Published in final edited form as:

Pharmacogenomics. 2014 January ; 15(1): 61–67. doi:10.2217/pgs.13.157.

Pharmacogenomics of Sterol Synthesis and Statin Use in Schizophrenia Subjects Treated With Antipsychotics

Thomas J. Vassas, Pharm.D.^{[1],*}, Kyle J. Burghardt, Pharm.D.^{[1],*}, and Vicki L. Ellingrod, Pharm.D., FCCP^{[1],[2]}

^[1]University of Michigan College of Pharmacy

^[2]University of Michigan School of Medicine, Department of Psychiatry

Abstract

Objective—Patients with schizophrenia, treated with antipsychotics often develop metabolic side effects including dyslipidemia. Antipsychotics potentially upregulate gene expression of a lipid metabolism pathway called sterol regulatory element binding protein (SREBP) via transcription factors (SREBF) and genetic variation within *SREBF* may contribute to dyslipidemias and lipid medication efficacy within schizophrenia.

Results—A cross-sectional study of 157 patients were genotyped for *SREBF1* (rs11868035) and *SREBF2* (rs1057217) variants, and assessed for fasting lipids. The cohort's mean age was 46.6 years, 64% male, and 86% were using atypical antipsychotics. When stratified by statin use, those receiving a statin and carrying the *SREBF1* T allele exhibited higher TC levels ($p=0.01$), TG levels ($p=0.04$) and LDL levels ($p=0.03$). A regression analysis controlling for gender differences in lipids showed that the *SREBF1* T allele and statin interaction remained only for TC levels ($F(4,149)=5.8$, $p<0.0001$).

Conclusions—For schizophrenia individuals with the *SREBF1* rs11868035 T allele incomplete response to statin medications may be seen. Future investigations may allow for personalizing dyslipidemia treatment based on pharmacogenetics within schizophrenia.

Keywords

Schizophrenia; Cholesterol; SREBF; Pharmacogenomics; Statins

INTRODUCTION

Epidemiological patterns have shown an increased proportion of individuals with schizophrenia developing symptoms of metabolic disorders including obesity, metabolic syndrome and cardiovascular disease(1). One potential metabolic abnormality, dyslipidemia, can manifest as a mix of increased total cholesterol (TC), low-density lipoproteins (LDL) and triglyceride (TG) levels, as well as lower levels of the high-density lipoproteins (HDL)

Corresponding Author: Vicki L. Ellingrod, Pharm.D. FCCP, John Gideon Searle Professor of Clinical and Translational Pharmacy, University of Michigan College of Pharmacy, 428 Church Street, Ann Arbor, Michigan 48109, Office: 734-615-4728, Fax: 734-763-4480.

*denotes equal effort on manuscript

(2, 3). Although disease related factors as well as lifestyle differences have been associated with these metabolic abnormalities, the use of atypical antipsychotics (AAPs) is most commonly attributed to these changes(4–6). Changes in lipids often are considered detrimental due to their link with cardiovascular disease and reduced life expectancy(7). More than two-thirds of schizophrenia patients die of coronary heart disease compared with one-half within the general population. Providers' treatment of choice for primary dyslipidemia are the hydroxymethylglutaryl Co-A reductase inhibitors or statins which are underused in the schizophrenia population(4, 8–11). There is a definite need to study these metabolic disorders in order to lessen their detrimental effects however, metabolic alterations, specifically lipid alterations, have also been examined in the context of schizophrenia susceptibility(12).

The sterol regulatory element binding transcription factors (*SREBF*) are involved in the pathway that controls cholesterol homeostasis and have been shown to upregulate sterol regulatory binding protein (*SREBP*) gene expression(13). Ultimately, this *SREBP* gene expression is responsible for the coding of proteins that facilitate the uptake and synthesis of TGs, cholesterol and unsaturated fatty acids(14–16). Given the link between antipsychotics' beneficial effects on schizophrenia symptom management yet common lipid side effects, the relationship between *SREBF* genetic variants and schizophrenia risk was investigated. These investigations identified genetic variation within the *SREBF1* and *SREBF2* genes that were associated with schizophrenia, specifically with the *SREBF1* rs11868035 and *SREBF2* rs1057217 polymorphisms(17). These findings were subsequently partially replicated in two independent samples of schizophrenia patients. Antipsychotics have also been linked to upregulation *SREBP* expression and in general to the disruption of lipoprotein trafficking(13, 18, 19), thus adding to the cholesterol hypothesis of schizophrenia(20–22). Although this pathway and its genetic variation of cholesterol regulation has garnered research interest from a schizophrenia risk standpoint, it is not known whether these variants may play a role in the dyslipidemia commonly seen with antipsychotic use in patents diagnosed with schizophrenia.

