORA1 and ADORA2A locus. Association between SNPs and IST15 was estimated with linear mixed models including a SNP*time*education interaction. In case of significant triple interaction, analyses in subgroups were performed according to education levels. Otherwise, models were run without this triple interaction to test the SNPs effect on ACD in the overall population. For SNPs associated with ACD, mediation analyses were performed to assess the role of caffeine consumption.

Results

The SNP rs5760440, located in the ADORA2A locus, showed a significant time*SNP*education interaction after Bonferroni correction on 70 tests ($p < 7.1 \times 10^{-4}$). For this SNP, analyses have been stratified on education level. The minor allele was associated with a worst IST15 evolution (beta = -9.2×10^{-2}, SE = 2.6×10^{-2}, p = 4.4×10^{-4}) in low educated subjects. This association was not mediated by caffeine consumption and no association was found in highly educated individuals. Of the 69 other SNPs tested, models were run without the triple interaction and none was associated with IST15 decline in the overall population.

Conclusion

Rs5760440, located in the ADORA2A locus, was associated with IST15 decline in low educated people. No SNP was associated with IST15 decline in the overall population.

Liste des abréviations

3C	Cohorte des 3 cités
ACD	Age-related cognitive decline
ADORA1	Adenosine A_1 receptors
ADORA2A	Adenosine A_{2A} receptors
APOE	Apolipoprotein E
BVRT	Benton Visual Retention Test
DCLA	Déclin cognitif lié à l'âge
DNA	Deoxyribonucleic acid
GWAS	Genome wide association studies
IST15	Isaac's Set Test, 15-second version
MMSE	Mini-mental state examination test
PCA	Principal component analysis
SNP	Single nucleotide polymorphisms

Contexte

Transition démographique et épidémiologique

La transition démographique est un modèle explicatif du changement qui s'opère dans chaque pays : le passage d'une population à hauts taux de natalité et de mortalité à une population à faibles taux de natalité et mortalité, entraînant notamment un vieillissement de la population (1). Les calendriers sont variables en fonction des pays mais cette mutation démographique a une dimension mondiale : 900 millions de personnes étaient âgées de plus de 60 ans en 2015 et ce nombre devrait doubler d'ici 2050 (2). Or cette transition démographique s'accompagne d'une transition épidémiologique liées aux changements de morbi-mortalité au sein des populations : le recul des maladies infectieuses a permis le vieillissement des populations mais, en parallèle, les pathologies liées au vieillissement dont les cancers, les maladies vasculaires et neurodégénératives progressent (3). L'étude relative au fardeau global des maladies (« Global burden of disease study ») datant de 2015 décrit les troubles neurologiques comme première cause de perte d'années de vie en bonne santé et comme deuxième cause de décès. La maladie d'Alzheimer et les autres démences font partie des troubles neurologiques les plus fréquents (4).

Vieillissement

Le vieillissement est un processus évolutif particulièrement hétérogène. Classiquement, comme l'ont proposé Rowe *et al*., trois modes d'évolution peuvent être décrits :

- le vieillissement réussi (*successful aging*) qui ne comporte pas d'atteinte des fonctions physiologiques ni de pathologie ;
- le vieillissement habituel ou usuel (*usual aging*) qui comporte des atteintes des fonctions considérées comme physiologiques pour l'âge mais sans pathologie particulière ;
- et le vieillissement avec pathologies sévères (*pathological aging*) évolutives ou compliquées et/ou handicap (5).

Syndrome de fragilité cognitive

La notion de fragilité, introduite par les Anglais sous le terme de *frailty*, désigne un vieillissement intermédiaire entre le vieillissement habituel et le vieillissement pathologique. Cet état est la résultante du déclin cumulatif des fonctions physiologiques sans pathologie identifiée. En cas de fragilité, le sujet âgé est plus à risque d'incapacité, d'hospitalisation ou de décès en cas de survenue d'un événement aigu auquel il ne sera pas en mesure de faire face (6). Cependant, il s'agit d'un état potentiellement réversible (7).

En 2013, un nouveau syndrome gériatrique a été défini par un groupe de consensus international organisé par l'Académie internationale sur la nutrition et le vieillissement et l'Association internationale de gérontologie et de gériatrie : la « fragilité cognitive » qui inclut une déficience cognitive liée à l'âge mais exclut une démence d'Alzheimer concomitante ou d'autres démences. La fragilité cognitive est décrite comme un précurseur des pathologies neurodégénératives et sa potentielle réversibilité est rappelée par le groupe de consensus (8). Le syndrome de fragilité cognitive est donc une cible privilégiée en matière de recherche et de prévention.

Introduction

"Cognitive fragility" is a complex geriatric syndrome involving cognitive impairment after excluding dementia (8). Age-related cognitive decline (ACD) depends on genetic and environmental risk factors. One modifiable risk factor associated with ACD is habitual caffeine consumption. Indeed, previous data support a beneficial impact of caffeine consumption towards cognitive decline in elderly but also a pro-cognitive effect in young individuals (9–11). In a normal consumption range, effects of caffeine are ascribed to its ability to block adenosine receptors, particularly A_1 and A_{2A} (12). Adenosine A_1 and A_{2A} receptors (ADORA1 and ADORA2A) are key elements in the control of plasticity and cognition by the adenosine neuromodulator (13). In rodents, both receptors have been described not only to fine tune synaptic plasticity in area important for cognitive functions (i.e. cortex and hippocampus) but also to control learning and memory in cognitively-impaired models (14–17). Besides caffeine consumption, ACD but also cognitive decline associated with Alzheimer's disease, is presumably delayed by a compensatory "cognitive reserve", particularly ascribed to the education level, lower education level being a known risk factor for ACD and Alzheimer's disease (18–20). Interestingly, in some cases, association between a risk factor and cognitive decline is only salient in populations exhibiting a low cognitive reserve (i.e. low education level) (21,22).

While some data are available regarding caffeine-induced anxiety and sleep impairments, impact of polymorphisms in ADORA1 and ADORA2A genes towards ACD has been overlooked (23). In the present study, we aimed to evaluate potential association between polymorphisms in ADORA1 and ADORA2A genes and ACD (excluding dementia), considering education level.

Material and methods

The Three-city cohort

The Three-city (3C) is a population-based observational and prospective cohort study conducted in three French cities to study the link between dementia and cardiovascular risk factors. Participants were drawn on electoral lists of Bordeaux, Dijon and Montpellier. Eligible persons were aged 65 and over and living at home. Between March 1999 and March 2001, 9294 people were included. They were followed for 10 years with an evaluation at baseline, 2, 4, 7 and 10 years. At each visit, investigators collected lifestyle and health status information using standardized survey questionnaires. The protocol was approved by the ethic committee of the university hospital in Kremlin Bicêtre. Participants signed a consent and were free to refuse a test (such as blood samples) (24). At the time of the study, cognitive data was available for the 7 first years only.

