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REVIEWS

New candidate SNPs for genetic association with Alzheimer's disease: a linkage disequilibrium analysis for the FCGRIIB and PILRA genes

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ABSTRACT

BACKGROUND Two new SNPs have been recently associated to Alzheimer's disease in African American populations: FCGRIIB rs1050501 C/T, and PILRA rs1859788 A/G. The risk of Alzheimer's disease in FCGRIIB C and PILRA A allele carriers is three times higher than in non-carriers. However, the association between these and other single nucleotide polymorphisms (SNPs) has not been assessed.

METHODS Linkage disequilibrium analysis, with r^2= 0.8 as a threshold value, was used to impute new candidate SNPs, on genomic data from both genes in 26 populations worldwide (n= 2504) from the 1000Genomes database.

RESULTS Four SNPs (rs13376485, rs3767640, rs3767639 and rs3767641) were linked to rs1050501 and one (rs2405442) to rs1859788 in the whole sample.

CONCLUSIONS Five novel SNPs could be associated with Alzheimer's disease susceptibility and play a causal role, even if none of them are exon variants since their potential roles in the regulation of gene expression.

KEYWORDS Alzheimer's disease, linkage disequilibrium, genetic association studies, Single Nucleotide Polymorphisms, FCGRIIB, PILRA

INTRODUCTION

According to PhengenI [1] 31 SNPs, included in 28 genes, have been associated with Alzheimer's disease. However, these studies are based on a variable number of screened SNPs and are performed on specific populations, mostly Europeans. Therefore, to include genetic evidence from a broader sample of genetic markers and populations could contribute to detect new associations between unexplored markers and populations in relation to Alzheimer's disease.

The Hardy-Weinberg equilibrium test and linkage disequilibrium analyses make it possible to explore genetic stratification and physical association among candidate SNPs, which in combination with the existence of large public genomic databases like 1000Genomes [2], open the possibility to test the association between SNPs and Alzheimer's disease in a broad set of populations.

No studies have yet found the ultimate causes of Alzheimer's disease. However, considering several genetic association studies these causes may be, in part, genetic. These association studies provide valuable information about genetic risk loci for the disease and give clues about its root causes [3].

Recently, Pandey et al. [4] studied a sample of African Americans and found that carriers of the SNPs rs1050501 C rs1859788 A alleles, at the low affinity immunoglobulin gamma Fc receptor region II-b (FCGRIIB) and Paired Immunoglobin-Like Type 2 Receptor Alpha (PILRA) genes, respectively, were three times more susceptible to Alzheimer's disease than non-carriers, an effect that was not observed among the European Americans in that study.

Previously, the SNP rs1050501 was found to be associated with lupus in Japanese population by Kyogoku et al. [5], by

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MAIN MESSAGES

- In this article we explored candidate SNPs for association with Alzheimer's disease through linkage diseased linkage disequilibrium testing with FCGRIIB rs1050501 C/T, and PILRA rs1859788 A/G using a dense microarray genomic database.
- Five candidate SNPs for association with Alzheimer's disease were identified: FCGRIIB rs13376485, rs3767640, rs3767639 and rs3767641 and PILRA rs2405442.
- The candidate SNPs for association with Alzheimer's disease reported here are suggested for inclusion in new genetic association studies of Alzheimer's disease.

screening the cDNA variation of a 4,323 bp region comprising exons 4 to 7. Hence, a sampling on greater population variation and gene domains, including both exons and introns, could shed light over other, markers associated to both lupus and Alzheimer's disease. That study is part of a research line that associates the gene polymorphisms to autoimmune diseases and neural uptake [6–8]. Costa et al. [9] did not find association between rs1050501 and Alzheimer's disease in a sample from an Italian health institution. However, Pandey et al. [4] reported a significant effect of the C/C genotype over Alzheimer's disease for that SNP in African American population.

On the other hand, the locus of PILRA rs1859788 was first associated to Alzheimer's disease by Rathore et al. [10]. They showed that, knowing that PILRA codifies for a cell surface inhibitory receptor, the substitution of arginine for glycine at position 78, in conjunction with *Herpes simplex* virus type 1 infection, have a risk effect on Alzheimer's disease. PILRA rs1859788 was further associated with Alzheimer's disease in a metanalysis by Jansen et al. [11]. However, there is confusion in the literature, since some studies cite Lambert et al. [12] for this finding (for example, Agostini et al. [13]).