Thus, the aim of this study was to examine the relationship between *SREBF* variants previously linked with schizophrenia risk (*SREBF1* rs11868035 and *SREBF2* rs1057217) and investigate any associations with lipid levels in schizophrenia subjects largely treated with AAPs. We hypothesized that that the *SREBF1* rs11868035 T allele carriers and *SREBF2* rs1057217 A allele carriers would be associated with higher LDL, TGs, TC, and lower HDL in patients diagnosed with schizophrenia stable on antipsychotic treatment compared to those without these genotypes. Furthermore we sought to investigate the effect of these alleles on statin efficacy. Determination of these relationships may allow for the identification and development of personalized interventions in schizophrenia subjects at greatest risk for cholesterol abnormalities with antipsychotic treatment.

METHODS

Subjects

As part of this cross-sectional study, subjects who met the following criteria were included; Diagnostic and Statistical Manual of Mental Disorders Fourth Edition Text Revision (DSM-

IV-TR) diagnosis of schizophrenia, schizophreniform, or schizoaffective disorder; age 18–90 years; and antipsychotic treatment with no medication changes for the previous 6 months. Exclusion criteria were as follows: unwillingness to participate, unable to give informed consent (assessed using a short questionnaire asking key questions about the study) or active substance abuse or dependence diagnosis. Subjects were outpatients recruited from the southeastern Michigan community and the study protocol was approved by the University of Michigan Medical School Institutional Review Board (IRBMED).

Clinical Assessments

Participants meeting study inclusion criteria underwent an informed consent process followed by a clinical interview that included the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID;)(23), performed by a trained research associate from our group and confirmed through chart review. A medication history was obtained from subject interview, and review of past medical and psychiatric records. Pharmacy records were obtained for verification whenever possible.

Physical Exam and Anthropometrics

Participants were asked to fast for at least 8 hours before the study visit which was reiterated with a call placed the day before the study visit as well as a screening question at the beginning of the actual visit. Those that indicated they did not fast were excluded from statistical analysis. Each visit was scheduled to take place between 8 and noon, as our goal was to have all visits occur within 2 hours of the participant's usual waking time based on appointment availability. Vital signs (measured after sitting for a minimum of 15 minutes), as well as height, weight, and hip and waist circumference were also measured for each participant by the Registered Dieticians at the Michigan Clinical Research Unit (MCRU). The Body Mass Index (BMI) was calculated from this data. Blood was drawn for the following fasting laboratory assessments: glucose, insulin, hemoglobin A1c, and lipids (TC, TG, HDL and LDL).

Genotyping

DNA extraction from whole blood was performed using the salt precipitation method(24). Each DNA sample was then genotyped for the *SREBF1* rs11868035 (C/T) and *SREBF2* rs1057217 (A/G) variants using pyrosequencing following polymerase chain reaction (PCR). Specific conditions for the PCR assay can be found in Table 1.

Data Analysis

Subjects were separated based on the following genotype groups: *SREBF1* T allele carrier vs. CC genotype and *SREBF2* A allele carriers vs. GG genotype due to the expected low genotype frequencies seen with these genotypes (NCBI dbSNP). Participants were also classified as AAP-users and non-AAP users (or typical antipsychotic users). Demographic differences between groups was determined with the use of simple t-tests for continuous variables (i.e., age, lipids) and chi-squared for dichotomous variables (i.e., race, gender, smoking status, AAP use, statin use). A general linear regression model was used to examine the relationship between lipid levels and the independent variables of gender,

genotype, and statin use. Given the directed, candidate-gene nature of this investigation our primary two sided p-value was set at 0.05 to test for significance.

RESULTS

A total of 157 subjects were included in this analysis and Table 2 is a listing of the demographic variables for this group. Briefly, the mean age of subjects was 46.6 ± 11.0 years and approximately 64% of patients were male. Ethnicity was separated to those of Caucasian decent (59%), African American (32%), and “other” (9%) (subgroups of Asian/pacific islander, American Indian, and Hispanic/Latino). Approximately 86% of our subjects were currently receiving an atypical antipsychotic and, approximately 30% were receiving a statin for their dyslipidemia.