Clinical data

At inclusion, the following clinical variables were collected: 1) socio-demographic characteristics: age, gender and education level; 2) cardiovascular risk factors: arterial tension, alcohol consumption, smoking status and depression; 3) lifestyle: caffeine consumption and 4) results of psychometric tests: mini-mental state examination test (MMSE), Benton Visual Retention Test (BVRT) and Isaac's Set Test in 15 seconds (IST15). MMSE is a global cognitive assessment test, BVRT evaluates a non-verbal aspect of cognition and IST15 appraises verbal fluency by the count of words spoken in 15 seconds by a subject from four defined semantic categories (animals, colors, fruits, cities). In each case, a lower score corresponds to worse performances. Conversely to MMSE and BVRT, IST15 has good metrological properties and a greater sensitivity to modulation of cognitive function. Indeed, verbal fluency, evaluated by IST15, is one of the first

abilities affected in ACD. Besides, it can detect small changes in all the range of cognition. Conversely, MMSE and BVRT are only good at detecting changes in low levels of cognition (25–28). IST15 was thus more appropriate in our population given heterogeneity of initial cognitive level. Psychometric tests were assessed at each visit of the follow-up.

Genetic data

Blood samples were transferred to the National Genotyping Center and DNA samples were genotyped with Illumina Human610-Quad BeadChips™ (Illumina, Inc., San Diego, CA, USA) (29). In this study, we considered only single nucleotide polymorphisms (SNPs) in ADORA1 and ADORA2A genes and 50 kb upstream and downstream. SNPs with call rates below 98%, with minor allele frequency below 5% or that did not meet Hardy–Weinberg equilibrium were excluded. Finally, 70 SNPs were analyzed, 55 in the ADORA1 locus and 15 in the ADORA2A locus.

Study population

6580 3C cohort participants who accepted the blood test were eligible. We excluded individuals with non-European ancestry, poor quality genotyping (call rate below 98%), discordance between clinical and genetic gender or with outlying heterozygosity rate. Related individuals were also excluded. 6220 subjects remained after this first selection. Subjects with a diagnosis of dementia at baseline or during the follow-up were excluded because they no longer met the definition of ACD, with the risk of highlighting a SNP associated with dementia rather than ACD. Only subjects whose native language was French were selected because of the cognitive test conditions, and subjects without information on education were excluded. Finally, only participants who attended more than one visit were considered. In total, 5019 subjects were remained in the analysis.

Statistical analyses

The association between SNPs and IST15 was estimated with linear mixed models. Dependent variable corresponded to the score obtained at IST15. Slope and intercept were random. Population structure was assessed by a principal component analysis (PCA) on the whole-genome genetic data. Models terms were SNP, time, gender, age at inclusion, first principal component of PCA, center, education and number of epsilon-4 alleles for apolipoprotein E (APOE). We considered an additive genetic effect model by coding genotypes as 0, 1 and 2 according to the number of minor alleles. The time variable measured the delay since inclusion (in years) and education was a binary variable with low education level corresponding to no schooling or primary school level and high education level corresponding to have attained more than primary school diploma. To reflect the learning effect on the scores due to the repetition of the psychometric tests, the square of the number of prior visits was also introduced in the models.(30) Three interaction terms were considered: SNP*time corresponded to IST15 decline over time according to the SNP, age*time was introduced because evolution of IST15 depends on age at inclusion, and SNP*time*education allowed considering the potential impact of cognitive reserve. In case of significant triple interaction, analyses in subgroups were performed according to education levels. Otherwise, models were run without this triple interaction to test the SNPs effect on ACD in the overall population. A Bonferroni correction was applied to address the issue of multiple testing. For SNPs associated with ACD, mediation analyses were conducted to assess the role of caffeine consumption, measured in cups per day at inclusion, in the association. Sensitivity analyses adjusted for cardiovascular risk factors and depression were performed. MMSE and BVRT were also explored. Since the distribution of the MMSE was not normal, it was normalized (nMMSE) by the following equation:$\sqrt{(30 - MMSE)}$. The minimal MMSE corresponded to a nMMSE score of 0 and the maximal MMSE to a nMMSE score of 100.(31) Analyses were conducted with R 3.2.2, using lme4 and lmertest packages (32).

Results

Table 1: Participants characteristics and comparison tests between the two groups at baseline

	Global population n = 5019	Low educated people n = 2334	Highly educated people n = 2685	p
Scores at inclusion, m ± sd[§]				
IST15	33.0 ± 6.7	31.4 ± 6.5	34.3 ± 6.7	<0.001
BVRT	11.6 ± 2.0	11.1 ± 2.0	12.0 ± 1.8	<0.001
MMSE	27.5 ± 1.8	27.1 ± 2.0	27.9 ± 1.5	<0.001
Number of visits, n (%)				<0.001
2	601 (12.0)	327 (14.0)	274 (10.2)	
3	1205 (24.0)	597 (25.6)	608 (22.6)	
4	3213 (64.0)	1410 (60.4)	1803 (67.2)	
Center, n (%)				<0.001
Bordeaux	1189 (23.7)	559 (24.0)	630 (23.4)	
Dijon	3317 (66.1)	1581 (67.7)	1736 (64.7)	
Montpellier	513 (10.2)	194 (8.3)	319 (11.9)	
Demographics				
Age (in years), m ± sd	73.8 ± 5.3	74.2 ± 5.3	73.4 ± 5.2	<0.001
Female gender, n (%)	3074 (61.2)	1615 (69.2)	1459 (54.3)	<0.001
Caffeine consumption (in cups/day), n (%)				0.160
0	1082 (21.5)	505 (21.6)	577 (21.5)	
1	1352 (27.0)	608 (26.1)	744 (27.7)	
2	1390 (27.7)	678 (29.1)	712 (26.5)	
+3	1183 (23.6)	533 (22.8)	650 (24.2)	
NA	12 (0.2)	10 (0.4)	2 (0.1)	
Number of epsilon-4 alleles for APOE, n (%)				0.267
0	4010 (79.9)	1896 (81.2)	2114 (78.6)	
1	961 (19.1)	418 (17.9)	543 (20.3)	
2	38 (0.8)	18 (0.8)	20 (0.8)	
NA	10 (0.2)	2 (0.1)	8 (0.3)	
Cardiovascular risk factors				
Alcohol consumption at inclusion (g/day), m ± sd	13.0 ± 14.8	11.5 ±13.9	14.3 ± 15.4	<0.001
Active smoker, n (%)	275 (5.5)	100 (4.3)	175 (6.5)	<0.001
Arterial hypertension, n (%)	3920 (78.1)	1887 (80.8)	2033 (75.7)	<0.001
Depression, n (%)	572 (11.5)	296 (12.8)	276 (10.4)	0.007

