the Diagnostic interview for Genetic Studies (version 2.0; which includes the Schedules for Positive and Negative Symptoms) and also underwent a urinary drug screen test for drugs of abuse. FISH analysis for chromosome 22 was performed on the whole sample whilst a subsample of fifty participants were also karyotyped.

Results: FISH analysis detected no chromosome 22 abnormalities in any of the subjects. Of the fifty participants who were karyotyped, chromosomal aberrations were identified in five (10%). These were: two cases of inversion of chromosome 9 [46,XY,inv(9)]; and one each of double satellites on chromosome 22 [46,XY,22pss]; a variant of the heterochromatic portion of chromosome 1 [46,XY,1qh−] and a low-grade mosaic [46,XY/47,XXY/47,XX,+acentric fragment]. All were reported as being probable normal variants. No specific clinical variables were associated with the chromosomal aberrations.

Conclusion: In contrast to previously reported Caucasian and Asian samples chromosomal aberrations did not occur frequently in this sample of Xhosa schizophrenia participants. Of particular interest was that no chromosome 22q11−13 deletions could be demonstrated in any of the participants. Although this seems to stand in contrast to previous findings suggesting 22q11 deletion syndrome to be the highest known genetic risk factor for schizophrenia it is important to note that previous results were based largely on Caucasian studies. Our findings seem to support the suggestion that ethnic specific susceptibility factors exists for schizophrenia. Future studies should explore the possibility that mechanisms other than chromosomal aberrations contribute more to schizophrenia in this African population than in Caucasian samples.

P1.a.005 Differences in TP53 and APC gene polymorphisms between Korean schizophrenic patients and colon cancer patients

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Compared with the general population, lower incidence of cancers in schizophrenic patients has been observed. The etiology of schizophrenia is unclear. However, it is generally accepted that genetic factors play an important role in the pathogenesis of schizophrenia. It has been proposed that genetic predisposition toward schizophrenia is associated with reduced vulnerability to cancer. Schizophrenia is generally considered to be a neurodevelopmental disorder. Both TP53 and adenomatous polyposis coli (APC) genes are tumor suppressor genes. Furthermore, both genes are involved in colorectal tumorigenesis as well. Studies on the their own functions, associations on neurodevelopmental process, and location of these two genes imply that both TP53 and APC genes may be involved in the pathogenesis of schizophrenia.

Therefore, in order to examine the role of TP53 and APC genes in the pathogenesis of schizophrenia and genetic difference, the polymorphisms of both genes were studied in Korean schizophrenic patients (SPR), colon cancer patients (CA) and normal controls (No. of each group = 248; male 139, female 109). Three SNPs (rs1042522, rs2078486, rs8064946) on the TP53 gene and seven SNPs (rs2439591, rs2546117, rs1816769, rs2439595, rs1914, rs2229992, rs465899) on APC were investigated. There were no significant differences between all three groups on the three TP53 polymorphisms. Also the APC gene polymorphisms in SPR were not significantly different from those of the controls. However, in the comparison of the genotype frequencies, the rs2439591 and rs2229992 of APC polymorphisms in the male CA were significantly different from those of controls. The T allele of rs2439591, T of rs2229992, and G of rs465899 displayed significantly lower frequencies in the male CA than controls. In the dominant model, the male CA showed significantly lower frequencies of CT/TT genotype of rs2439591, CT/CT of rs2229992 and GA/GG of rs465899 than in controls after adjusting for age (Odds Ratio (OR) = 0.53; 95% Confidence Interval (CI) 0.31–0.91, OR = 0.61; 95% CI 0.37–0.99, OR = 0.56; 95% CI 0.32–0.97). When compared with CA, the male SPR showed the significant differences regarding the APC polymorphisms. In the comparison of genotype frequencies, the rs1914 and rs2229992 of APC polymorphisms in the male SPR were distinguishably different from those of CA. The A allele of rs1914 and T allele of rs2229992 appeared more frequently in the male SPR than in CA. In the dominant model, SPR showed significantly higher frequencies of GC/CC genotype of rs2546117, AT/AA of rs1914 and CT/TT of rs2229992 after adjusting for age and sex (OR = 2.06; 95% CI 1.11–3.78, OR = 1.84; 95% CI 1.83–3.27, OR = 2.17; 95% CI 1.20–3.94). These results were more definite in the male SPR. Also the male SPR revealed significant differences on the T-C haplotype of rs2439591-rs2546117 and A-T-G of rs1914-rs2229992-rs465899 when compared to CA. These above results suggest that the APC polymorphisms in schizophrenic patients, especially those found in males, may be associated with reduced vulnerability to colon cancer.