Both genotypes investigated in this study were in hardy-weinberg equilibrium (*SREBF1* $p=0.8$ and *SREBF2* $p=0.4$). Three participants for the *SREBF1* and 2 participants for the *SREBF2* polymorphism were unable to be genotyped due to sample fatigue. Overall, there were no significant demographic differences identified when comparing subjects between the genotype groups (all $p>0.05$). Genotype distributions did not significantly differ based on race (distributions found in Table 3) or by statin use (*SREBF1* $p=0.6$ and *SREBF2* $p=0.2$). Furthermore, analyses to identify baseline differences found lipid levels to be significantly affected by gender and statin use. Please see Table 4 for a breakdown of lipid levels based on gender.

Analyzing our primary hypotheses of this study revealed the following results: A trend seen in triglyceride levels, where subjects with the *SREBF1* T allele had higher triglyceride levels (154.7 ± 11.7 mg/dl $\pm$ s.e. vs. 122 ± 11.7 mg/dl, $p = 0.05$, effect size =0.32). The *SREBF2* polymorphism investigated in this study did not significantly influence lipid levels. We also examined the effect of statin use and *SREBF* genotype on lipid levels. This analysis found significantly different lipid levels based on the *SREBF1* genotype for subjects currently taking a statin. Those taking a statin and carrying the *SREBF1* T allele had significantly higher TC levels ($F(1,44)=6.0$, $p=0.01$), TG levels ($F(1,44)=4.2$, $p=0.04$) and LDL levels ($F(1,44)=4.5$, $p=0.03$).

A regression analysis controlling for gender and statin use was conducted since these variables were shown to significantly affect lipid levels in our baseline analysis. The interaction between *SREBF1* and statin use held only for TC levels ($F(4,149)=5.8$, $p<0.0001$) when controlling for gender (see figure 1 for *SREBF1* comparisons of lipid levels in subjects taking statins when controlling for gender). Subjects that were taking a statin and had the *SREBF1* CC genotype had significantly lower TC levels (140.8 ± 8.5 mg/dL $\pm$ s.e.) compared to all other groups. Of note, the closest TC level was that of subjects taking statins and carrying *SREBF1* rs11868035 T allele (167 ± 8.3 mg/dL $\pm$ s.e.) which is both statistically significant and clinically significant. No relationships were identified for the *SREBF2* genotype with lipid levels or lipid medications ($p>0.05$ for all).

DISCUSSION

Our results show a relationship between the *SREBF1* rs11868035 T allele, statin use and higher TC levels within schizophrenia. This finding is significant as it may predict patients in which a statin medication may not be the best option for the treatment of lipid abnormalities despite statins generally being chosen as first line given their many known benefits. To our knowledge this is the first report of this statin-pharmacogenetic interaction within the schizophrenia population however pharmacogenetic variation of statins with the SREB-SCAP pathway has been investigated in other populations.

Within the general population two studies have examined the relationship between statin use and genetic variation within the SREBF pathway. A study by Salek and colleagues found an association between a different *SREBF1* polymorphism and fluvastatin response(25). In this study, using the Lipoprotein and Coronary Atherosclerosis Study (LCAS) population, they found that after 2.5 years of fluvastatin treatment, apoA-I levels were significantly higher in the GG *SREBF1* genotype versus the del/del genotype. They also found a modest interaction between the *SREBF1* genotype and fluvastatin treatment with changes in HDL and apoC-III levels. A followup study by Fiegenbaum and colleagues found no pharmacogenetic relationships between the *SREBF1/2* variants used in this study and simvastatin use when this medication was given for 6 months(26). This second study was conducted within 99 subjects of European descent recruited from Brazil, which, demographically and potentially metabolically, is different when compared to our study population. Furthermore these two studies used different *SREBF1* and *SREBF2* polymorphisms which, makes direct comparisons to our study difficult.

Our study utilized two polymorphisms that have been previously correlated with the disease of schizophrenia itself. It may be that given this previously reported relationship between *SREBF1/2* and schizophrenia risk, coupled with the elevated risk for cardiovascular disease that exists within this population due to lifestyle and treatment, the relationship found between *SREBF1* and statin use may be more pronounced thus exposing this pharmacogenetic finding.