[§] m ± sd: mean ± standard deviation

5019 subjects were included in the analysis. Their characteristics at baseline are described in *Table 1*. The mean IST15 was 33.0 ± 6.7 points, the mean Benton (BVRT) was 11.6 ± 2.0 and the median MMSE was 28, interquartile range from 27 to 29. 70 SNPs were analyzed: 55 in the ADORA1 locus and 15 in the ADORA2A locus. The SNP rs5760440, located in the ADORA2A locus, showed a significant triple interaction between time, SNP and education level after Bonferroni correction on 70 tests ($p < 7.1 \times 10^{-4}$) (*Figures 1A and 1B*). 15.0% of the samples were homozygous for the C-allele of the SNP rs5760440, 38.6% were homozygous for the T-allele and 47.4% were heterozygous. For this SNP, analyses were further stratified on education level. The minor allele (C) was associated with a worst IST15 evolution (beta = -9.2×10^{-2}, SE = 2.6×10^{-2}, p = 4.4×10^{-4}) in low educated subjects but no association was found in highly educated individuals (beta = 3.4×10^{-2}, SE = 2.6×10^{-2}, p = 0.19). Results were similar with beta = -8.8×10^{-2}, SE = 2.6×10^{-2}, p = 8.7×10^{-4} in low educated people after additional adjustment for depression and cardiovascular risk factors. This association in low educated people was not related to caffeine since caffeine consumption at baseline was not correlated with the IST15 evolution (p = 0.66). Finally, this SNP was not associated with MMSE or BVRT in low educated people (respectively p = 0.62 and p = 0.25). Of the 69 other SNPs, models were run without the triple interaction but none was associated with IST15 decline in the overall population.

Figure 1A: Regional plot at ADORA1 gene for the association between SNP*time*education interaction and IST15

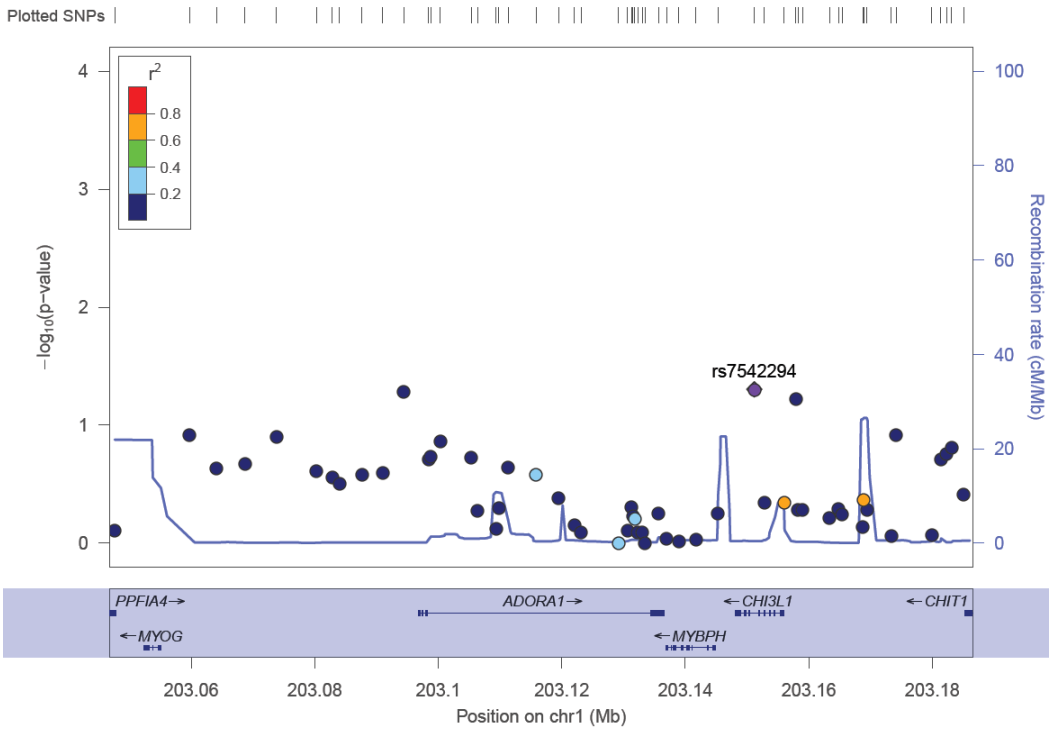
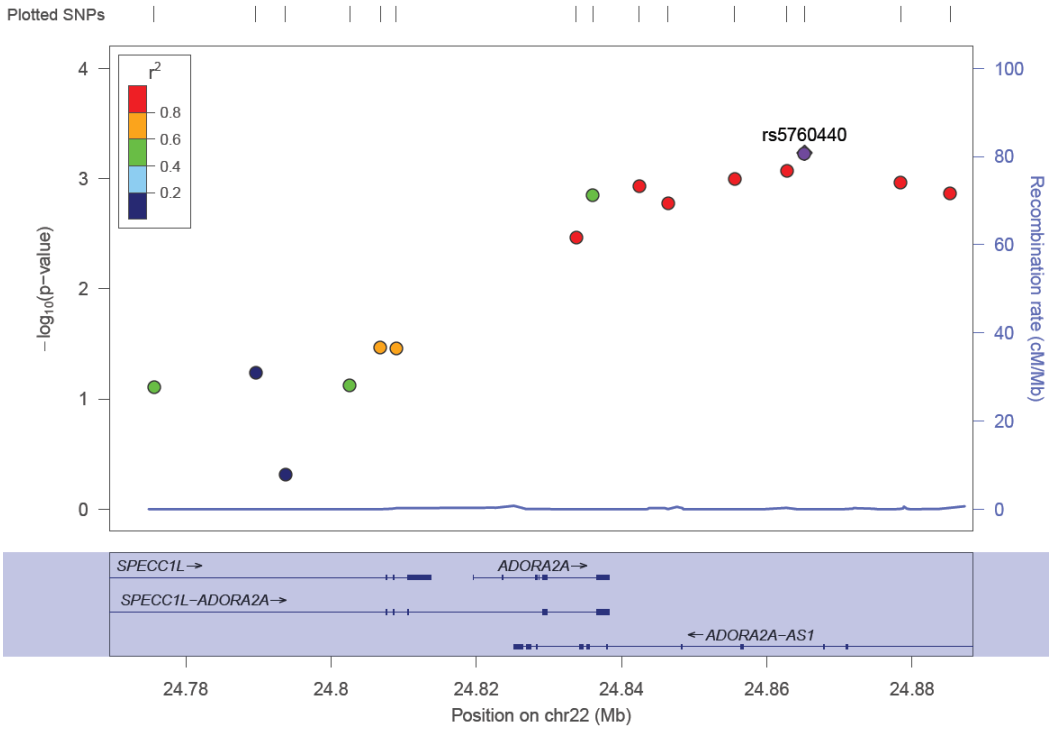


Figure 1B: Regional plot at ADORA2A gene for the association between SNP*time*education interaction and IST15



Discussion

The present study aimed at evaluating the potential association of ADORA1 and ADORA2A polymorphisms with cognitive decline in the Three-City Cohort. In low educated people, after Bonferroni correction on 70 SNPs, the SNP rs5760440, located in ADORA2A, was associated with cognitive decline assessed by IST15 score (beta = -9.2×10^{-2}, SE = 2.6×10^{-2}, $p < 4.4 \times 10^{-4}$). In other words, compared with low educated people without risk allele, low educated people with one risk allele lost almost one word more every decade, and low educated people with two risk alleles lost almost 2 words more every decade. This association was not observed in highly education people and was independent of caffeine consumption.