In this study, linkage disequilibrium between SNPs on FCGRIIB and PILRA, in relation to FCGRIIB rs1050501 and PILRA rs1859788, is analyzed by using the whole sample provided by 1000Genomes database, to identify new markers potentially associated to Alzheimer's disease. The hypothesis here is that new variants located on FCGRIIB and PILRA can be imputed to Alzheimer´s disease due to linkage disequilibrium to rs1050501 and rs1859788, respectively. This is the first study analyzing the imputation of new candidate SNPs for the FCGRIIB and PILRA genes.

METHODS

Sample

Genotypes for FCGRIIB rs1050501 and PILRA rs1859788 SNPs were collected using VCFtools [14], from the 1000Genomes consortium database, which contains whole genome information from 2504 individuals grouped in 5 super populations and 26 populations around the world (Table 1).

Genetic analyses

First, a Hardy Weinberg (HW) test was conducted using VCFtools, on each super-population and populations for FCGRIIB rs1050501 and PILRA rs1859788, to evaluate the null hypothesis: absence of micro-evolutionary factors like natural selection or stratification, as the more plausible factors for human populations. Then, linkage disequilibrium analyses was performed using VCFtools, conducted for FCGRIIB and PILRA SNPs in relation to rs1050501 and rs1859788, respectively. The first analysis was carried out against 760 SNPs, and the second against 95 SNPs sampled in the respective genes. VCFtools outputs an R^2 statistics for the estimation of independent association (i.e., linkage disequilibrium) between each pair of loci. As suggested by Wray [15], a threshold of R^2= 0.8 was established as a strong linkage.

RESULTS

Three super-populations were found to depart from the Hardy-Weinberg equilibrium for FCGRIIB rs1050501: Africa, Latin America, and Europe (P= $2.7x10^{-4}$, $2.4x10^{-4}$ and $5.2x10^{-3}$ respectively). Within those super-populations, two African populations were found to depart from the equilibrium: the Luhya in Webuye, Kenya and the Esan in Nigeria ($8.1x10^{-3}$ and $4.1x10^{-2}$ respectively). As for PILRA rs1859788, only the Gambians in the western divisions of Gambia ($3.3x10^{-2}$), inside Africa, were found to be in disequilibrium.

About the observed heterozygosity in the above populations, for FCGRIIB rs1050501 heterozygosity loss was found in Europe and Latin America (P= $2.2x10^{-4}$ and $5.3x10^{-3}$ respectively) and excess of heterozygosity in Africa, the Esan in Nigeria and the Luhya in Webuye, Kenya (1.7x10-4, $2.3x10^{-2}$ and $6.3x10^{-3}$ respectively). As for PILRA rs1859788, Gambian population showed heterozygosity deficit ($3.3x10^{-2}$).

For FCGRIIB rs1050501, LD analysis tagged four SNPs with R^2 values over 0.8 in each super-population: rs13376485, rs3767640, rs3767639 and rs3767641 (Table 2). It is worth noting that the R^2 values are very similar for each super-population. As for PILRA rs1859788, only one SNP was tagged for each super-population: rs2405442 (Table 3).

DISCUSSION

FCGRIIB rs1050501 and PILRA rs1859788 have been previously associated to Alzheimer's disease in African American population. Here, through linkage disequilibrium analysis four SNPs showed to be associated to rs1050501 and one to rs1859788. This suggests that there is a set of seven markers

Table 1. Sample used in this study. Super populations, populations, and sample sizes (N) is indicated according to the 1000Genomes database.

Super-population	Population	N
African	African Caribbeans in Barbados	96
	Americans of African Ancestry in Southwest, USA	61
	Esan in Nigeria	99
	Gambians in western divisions of Gambia	113
	Luhya in Webuye, Kenya	99
	Mende in Sierra Leone	85
	Yoruba in Ibadan, Nigeria	108
	Total	661
Latin American	Colombians from Medellin, Colombia	94
	Mexican Ancestry from Los Angeles, USA	64
	Peruvians from Lima, Peru	85
	Puerto Ricans from Puerto Rico	104
	Total	347
East Asian	Chinese Dai in Xishuangbanna, China	93
	Han Chinese in Beijing, China	103
	Southern Han Chinese	105
	Japanese in Tokyo, Japan	104
	Kinh in Ho Chi Minh city, Vietnam	99
	Total	504
European	Utah residents with northern and western European ancestry	99
	Finnish in Finland	99
	British in England and Scotland	91
	Iberian population in Spain	107
	Toscani in Italia	107
	Total	503
South Asian	Bengali from Bangladesh	86
	Gujarati Indian from Houston, Texas	103
	Indian Telugu from the UK	102
	Punjabi from Lahore, Pakistan	96
	Sri Lankan Tamil from the UK	102
	Total	489

Source: Prepared by the authors based on the results of the study.