References

P1.a.006 Serotonin transporter: an example of gene influence on human behaviour

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The complexity of gene influences on behavioural features has been extensively considered. A single gene variant modulates many behavioural traits, but with a moderate effect size. The best available example in psychiatric genetics is represented by the gene coding for the serotonin transporter (5-HTT), the SLC6A4. Among the recognized polymorphisms of this gene, the one located in the transcriptional control region upstream of the coding sequence (5-HTTLPR) is thought to greatly influence the modulation of behaviour. It consists of a 43-bp insertion or deletion, involving repeat elements 6 to 8; deletion characterizes a short variant (S), while insertion characterizes a long variant
The S variant reduces the transcriptional efficiency of the 5-HTT gene promoter, resulting in decreased 5-HTT expression and availability.

Although a review on the association between 5-HTTLPR polymorphism and behavioural features has been previously performed by our group [1], the enormous amount of association studies requires a new review of the literature. The present review includes a summary of our previous results and conclusions but it mainly focuses on new studies and ways of integrating and explaining the overall results.

To identify studies eligible for this review, we searched Medline for all publications available up to February 2008 that studied the association between 5-HTTLPR and psychiatric disorders, temperamental traits and all the related features. The search strategy only sought out studies published in English. The main search terms were serotonin transporter, 5-HTTLPR, SERTPR and gene.

The 5-HTTLPR S variant was found to relate to a higher amygdala response to negative stimuli, to anxiety-related personality traits, but not to anxiety disorders. Moreover, a carriers of the S form shows elevated vulnerability in front of stressors, a worse response to selective serotonin reuptake inhibitors in different diagnoses and worse side effects during the use of psychotropic drugs. In addition, bipolar disorder, alcohol dependence, eating disorders, attention deficit hyperactivity disorder and suicide attempts were found to be associated with the S allele as well.

The high discrepancy among results of some studies could have various explanations. Firstly, the dominance of 5-HTTLPR has not been addressed unequivocally. Moreover, the discovery of other polymorphisms, such as the A/G SNP within the 5-HTTLPR insertion and the rs25531 SNP, justifies a re-evaluation of previous association studies and more detailed genotyping in future analyses [2]. In addition, the higher number as possible of SLC6A4 SNPs should be considered to avoid biases [3]. Another explanation is represented by the growing body of evidence suggesting that many influencing variants could play a role in the modulation of behaviour, and focusing on 5-HTTLPR alone could be misleading.

In conclusion, 5-HTTLPR polymorphism appears to modulate a widespread variety of human characteristics. However, future studies should further examine previous results and expand them, investigating both other 5-HTT polymorphisms, such as the A/G SNP within the 5-HTTLPR insertion and/or the rs25531, and different interacting genes.

References

A genetic assessment of antipsychotic and antidepressant cardiac iatrogenicity: focus on the proarrhythmic profile
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Objective: Antidepressants and antipsychotics may affect several ion channels involved in the control of cardiac action potential and be proarrhythmic. In this field, accurate understanding of genetics, which per se is a non-controllable risk factor, may help clinicians to prevent life-threatening side effects. Starting from evidence found in literature, we hypothesize that mutation running in the genetic sequence coding for sodium, potassium and calcium channels may impact the proarrhythmic activity of antipsychotic and antidepressant drugs, as these channels orchestrate the events that rule the myolectrical activity of cardiac myocytes. Patients would strongly benefit from the identification of a set of variations at risk for drug induced fatal event: a genetic pretreatment assessment would integrate the other relevant known risks associated with arrhythmias, providing the clinician with a powerful tool facilitating the choice of the best fitting drug therapy for a specific patient.

Methods: Candidate genes were selected by two ways: i) genes associated with congenital forms of long or short QT syndromes; ii) genes coding for proteins associated with the molecular path which rules the myocytes’ cycles of polarization. By this method, we listed and described 17 candidate genes: SCN5A, SCN4B, CACNL1AC, KCNH2, KCNJQ1, KCNE1, ANK2, ALG10, KCNJ2, KCNE2, RYR2, KCND3, KCND2, ACE, NOSAP1, CASQ2 and Rad. This list is not meant to be complete as a part (at least 20%) of long QT syndromes do not have a genetic profile recognized. Within these genes, mutations that might be associated with lethal arrhythmic side effects have been selected and described starting from three mainstays: i) mutations associated with congenital forms of long or short QT syndromes; ii) mutations which has been associated with iatrogenic QT disorders; iii) mutations covering the whole sequence of the candidate genes.

Results: We report the most up-to-now complete list of variations which should be analyses in order to detect the antipsychotic and antidepressant drugs induced proarrhythmic events in genetic association studies. List is comprehensive of both validated tag variations covering all the sequences, and of the more uncommon variations which have been strongly associated with congenital or iatrogenic forms of long QT syndromes.

Conclusion: The genetic background we report here is meant to be used in keen investigations in the field of proarrhythmic iatrogenic events. The result of such studies would help toward the definition of a reliable biological profile risk associated with fatal drug-induced pro-arrhythmic side effects. This result is consistent with nowadays community effort toward the identification of specific genetic pretreatment tests: the advantages associated with this project completed are clear. Moreover, this study completed will bring the evidence to start the creation of a genetic database focused on this topic. This genetic database could be shared and enriched by the results coming from other similar studies.