The strengths of this study include the large elderly sample, the length of follow-up, the longitudinal modeling of cognitive outcomes and the consideration of education. However, the clinical interpretation might seem to be debatable because of the following limitations: the effect size was small (0.1 more word lost by year for one risk allele, 0.2 for two risk alleles) and only observed in low educated people. But considering the level of education allowed illustrating the role of cognitive reserve. Cognitive reserve, corresponding to higher intelligence quotient or higher education level, is known as a protective factor in ACD with expression delayed in highly educated people. Some studies have shown that cognitive reserve modifies association between risk factors and cognitive-related diseases like Alzheimer's disease, mild cognitive impairment or MMSE decline (21,33,34). Studying the overall population without stratifying on education level may lead to miss some avenues of investigation in low educated people, which is regrettable in a context of population ageing and of global efforts against epidemic age-related diseases. Furthermore, there may be an association in highly educated people, but with smaller effect size. However, our results did not support this. It

should be noted that ACD begins at 45 years and extends over an entire life, but participants of the study are included at 65 years at least and followed for 7 years (35). The magnitude of the effect could thus be weakened by the inclusion of already affected people, less likely to decline considerably.

We did not find an association between the SNP rs5760440 and MMSE or BVRT but these scores are known to be less sensitive to ACD and do not measure the same cognitive function than IST15. Indeed, a study of Amieva *et al.* showed that IST15 is the first score to decline in the elderly. It is the most sensible test to detect cognitive decline, compared to BVRT and MMSE (36). This could be explained by the fact that IST15 involves the rapidity of the response whereas processing speed begins to decline early in life (37).

The present study is consistent with the involvement of adenosine A_{2A} receptors towards aged-dependent cognitive decline, as previously studied using experimental models. Indeed, adenosine A_{2A} receptors are known to be a fine tuner of cortical plasticity and A_{2A} dysfunctions are involved in age-related cognitive decline in rat and mouse models (13,17). Our data further emphasize that contribution of A_{2A} receptor towards ACD would be more important in the low-educated population, strengthening the important of the receptor in plasticity processes. While large genome wide association studies (GWAS) has been previously performed on cognitive decline, our study is the first to report an association with ADORA2A in Humans (38–40). The lack of previously association could be explained by several factors: 1) scores used in these studies are not IST15 and each score evaluates a particular cognitive function affected in ACD so that verbal fluency may not have been tested in those previous studies; 2) correction for multiple testing in GWAS is particularly severe which increases risk of false negatives; and 3) these studies did not stratify on education level which might lead to miss the association between ADORA2A and ACD; 4) because, observed effect in our population is weak.

According to linkage disequilibrium calculations from the 1000 genomes data (hg19/*GRCh37* assembly, CEU panel, phase 3), the rs5760440 SNP is in high linkage disequilibrium ($r^2 > 0.8$) with 68 other SNPs. We performed *in silico* analyses using the SNPinfo web portal to investigate the potential functionality of the 68 SNPs in high linkage disequilibrium ($R^2 > 0.80$) with rs5760440 (41). According to this tool, which predicts the effect of a SNP on protein structure, gene regulation and splicing, the rs5760440 SNP (intronic and located in *ADORA2A-AS1*) had no apparent functionality, neither 67 of the 68 SNPs in the linkage disequilibrium block. However, rs5760440 is in complete disequilibrium with the SNP rs5751876 ($R^2 = 1$), not analyzed in this study. The SNP rs5751876 is a synonymous substitution (i.e., not causing a change in the amino acid) occurring in the gene coding regions. Even if the primary sequence of the protein is retained in case of synonymous substitution, it is now known that they may still be involved in the occurrence of pathologies (42). Moreover, it has been shown that SNP rs5751876 is involved in the level of anxiety induced by caffeine consumption (43,44). In our study, caffeine mediation was not found. However, caffeine consumption was collected declaratively and in cups per day. The accuracy of the information can therefore be discussed. Conversely, the linkage disequilibrium between SNP rs5760440 and SNP rs5751876 suggests that further research is needed on caffeine mediation. Furthermore, the rs5760440 SNP may be in linkage disequilibrium with other still uncharacterized variant(s) and *in vitro* functional tests are required to fully explore the potential functionality of SNPs within the ADORA2A locus. Finally, Horgusluoglu-Moloch *et al.* discovered recently that SNP rs9608282, located in the ADORA2A locus, was associated with hippocampal volume in mild cognitive impairment and Alzheimer's disease (45). In our study, we found no association between this SNP and ACD. Moreover, SNP rs9608282 was not in linkage disequilibrium with SNP rs5760440 ($R^2 = 0,154$) which could suggest that both SNPs differentially impact ACD and mild cognitive impairment or Alzheimer's disease.

In summary, our study identified that SNP rs5760440, located in the ADORA2A locus, is associated with ACD in low educated people. Replication analyses in independent studies should be performed to confirm this association.

Perspectives

D’après le modèle de Dahlgren et Whitehead ou celui de l’OMS, l’état de santé d’un individu, à un moment donné, résulte de l’interaction complexe entre plusieurs facteurs appelés déterminants de santé. Ces facteurs peuvent être comportementaux, sociaux, économiques, environnementaux, culturels, psychologiques et génétiques. Ces facteurs ne sont pas indépendants les uns des autres mais s’influencent réciproquement (46,47). C’est également valable pour les variations génétiques qui participent de la susceptibilité aux facteurs exogènes.

La génétique humaine et l’épidémiologie ont d’abord été deux branches aux intérêts différents dans la compréhension des états de santé : l’une explorant les facteurs génétiques, en particulier à des fins diagnostiques ou dans l’identification des mutations causales dans le cadre de pathologies monogéniques ; l’autre se concentrant sur l’identification des facteurs exogènes afin d’éclairer les efforts de prévention (48–50).

Depuis quelques années, après s’être focalisée sur les facteurs comportementaux (tabac, alcool), l’épidémiologie fait face à des nouvelles opportunités et s’ouvre à la génétique. L’épidémiologie génétique est définie comme l'étude du rôle des facteurs génétiques et de leur interaction avec des facteurs environnementaux dans la survenue de maladies au sein de populations humaines (51). Elle cherche à élucider le fonctionnement, les causes des maladies complexes, multifactorielles.

Le déclin cognitif lié à l’âge (DCLA) est une de celles-ci. Cette étude apporte sa contribution dans la volonté d’expliquer les mécanismes à l’œuvre dans la survenue du DCLA en montrant l’implication du SNP rs5760440 chez les personnes à bas niveau d’éducation. Le fait que cette

association n'ait pas été retrouvée chez les personnes à haut niveau d'éducation illustre la complexité du phénomène mêlant facteurs génétiques et exogènes comme la réserve cognitive.

