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SCHIZOPHRENIA AND HLA: WORK IN PROGRESS ABOUT TYPING USEFULNESS AND DIAGNOSTIC THERAPEUTIC OUTLOOKS

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INTRODUCTION

Schizophrenia is a multifactorial chronic disease characterized by heterogeneity of psychiatric manifestations. Among mental diseases it's the most investigated one, the archetype of mental disease," it's the twist from normal to very important disorder of mental functions, it's leaving social community" (P.Pancheri). Three syndromic groups identify schizophrenia psycopathologic dimensions: Positive syndrome (Paranoid schizophrenia, deliria and hallucinations, dopaminergic D2-D4 hyperactivity in meso limbic pathway); Negative syndrome(residual schizophrenia, flat affect, apathy, alogia, D1- D2 hypoactivity in meso cortic pathway) and Disorganization syndrome (disorganized schizophrenia, ideal-affective and behavioural disorganization, D3 alteration in nucleus accumbens shell).

Nowaday experts using a dimensional approach talk about *schizophrenia* as a *spectrum* disorder: a group of related mental disorders that share some symptoms.

In the past spectrum was used to define all of disorders having in common genetic determinant. Kety in 1976 was the first one who introduced the "Schizophrenic spectrum" definition after observing that children born from schizophrenic mothers but adopted in normal families had higher incidence in schizophrenia and in schizotypal personality disorders than control groups. This leads to think that more disorders, with different nosographic classification share a common morbose process, where genetics, age onset, and quick symptom manifestation have a specific pathoplastic meaning.

DSM IV clusters as only one diagnosis group - Schizophrenia and other psychotic disorders- five schizophrenia subtypes (Paranoid, Disorganized, Catatonic, Undifferentiated and Residual) based on the predominant symptom and divides them from the same spectrum ones as schizophreniphorm disorder, Schizoaffective disorder ,delirant disorder , short psychotic disorder , Shared Psychotic, Psychotic disorder caused by a general medical condition, substances induced disorder and psychotic disorder not otherwise specified (NOS).

Schizophrenia aetiology is still not well defined; many hypotesis have been discussed and the most interesting pathogenetic one seems to be the "inflammation", based on several most recent researches that relate schizophrenia and a low grade chronic inflammation caused by several pathogen agents and autoimmune diseases among which psoriasis, celiac disease, and Erithematous Systemic Lupus are more accreditated. Increased proinflammatory circulating cytokines and gammaglobulin levels, the presence of circulating antineurotransmitters autoantibodies highlight such a pathogenesis ; moreover if the use of antipsycotic drugs seems to reduce inflammation in some schizophrenic patients , on the other hand patients treated with biological drugs for autoimmune diseases improve their psychiatric symptoms.

The first study about Schizophrenia and HLA association was carried out by Cazzullo et al. in 1974, by then several researches and most recently other Genome Wide Association Studies (GWAS) founded genetic variants nearby and inside the MHC region on chromosome 6, thus confirmed that the MHC plays an important role both as key regulatory region of the immune response, and in neuronal function, with expression levels affecting synaptic plasticity and potentially the formation of new memories. Specifically, there is now evidence that class I MHC proteins regulate synaptic responses, are required for normal postnatal brain development and plasticity, but they are also widely expressed in the mammalian brain prenatally during the earliest stages of neuronal differentiation, consistent with a possible role in neurodevelopmental disorders.

Our study, still in progress, has been started at Tissue Typing Center U.O.S. of Grande Ospedale Metropolitano "Bianchi- Melacrino- Morelli" in collaboration with Reggio Calabria Mental Health and Dependences Department ASP 5, is going to be extended to other psychiatric depts, and aims to evaluate if and which ones of autoimmune diseases and/or ADR related HLA alleles our schizophrenic patients have, and whether any other allele/haplotype has a particular frequency

MATHERIALS AND METHODS

27 Patients aged 20-70 have been selected overall schizophrenic spectrum and anamnestic forms have been provided to get informations about diagnosis, positive family anamnesis for psychiatric disorders, past and recent drug treatment, indicating pharmacological response level and any occurred drug reaction or resistance. Genomic DNA was extracted with magnetic beads support technology on automatic nucleic acids extractor and HLA typing for loci A, B, C, DRB1 performed by reverse SSO DNA typing assays- (One-Lambda Luminex Technology LABScan™ 100 , HLA Fusion™ Software)

Alleles frequency among patients was compared in percentage with a 127 healthy calabrian donor population, and considered possible relations with identified alleles frequency and schizophrenia subtype, autoimmune comorbidities association and drug reactions.

DISCUSSION

MCH region is one of the most polymorphic ones in human genome and alleles frequency depends on several population variable factors such as ancestry, ethnicity, and geography; to compare alleles frequency we chose our control group between healthy donors already used by our HLA team for alleles frequency populations studies.

Table 1 compares HLA class I and II alleles incidence between these two groups.