Table 2. Significant LDs between SNPs in FCGRIIB and rs1050501 in super populations.

		Candidate SNPs in FCGRIIB (Position at chromosome 1)				
		rs1050501* (161643798)	rs13376485 (161645877)	rs3767640 (161646116)	rs3767639 (161646120)	rs3767641 (161646112)
African	R^2	-	0.85	0.82	0.82	0.82
	A1	T (0.75)	G (0.73)	T (0.74)	T (0.74)	C (0.74)
	A2	C (0.25)	A (0.27)	C (0.26)	C (0.26)	T (0.26)
East Asian	R^2	-	0.98	0.96	0.96	0.96
	A1	T (0.75)	G (0.74)	T (0.75)	T (0.74)	C (0.74)
	A2	C (0.25)	A (0.26)	C (0.25)	C (0.26)	T (0.25)
South Asian	R^2	-	0.95	0.92	0.92	0.92
	A1	T (0.86)	G (0.86)	T (0.86)	T (0.84)	C (0.86)
	A2	C (0.14)	A (0.14)	C (0.14)	C (0.13)	T (0.14)
European	R^2	-	0.85	0.87	0.87	0.87
	A1	T (0.86)	G (0.88)	T (0.88)	T (0.88)	C (0.88)
	A2	C (0.14)	A (0.12)	C (0.12)	C (0.12)	T (0.12)
Latin American	R^2	-	0.90	0.88	0.90	0.88
	A1	T (0.91)	G (0.91)	T (0.91)	T (0.91)	C (0.91)
	A2	C (0.09)	A (0.09)	C (0.09)	C (0.09)	T (0.09)

R^2 = correlation between pairs of loci; A1= allele 1; A2= allele 2. In parenthesis allele frequencies.
Source: Prepared by the authors based on the results of the study.

which could be used in future genetic association studies related to Alzheimer's disease.

Hardy-Weinberg equilibrium departure was detected for FCGRIIB rs1050501 in three super populations: African, European and Latin American and two populations, the Luhya in Webuye, Kenya and the Esan in Nigeria. Loss of heterozygosity was observed in two super populations (European and Latin American), suggesting population stratification [16]. On the

Table 3. Significant LDs between SNPs in PILRA rs1859788 in super populations.

		Candidate SNPs in PILRA (Position at chromosome 7)	
		rs1859788*	rs2405442
		99971834	99971313
	R^2		0.88
African	A1	A (0.10)	T (0.09)
	A2	G (0.90)	C (0.91)
	R^2		1.00
East Asian	A1	A (0.61)	T (0.61)
	A2	G (0.39)	C (0.39)
	R^2		0.99
South Asian	A1	A (0.29)	T (0.29)
	A2	G (0.71)	C (0.71)
	R^2		0.96
European	A1	A (0.32)	T (0.32)
	A2	G (0.68)	C (0.68)
	R^2		1.00
Latin American	A1	A (0.50)	T (0.50)
	A2	G (0.50)	C (0.50)

R^2 = correlation between pairs of loci; A1= allele 1; A2= allele 2. In parenthesis allele frequencies.
Source: Prepared by the authors based on the results of the study.

other hand, Africa, the Esan in Nigeria and the Luhya in Webuye, Kenya show an excess of heterozygosity, which could be due to demographic process, like recent migration. The same explanation is reasonable for PILRA rs1859788.

Further studies of genetic association in these populations should identify the subpopulations accounting for the Hardy-Weinberg Test departure. Also, this potential stratification must be analyzed to interpret the results of genetic associations studies using this SNP in the mentioned populations. The article by Pandey et al. [4] included individuals from African American ancestry, which is represented in this study by the Americans of African Ancestry in Southwest, USA, under the Hardy-Weinberg equilibrium. The linked SNPs for FCGRIIB and PILRA reported in this study show very similar frequencies within them (tables 2 and 3). Since the linkage with the target SNPs is highly probable, one explanation could be that both sets of derivate alleles at each SNP arose very close in time.