Comme nous le rappelle ce résultat, le poids des facteurs exogènes est majeur en matière de santé publique : les facteurs comportementaux, par exemple, comme la consommation de tabac, d'alcool ou l'inactivité physique font partie des premières causes de morbidité et de mortalité dans le monde. Et ces facteurs comportementaux sont largement influencés par les facteurs socio-économiques (52).

Cependant, l'apport de la génétique est primordial dans l'exploration de l'étiologie de des pathologies complexes. L'identification des gènes impliqués permet notamment de comprendre le mécanisme d'une pathologie et d'identifier des facteurs modifiables potentiellement impliqués. Ces derniers peuvent alors faire l'objet de stratégie de prévention. Dans cette étude, par exemple, nous avons constaté que les SNP rs5760440 et rs5751976 étaient en déséquilibre de liaison ($R^2 = 1$) et que le SNP rs5751976 était impliqué dans la réponse à la consommation de caféine. Or la consommation de caféine est une piste en cours d'exploration pour prévenir le DCLA et les pathologies neurodégénératives.(53,54)

Le progrès de la génétique et le nombre de pathologies avec déterminants génétiques sont tels que la médecine de prévision est en plein essor (55). Le succès d'une telle entreprise n'aura de sens, sur le plan sanitaire, que si le fait de prévoir peut déboucher sur le fait de prévenir. Et même si nous n'en sommes qu'aux prémices, cette perspective sanitaire ne doit pas faire oublier les enjeux que soulève la médecine prédictive sur les autres plans : sociétaux, éthiques, moraux (56).

Références bibliographiques

1. Lee R. The Demographic Transition: Three Centuries of Fundamental Change. Journal of Economic Perspectives. 2003; Available from: http://www.economie.ens.fr/IMG/pdf/lee_2003.pdf

2. OMS. Vieillissement et santé. 2015 Sep; Available from: http://www.who.int/mediacentre/factsheets/fs404/fr/

3. Omran AR. The Epidemiologic Transition: A Theory of the Epidemiology of Population Change. Milbank Q. 2005 Dec;83(4):731–57.

4. Feigin VL, Abajobir AA, Abate KH, Abd-Allah F, Abdulle AM, Abera SF, et al. Global, regional, and national burden of neurological disorders during 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet Neurol. 2017 Nov 1;16(11):877–97.

5. Rowe JW. Physiologic changes of aging and their clinical impact. Psychosomatics. 1984 Dec 1;25(12, Supplement):6–11.

6. Frailty in Older People. Lancet. 2013 Mar 2;381(9868):752–62.

7. Puts MTE, Toubasi S, Atkinson E, Ayala AP, Andrew M, Ashe MC, et al. Interventions to prevent or reduce the level of frailty in community-dwelling older adults: a protocol for a scoping review of the literature and international policies. BMJ Open [Internet]. 2016 Mar 2;6(3). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4785293/

8. Kelaiditi E, Cesari M, Canevelli M, van Kan GA, Ousset P-J, Gillette-Guyonnet S, et al. Cognitive frailty: rational and definition from an (I.A.N.A./I.A.G.G.) international consensus group. J Nutr Health Aging. 2013 Sep;17(9):726–34.

9. Borota D, Murray E, Keceli G, Chang A, Watabe JM, Ly M, et al. Post-study caffeine administration enhances memory consolidation in humans. Nat Neurosci. 2014 Feb;17(2):201–3.

10. Panza F, Solfrizzi V, Barulli MR, Bonfiglio C, Guerra V, Osella A, et al. Coffee, tea, and caffeine consumption and prevention of late-life cognitive decline and dementia: a systematic review. J Nutr Health Aging. 2015 Mar;19(3):313–28.

11. Ritchie K, Carrière I, de Mendonca A, Portet F, Dartigues JF, Rouaud O, et al. The neuroprotective effects of caffeine: a prospective population study (the Three City Study). Neurology. 2007 Aug 7;69(6):536–45.

12. Fredholm BB, Bättig K, Holmén J, Nehlig A, Zvartau EE. Actions of Caffeine in the Brain with Special Reference to Factors That Contribute to Its Widespread Use. Pharmacol Rev. 1999 Mar 1;51(1):83–133.

13. Cunha RA. How does adenosine control neuronal dysfunction and neurodegeneration? J Neurochem. 2016 Jul 1;

14. Machado NJ, Simões AP, Silva HB, Ardais AP, Kaster MP, Garção P, et al. Caffeine Reverts

Memory But Not Mood Impairment in a Depression-Prone Mouse Strain with Up-Regulated Adenosine A2A Receptor in Hippocampal Glutamate Synapses. Mol Neurobiol. 2016 Feb 9;

15. Dias RB, Rombo DM, Ribeiro JA, Sebastião AM. Ischemia-induced synaptic plasticity drives sustained expression of calcium-permeable AMPA receptors in the hippocampus. Neuropharmacology. 2013 Feb;65:114–22.

16. Laurent C, Burnouf S, Ferry B, Batalha VL, Coelho JE, Baqi Y, et al. A2A adenosine receptor deletion is protective in a mouse model of Tauopathy. Mol Psychiatry. 2016 Jan;21(1):97–107.

17. Batalha VL, Ferreira DG, Coelho JE, Valadas JS, Gomes R, Temido-Ferreira M, et al. The caffeine-binding adenosine A2A receptor induces age-like HPA-axis dysfunction by targeting glucocorticoid receptor function. Sci Rep. 2016;6:31493.

18. Amieva H, Mokri H, Le Goff M, Meillon C, Jacqmin-Gadda H, Foubert-Samier A, et al. Compensatory mechanisms in higher-educated subjects with Alzheimer's disease: a study of 20 years of cognitive decline. Brain J Neurol. 2014 Apr;137(Pt 4):1167–75.

19. Osone A, Arai R, Hakamada R, Shimoda K. Cognitive and brain reserve in conversion and reversion in patients with mild cognitive impairment over 12 months of follow-up. J Clin Exp Neuropsychol. 2016 juin;0(0):1–10.

20. Caffò AO, Lopez A, Spano G, Saracino G, Stasolla F, Ciriello G, et al. The role of pre-morbid intelligence and cognitive reserve in predicting cognitive efficiency in a sample of Italian elderly. Aging Clin Exp Res. 2016 May 5;

21. Almeida RP, Schultz SA, Austin BP, Boots EA, Dowling NM, Gleason CE, et al. Cognitive Reserve Modifies Age-Related Alterations in CSF Biomarkers of Alzheimer's Disease. JAMA Neurol. 2015 Jun;72(6):699–706.

22. Yaffe K, Weston A, Graff-Radford NR, Satterfield S, Simonsick EM, Younkin SG, et al. Association of plasma beta-amyloid level and cognitive reserve with subsequent cognitive decline. JAMA. 2011 Jan 19;305(3):261–6.