Comparing patients' group allele frequency and healthy control one we found

HLA-A*03 allele: slightly more frequent

HLA-A19 (A*29, A*30, A*31, A*32, A*33, especially HLA-A*30 and A*32 alleles: higher frequency;

HLA-A10(A*26 and **A*66** alleles): significative incidence

HLA-A9(A*23 allele) : slightly higher frequency.

HLA- B*18, B*27, B*37, B*38, B*39, B*51, B*55 alleles : higher frequency;

HLA- C*06, C*12, C*15, alleles frequency is quite higher while **HLA-C*04, C*16** are slightly more frequent;

Among 10 patients with positive family anamnesis for various mental disorders, 4 of them share **HLA-A*03** allele, 3 **HLA-A*24** and 2 **HLA-A*32** only one **HLA-A*66**; no particular association was found on loci B, C and DRB1 nor any haplotype. 2 patients resistant to common drugs treatment share a **HLA-A*03, B*18, C*07, DRB1*14** haplotype

HLA-A*	f% PATIENTS	f% CONTROL GROUP	HLA-B*	f% PATIENTS	f % CONTROL GROUP	HLA-C*	f % PATIENTS	f% CONTROL GROUP	HLA-DRB1*	f % PATIENTS	f% CONTROL GROUP
*01	22,0	23,0	*07	11,0	11,0	*01	11,0	4,0	*01	7,0	11,0
*02	33,0	39,0	*08	4,0	9,0	*02	7,0	10,0	*03	14,0	18,0
*03	16,0	14,0	*13	7,0	8,0	*03	11,0	11,0	*04	14,0	17,0
*11	11,0	2,0	*14	7,0	6,0	*04	22,0	20,0	*07	26,0	24,0
*23	4,0	2,0	*15	7,0	9,0	*05	7,4	11,0	*08	3,0	2,0
*24	7,0	11,0	*18	37,0	20,0	*06	19,0	12,0	*10	7,0	6,0
*26	4,0	1,0	*27	7,0	2,0	*07	33,0	42,0	*11	41,0	42,0
*29	4,0	2,0	*35	26,0	23,0	*08	7,0	6,0	*13	18,0	28,0
*30	11,0	1,0	*37	7,0	2,0	*12	30,0	24,0	*14	11,0	13,0
*31	4,0	3,0	*38	7,0	3,0	*15	15,0	9,0	*15	3,0	18,0
*32	18,0	0,0	*39	7,0	2,0	*16	7,0	5,0	*16	11,0	11,0
*33	7,0	5,0	*40	4,0	9,0	*17	4,0	5,0			
*66	7,0	4,0	*41	4,0	3,0						
			*44	7,0	16,0						
			*49	11,0	17,0						
			*50	4,0	6,0						
			*51	18,0	14,0						
			*52	4,0	11,0						
			*55	11,0	0,0						
			*56	4,0	5,0						
			*57	4,0	6,0						

TABLE 1

CONCLUSIONS

Scientific literature, especially in last decades, seems to have "rediscovered the HLA and Schizophrenia wheel" and many researches have been carried out; HLA-A9, A10, B5 serologic broads and C*04 allele seems to be more likely linked to Schizophrenia Spectrum Disorders.

Our results show a higher frequency in schizophrenic patients group than in healthy control one of some HLA class I alleles; no significative frequency difference outcomes between the two groups was found in HLA II class DRB1 alleles.

Complying with literature data we found frequent incidence of HLA- A10(A*26 and A*66 alleles), slightly higher frequency in HLA- A9 (A*23), HLA- B5(B*51), and a slight prevalence of HLA-C*04 allele comparing to our healthy control group.

In terms of allele frequency in our schizophrenic patients group , the most consistent one was found with HLA-A19 (A*30, A*32 but also A*29, A*31, A*33 alleles), HLA- B*18, B*27, B*37, B*38, B*39, B*51, B*55 and HLA- C*06, C*12, C*15.

Because of HLA-B*27, B*51 and C*06 well-known association with autoimmune diseases these alleles should be better investigated in their possible linkage to Schizophrenia if we consider the Schizophrenic Spectrum Disorders "inflammatory" aetiology. From this point of view also HLA-A*03 allele that in our study is slightly, but more frequent in patients' group than in healthy control one, worths to be investigated about its linkage to hemochromatosis which since several studies demonstrated correlation between this pathology and schizophrenia , and its frequency in patients that develop post-vaccinations Central Nervous System pathologies.

No particular genetic linkage resulted both in I and II HLA Class alleles within patients with positive family anamnesis for various mental disorders.

An outcome to investigate about is the haplotype HLA-A*03, B*18, C*07, DRB1*14 shared by the two patients resistant to common drugs used for Schizophrenia Disorders treatment.

In this study most of the enrolled subjects were outpatients so it has not been possible to obtain specific data on eventual autoimmune comorbidity, an extended research to autoantibodies and specific disease markers, attention to individual drugs reaction might complete the results and have better research outcomes. In spite of little number of patients typed up today, data are interesting and if confirmed by a larger individuals' sample, HLA typing in schizophrenic patients in the near future could become a valid clinic tool for a more accurate and personalised diagnostic and therapeutic route.

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