According to Ensembl [17], rs13376485, rs3767640, rs3767639, and rs3767641, on the FCGRIIB gene, are included in seven known transcripts determining one non-coding transcript exon variant and six intron variants. Only the target SNP (rs1050501) has been associated to a broad range of phenotypes as susceptibility to Lupus disease [18], malaria resistance [19], and other immune system pathologies. For PILRA rs1859788, the only linked SNP (rs2405442) has been previously associated to AD [20–22]. While PILRA rs1859788 produces a missense variant, rs2405442 produces a synonym variant, which implies that it is more probable that the first one is causally associated to AD [22]. SNPs having functional effects are robust candidates to predict disease across populations, therefore it should be integrated in further genetic association studies for Alzheimer´s disease.

The five candidate SNPs here reported are either on intron variants or noncoding transcript exon variants. Nevertheless, as is well known introns have an important role in the regulation of gene expression, splicing, mRNA export, transcription coupling, and enhancing the protein variation by exon shuffling and alternative splicing [23–26]. Thus, we suggest including the five SNPs here reported in further studies of genetic association and genotype-phenotype architecture for Alzheimer's disease.

The use of SNPs with functional effects in the calculation of Polygenic Risk Scores for Alzheimer's Disease aligns with the evolving understanding of complex diseases and the need for more precise and informative genetic markers. Functional SNPs are more likely to directly contribute to the pathophysiological processes underlying Alzheimer's disease, providing a stronger basis for prediction across populations. In addition, understanding the functional impact of SNPs can provide insights into the underlying biological mechanisms of Alzheimer's disease (disease etiology) to identify therapeutic targets: if a specific SNP is linked to a critical biological process in Alzheimer's disease, targeting that SNP or its associated pathway could be an approach for therapeutic interventions.

One limitation of the present study is that there are population particularities that are not covered, as is the existence of other human groups from different ancestries within the macro populations here analyzed, like indigenous and Africans populations, which may present genetic differentiation with respect to other neighboring populations.

CONCLUSIONS

FCGRIIB rs13376485, rs3767640, rs3767639 and rs3767641 and PILRA rs2405442 are candidate SNPs for association with Alzheimer's disease.

The candidate SNPs here reported are in intronic regions. Therefore, causal roles in Alzheimer´s disease susceptibility, through regulation of FCGRIIB and PILRA gene expression, remain unclear.

Further genetic association studies on the Alzheimer´s disease susceptibility including FCGRIIB rs13376485, rs3767640, rs3767639 and rs3767641 and PILRA rs2405442 are necessary to confirm the result from this study.

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Nuevos SNP candidatos para la asociación genética con la enfermedad de Alzheimer: un análisis de desequilibrio de ligamiento para los genes FCGRIIB y PILRA

RESUMEN

ANTECEDENTES Recientemente se han asociado dos nuevos polimorfismos de un solo nucleótido (SNP) a la enfermedad de Alzheimer en poblaciones afroamericanas: FCGRIIB rs1050501 C/T, y PILRA rs1859788 A/G. El riesgo de enfermedad de Alzheimer en los portadores de los alelos FCGRIIB C y PILRA A es tres veces mayor que en los no portadores. Sin embargo, no se ha evaluado la asociación entre estos y otros SNP.
MÉTODOS Se utilizó el análisis de desequilibrio de ligamiento, con r2= 0,8 como valor umbral, para imputar nuevos SNPs candidatos, sobre datos genómicos de ambos genes en 26 poblaciones de todo el mundo (n= 2504) de la base de datos 1000Genomes.
RESULTADOS Cuatro SNPs (rs13376485, rs3767640, rs3767639 y rs3767641) se vincularon al rs1050501 y uno (rs2405442) al rs1859788 en toda la muestra.
CONCLUSIONES Cinco nuevos SNP podrían estar asociados con la susceptibilidad a la enfermedad de Alzheimer y desempeñar un papel causal, aunque ninguno de ellos sea una variante de exón, dado su papel potencial en la regulación de la expresión génica.