23. Rogers PJ, Hohoff C, Heatherley SV, Mullings EL, Maxfield PJ, Evershed RP, et al. Association of the Anxiogenic and Alerting Effects of Caffeine with ADORA2A and ADORA1 Polymorphisms and Habitual Level of Caffeine Consumption. Neuropsychopharmacology. 2010 août;35(9):1973–83.

24. 3C Study Group. Vascular factors and risk of dementia: design of the Three-City Study and baseline characteristics of the study population. Neuroepidemiology. 2003 Dec;22(6):316–25.

25. Proust-Lima C, Amieva H, Dartigues J-F, Jacqmin-Gadda H. Sensitivity of four psychometric tests to measure cognitive changes in brain aging-population-based studies. Am J Epidemiol. 2007 Feb 1;165(3):344–50.

26. Sebaldt R, Dalziel W, Massoud F, Tanguay A, Ward R, Thabane L, et al. Detection of cognitive impairment and dementia using the animal fluency test: the DECIDE study. Can J Neurol Sci J Can Sci Neurol. 2009 Sep;36(5):599–604.

27. Isaacs B, Kennie AT. The Set Test as an Aid to the Detection of Dementia in Old People. Br

J Psychiatry. 1973 Oct 1;123(575):467–70.

28. Amieva H, Jacqmin-Gadda H, Orgogozo J-M, Carret NL, Helmer C, Letenneur L, et al. The 9 year cognitive decline before dementia of the Alzheimer type: a prospective population-based study. Brain. 2005 May 1;128(5):1093–101.

29. Lambert J-C, Heath S, Even G, Campion D, Sleegers K, Hiltunen M, et al. Genome-wide association study identifies variants at CLU and CR1 associated with Alzheimer's disease. Nat Genet. 2009 Oct;41(10):1094–9.

30. Vivot A, Power MC, Glymour MM, Mayeda ER, Benitez A, Spiro A, et al. Jump, Hop, or Skip: Modeling Practice Effects in Studies of Determinants of Cognitive Change in Older Adults. Am J Epidemiol. 2016 Feb 15;183(4):302–14.

31. Philipps V, Amieva H, Andrieu S, Dufouil C, Berr C, Dartigues J-F, et al. Normalized Mini-Mental State Examination for assessing cognitive change in population-based brain aging studies. Neuroepidemiology. 2014;43(1):15–25.

32. Team RC, others. R: A language and environment for statistical computing. 2013 [cited 2016 Jul 6]; Available from: http://cran.fiocruz.br/web/packages/dplR/vignettes/timeseries-dplR.pdf

33. Perneczky R, Wagenpfeil S, Lunetta KL, Cupples LA, Green RC, DeCarli C, et al. Education attenuates the effect of medial temporal lobe atrophy on cognitive function in Alzheimer's disease: the MIRAGE study. J Alzheimers Dis JAD. 2009;17(4):855–62.

34. Mortamais M, Portet F, Brickman AM, Provenzano FA, Muraskin J, Akbaraly TN, et al. Education modulates the impact of white matter lesions on the risk of mild cognitive impairment and dementia. Am J Geriatr Psychiatry Off J Am Assoc Geriatr Psychiatry. 2014 Nov;22(11):1336–45.

35. Singh-Manoux A, Kivimaki M, Glymour MM, Elbaz A, Berr C, Ebmeier KP, et al. Timing of onset of cognitive decline: results from Whitehall II prospective cohort study. The BMJ [Internet]. 2012 Jan 5 [cited 2016 May 27];344. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3281313/

36. Amieva H, Le Goff M, Millet X, Orgogozo JM, Pérès K, Barberger-Gateau P, et al. Prodromal Alzheimer's disease: successive emergence of the clinical symptoms. Ann Neurol. 2008 Nov;64(5):492–8.

37. Harada CN, Natelson Love MC, Triebel K. Normal Cognitive Aging. Clin Geriatr Med. 2013 Nov;29(4):737–52.

38. Debette S, Ibrahim Verbaas CA, Bressler J, Schuur M, Smith A, Bis JC, et al. Genome-wide Studies of Verbal Declarative Memory in Nondemented Older People: The Cohorts for Heart and Aging Research in Genomic Epidemiology Consortium. Biol Psychiatry. 2015 avril;77(8):749–63.

39. Davies G, Marioni RE, Liewald DC, Hill WD, Hagenaars SP, Harris SE, et al. Genome-wide association study of cognitive functions and educational attainment in UK Biobank (N=112 151). Mol Psychiatry. 2016 juin;21(6):758–67.

40. Davies G, Armstrong N, Bis JC, Bressler J, Chouraki V, Giddaluru S, et al. Genetic

contributions to variation in general cognitive function: a meta-analysis of genome-wide association studies in the CHARGE consortium (N=53 949). Mol Psychiatry. 2015 février;20(2):183–92.

41. Xu Z, Taylor JA. SNPinfo: integrating GWAS and candidate gene information into functional SNP selection for genetic association studies. Nucleic Acids Res. 2009 Jul;37(Web Server issue):W600–5.

42. Hunt R, Sauna ZE, Ambudkar SV, Gottesman MM, Kimchi-Sarfaty C. Silent (synonymous) SNPs: should we care about them? Methods Mol Biol Clifton NJ. 2009;578:23–39.

43. Alsene K, Deckert J, Sand P, de Wit H. Association between A2a receptor gene polymorphisms and caffeine-induced anxiety. Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol. 2003 Sep;28(9):1694–702.

44. Childs E, Hohoff C, Deckert J, Xu K, Badner J, de Wit H. Association between ADORA2A and DRD2 polymorphisms and caffeine-induced anxiety. Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol. 2008 Nov;33(12):2791–800.

45. Horgusluoglu-Moloch E, Nho K, Risacher SL, Kim S, Foroud T, Shaw LM, et al. Targeted neurogenesis pathway-based gene analysis identifies ADORA2A associated with hippocampal volume in mild cognitive impairment and Alzheimer's disease. Neurobiol Aging. 2017 Dec;60:92–103.

46. Dahlgren, Whitehead. Policies and strategies to promote social equity in health. 1991; Available from: https://core.ac.uk/download/pdf/6472456.pdf

47. OMS. Commission des déterminants sociaux de la santé. 2007; Available from: http://www.who.int/social_determinants/thecommission/finalreport/fr/

48. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. The Huntington's Disease Collaborative Research Group. Cell. 1993 Mar 26;72(6):971–83.

49. Doll R, Hill AB. A study of the aetiology of carcinoma of the lung. Br Med J. 1952 Dec 13;2(4797):1271–86.

50. Dawber TR, Meadors GF, Moore FE. Epidemiological approaches to heart disease: the Framingham Study. Am J Public Health Nations Health. 1951 Mar;41(3):279–81.

51. Vaessen N, van Duijn CM. Opportunities for Population-Based Studies of Complex Genetic Disorders after the Human Genome Project. Epidemiology. 2001;12(3):360–4.

52. OMS. Global status report on noncommunicable diseases. 2010;

53. Panza F, Solfrizzi V, Barulli MR, Bonfiglio C, Guerra V, Osella A, et al. Coffee, tea, and caffeine consumption and prevention of late-life cognitive decline and dementia: a systematic review. J Nutr Health Aging. 2015 Mar;19(3):313–28.

54. Camandola S, Plick N, Mattson MP. Impact of Coffee and Cacao Purine Metabolites on Neuroplasticity and Neurodegenerative Disease. Neurochem Res. 2018 Feb 8;

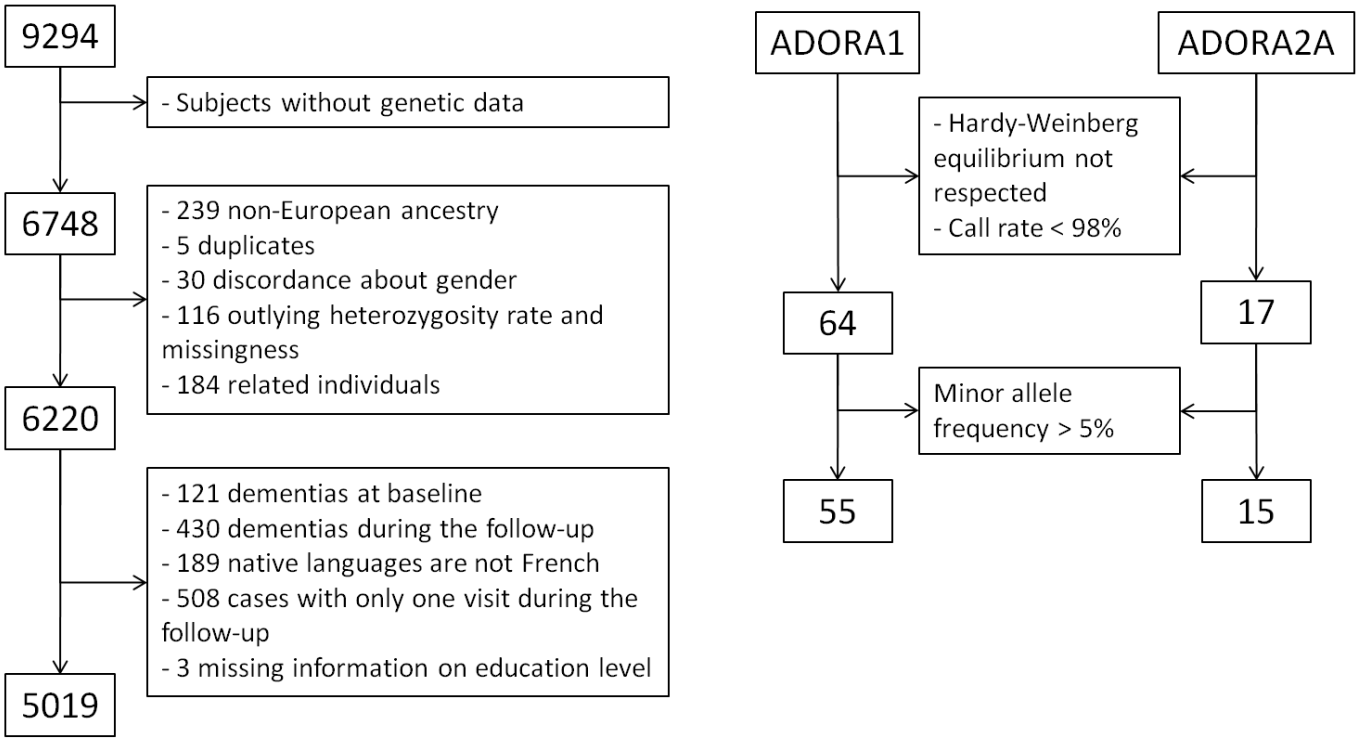
55. Collins FS, Varmus H. A New Initiative on Precision Medicine. N Engl J Med. 2015 Feb

26;372(9):793–5.

56. Centre d’analyse stratégique. Médecine prédictive : les balbutiements d’un concept aux enjeux considérables. 2012 Oct; Available from: http://archives.strategie.gouv.fr/cas/system/files/2012-10-02-medecinepredictive-na289.pdf

Annexes

Annexe 1 : Flow-chart for individuals (left) and for SNPs (right)



Annexe 2 : SNP in high linkage disequilibrium with SNP rs5760440

Calculations from the 1000 genomes data (hg19/GRCh37 assembly, CEU panel, phase 3)

SNP	Chr	Alleles	MAF	Distance	Dprime	R2	Function
rs5760440	22	(C/T)	0.3788	0	1.0	1.0	NA
rs5751882	22	(T/C)	0.3788	-273	1.0	1.0	NA
rs738813	22	(A/G)	0.3788	-2449	1.0	1.0	NA
rs9624479	22	(A/G)	0.3788	3402	1.0	1.0	NA
rs2032115	22	(A/G)	0.3788	4472	1.0	1.0	NA
rs4822493	22	(T/A)	0.3788	4877	1.0	1.0	NA
rs4822494	22	(T/C)	0.3788	4939	1.0	1.0	NA
rs5760441	22	(A/G)	0.3788	6644	1.0	1.0	NA
rs5760435	22	(C/T)	0.3788	-6687	1.0	1.0	NA
rs9612627	22	(T/C)	0.3788	-8858	1.0	1.0	NA
rs1008931	22	(G/A)	0.3788	-9646	1.0	1.0	NA
rs9620391	22	(T/C)	0.3788	9936	1.0	1.0	NA
rs1008932	22	(C/T)	0.3788	-10005	1.0	1.0	NA
rs12168879	22	(C/T)	0.3788	-11514	1.0	1.0	NA
rs738816	22	(T/A)	0.3788	-12954	1.0	1.0	NA
rs1547358	22	(C/T)	0.3788	13243	1.0	1.0	NA
rs5760446	22	(T/C)	0.3788	13617	1.0	1.0	NA
rs5760447	22	(A/G)	0.3788	14102	1.0	1.0	NA
rs1548302	22	(T/C)	0.3788	14370	1.0	1.0	NA
rs1972487	22	(T/C)	0.3788	14469	1.0	1.0	NA
rs11419504	22	(-/T)	0.3788	14477	1.0	1.0	NA
rs4822500	22	(T/C)	0.3788	16046	1.0	1.0	NA
rs4822501	22	(A/G)	0.3788	16498	1.0	1.0	NA
rs11313319	22	(T/-)	0.3788	16647	1.0	1.0	NA
rs2186376	22	(A/G)	0.3788	-16727	1.0	1.0	NA
rs5760448	22	(G/A)	0.3788	17000	1.0	1.0	NA
rs1041750	22	(T/A)	0.3788	-17581	1.0	1.0	NA
rs5760450	22	(T/C)	0.3788	18341	1.0	1.0	NA
rs1041749	22	(T/C)	0.3788	-18796	1.0	1.0	NA
rs5760452	22	(C/T)	0.3788	20036	1.0	1.0	NA
rs33966192	22	(-/AA)	0.3788	20743	1.0	1.0	NA
rs4822504	22	(A/G)	0.3788	21200	1.0	1.0	NA
rs5760454	22	(T/C)	0.3788	21289	1.0	1.0	NA
rs9612623	22	(A/G)	0.3788	-24453	1.0	1.0	NA
rs5760423	22	(T/G)	0.3788	-25069	1.0	1.0	NA
rs4822491	22	(G/A)	0.3788	-25801	1.0	1.0	NA
rs4822490	22	(G/C)	0.3788	-25815	1.0	1.0	NA
rs35320474	22	(-/T)	0.3788	-27278	1.0	1.0	NA
rs5751876	22	(T/C)	0.3788	-27886	1.0	1.0	synonymous
rs3761422	22	(T/C)	0.3788	-38515	1.0	1.0	NA
rs4822498	22	(T/C)	0.3838	11613	1.0	0.9788	NA
rs4822499	22	(C/T)	0.3838	11659	1.0	0.9788	NA
rs5760425	22	(T/G)	0.3838	-22735	1.0	0.9788	NA
rs2032116	22	(A/G)	0.3737	23609	1.0	0.9787	NA
rs36066697	22	(-/A)	0.399	-21385	1.0	0.9185	NA
rs200443659	22	(-/TT)	0.4091	764	1.0	0.8808	NA
rs3966269	22	(G/C)	0.4091	2695	1.0	0.8808	NA
rs4820590	22	(T/C)	0.4091	9510	1.0	0.8808	NA
rs5760444	22	(T/C)	0.4091	13031	1.0	0.8808	NA
rs7288789	22	(C/T)	0.4091	-14290	1.0	0.8808	NA
rs150902635	22	(AAAACAAAAACA/-)	0.4091	14623	1.0	0.8808	NA
rs4822502	22	(C/T)	0.4091	16594	1.0	0.8808	NA
rs4822503	22	(T/C)	0.4091	19469	1.0	0.8808	NA
rs11703648	22	(C/G)	0.4091	-21301	1.0	0.8808	NA

rs11703436	22	(G/C)	0.4091	-21456	1.0	0.8808	NA
rs4822492	22	(C/G)	0.4091	-21593	1.0	0.8808	NA
rs35814840	22	(AT/-)	0.4091	21973	1.0	0.8808	NA
rs5760424	22	(G/A)	0.4091	-24934	1.0	0.8808	NA
rs4822489	22	(T/G)	0.4091	-31427	1.0	0.8808	NA
rs2298383	22	(C/T)	0.4091	-39676	1.0	0.8808	NA
rs9624470	22	(G/A)	0.4091	-44919	1.0	0.8808	NA
rs2267076	22	(T/C)	0.3485	-34592	1.0	0.8772	NA
rs2070474	22	(C/G)	0.3889	26105	0.9564	0.8764	NA
rs4820593	22	(A/T)	0.4141	21900	1.0	0.8626	NA
rs140324	22	(T/C)	0.399	40101	0.9334	0.8003	NA
rs131452	22	(T/-)	0.399	40526	0.9334	0.8003	NA
rs140330	22	(A/G)	0.399	43165	0.9334	0.8003	NA
rs140333	22	(A/G)	0.399	46525	0.9334	0.8003	NA

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Date de Soutenance : 30/05/2018

Titre de la Thèse : Polymorphismes des gènes des récepteurs A_1 et A_{2A} de l'adénosine et déclin cognitif lié à âge - Cohorte des 3 cités

Thèse - Médecine - Lille 2018

Cadre de classement : Médecine

DES + spécialité : DES de santé publique et médecine sociale

Mots-clés : déclin cognitif lié à l'âge, épidémiologie génétique, caféine, prédisposition génétique, ADORA

Résumé :

Introduction. Le "syndrome de fragilité" est un syndrome gériatrique complexe impliquant un déficit cognitif en l'absence de démence. Des études ont suggéré que les récepteurs A_1 et A_{2A} de l'adénosine (ADORA1 et ADORA2A), éléments clés du fonctionnement cognitif, pouvaient être impliqués dans le déclin cognitif lié à l'âge (DCLA). En outre, la caféine, antagoniste des récepteurs de l'adénosine le plus consommé, pourrait avoir un effet protecteur contre le DCLA. L'objectif de cette étude était d'étudier l'association entre les polymorphismes des gènes d'ADORA1 et ADORA2A et le DCLA. En cas d'association, la médiation par la caféine était testée. A noter que la « réserve cognitive » a été prise en compte en raison de la capacité des personnes à haut niveau d'éducation à compenser le DCLA.

Méthodes. 5019 participants à la Cohorte des 3 cités ont été analysés. Le DCLA était mesuré par le test d'Isaac en 15 secondes (IST15) à l'inclusion puis à 2, 4 et 7 ans. 70 polymorphismes mononucléotidiques (SNPs) des locus d'ADORA1 et ADORA2A ont été testés. Des modèles linéaires mixtes ont estimé l'association entre ces SNPs et l'IST15 au moyen d'une triple interaction SNP*temps*éducation. En cas de triple interaction significative, les analyses étaient stratifiées sur le niveau d'éducation. Dans le cas contraire, les modèles étaient exécutés sans triple interaction pour tester l'effet des SNPs sur le DCLA dans la population totale. Pour les SNPs associés au DCLA, des analyses de médiation évaluaient le rôle de la caféine.

Résultats. Le SNP rs5760440, situé dans le locus d'ADORA2A, a montré une triple interaction temps*SNP*éducation significative après correction de Bonferroni sur 70 tests ($p < 7{,}1 \times 10^{-4}$). Pour ce SNP, les analyses ont été stratifiées sur le niveau d'éducation. L'allèle mineur était associé à une diminution de l'IST15 (bêta = $-9{,}2 \times 10^{-2}$, ET = $2{,}6 \times 10^{-2}$, $p = 4{,}4 \times 10^{-4}$) chez les sujets à bas niveau d'éducation. Cette association n'était pas médiée par la caféine et aucune association n'a été montrée chez les individus à haut niveau d'éducation. Pour les 69 autres SNPs, les modèles ont été exécutés sans la triple interaction et aucun SNP n'était associé au déclin de l'IST15 dans la population globale.

Conclusion. Le SNP rs5760440, situé dans le locus ADORA2A, était associé au déclin de l'IST15 chez les personnes à bas niveau d'éducation. Aucun SNP n'était associé au déclin de l'IST15 dans la population totale.

Composition du Jury :

Président :	Monsieur le Professeur Philippe AMOUYEL
Assesseurs :	Monsieur le Docteur Luc DAUCHET
	Monsieur le Docteur David BLUM
Directeur de thèse :	Madame le Professeur Florence RICHARD