Although every effort was made to reduce bias within this study, a few limitations do exist. Our study was cross-sectional in design which does not allow us to make firm conclusions about the relationships we have outlined and only gives us a snapshot of the population at a given time. Additionally, we only chose two *SREBF* variants to investigate, nor did we examine genetic variation within other linked genes such as *SREBP* and the SREBF-cleavage-activating protein (*SCAP*), which have been implicated in the etiology of metabolic syndrome and the pharmacogenetics of statin medications(26–28). Additionally, a low percentage of our subjects were currently receiving statin medication at the time of assessments (30%), but this is a limitation of most schizophrenia research related to metabolic syndrome treatment as national trends repeatedly show low monitoring and treatment within this population(4, 9–11). Lastly due to the pilot nature of this investigation, our sample size is small and we did not control for multiple testing however our research investigated only two candidate-genes with mechanistic plausibility regarding cholesterol synthesis which helps to strengthen our major finding in the *SREBF1* gene. The p-value of

our main finding (<0.0001) would have survived a more stringent cutoff as well. Furthermore, the clinical implication of this work may overcome this limitation as a greater than 35mg/dl difference was seen in total cholesterol for the subjects taking statins and carrying either the *SREBF1* rs11868035 T allele or CC genotype.

CONCLUSION

Overall our investigation found a significant relationship between the *SREBF1* rs11868035 T allele and statin use in schizophrenia subjects largely receiving atypical antipsychotic medications. This relationship may indicate that for schizophrenia patients taking statins for hypercholesteremia, an incomplete response may be seen leaving patients without the many benefits that have been documented with statin use. As such alternative pharmacologic strategies or additional lifestyle modifications may be necessary to achieve the lipid goals in this population at high risk for cardiovascular disease. Although these results may allow for the personalized treatment of high cholesterol within schizophrenia, the results need to be cautiously interpreted until they can be replicated prospectively in a larger sample size.

FUTURE PERSPECTIVE

Although personalized medicine is not the standard of practice within psychiatry, investigations such as this will continue to provide the evidenced based medicine needed to advance this practice.

Acknowledgments

Funding Sources:

The following sources were utilized for this publication: NIMH (R-1MN082784, 2R01MH082784), NIH-NCCR, GCRC Program (UL1RR024986 and 2UL1TR000433), the Chemistry Core of the Michigan Diabetes Research and Training Center (NIH5P60 DK 20572).

References

1. McEvoy JP, Meyer JM, Goff DC, Nasrallah HA, Davis SM, Sullivan L, et al. Prevalence of the metabolic syndrome in patients with schizophrenia: Baseline results from the clinical antipsychotic trials of intervention effectiveness (CATIE) schizophrenia trial and comparison with national estimates from NHANES III. *Schizophr Res.* 2005 Dec 1; 80(1):19–32. [PubMed: 16137860]
2. Meyer JM, Davis VG, McEvoy JP, Goff DC, Nasrallah HA, Davis SM, et al. Impact of antipsychotic treatment on nonfasting triglycerides in the CATIE schizophrenia trial phase 1. *Schizophr Res.* 2008 Aug; 103(1–3):104–9. [PubMed: 18534821]
3. Meyer JM, Davis VG, Goff DC, McEvoy JP, Nasrallah HA, Davis SM, et al. Change in metabolic syndrome parameters with antipsychotic treatment in the CATIE schizophrenia trial: Prospective data from phase 1. *Schizophr Res.* 2008 Apr; 101(1–3):273–86. [PubMed: 18258416]
4. Correll CU, Druss BG, Lombardo I, O’Gorman C, Harnett JP, Sanders KN, et al. Findings of a U.S. national cardiometabolic screening program among 10,084 psychiatric outpatients. *Psychiatr Serv.* 2010 Sep; 61(9):892–8. [PubMed: 20810587]
5. Correll CU, Lencz T, Malhotra AK. Antipsychotic drugs and obesity. *Trends Mol Med.* 2011 Feb; 17(2):97–107. [PubMed: 21185230]
6. Vincenzi B, Borba CP, Gray DA, Copeland PM, Wang X, Fan X, et al. An exploratory study examining lipid-lowering medications in reducing fasting serum lipids in schizophrenia patients treated with atypical antipsychotics. *Ann Clin Psychiatry.* 2013 May; 25(2):141–8. [PubMed: 23638445]

7. Hennekens CH, Hennekens AR, Hollar D, Casey DE. Schizophrenia and increased risks of cardiovascular disease. *Am Heart J.* 2005 Dec; 150(6):1115–21. [PubMed: 16338246]
8. Jellinger PS, Smith DA, Mehta AE, Ganda O, Handelsman Y, Rodbard HW, et al. American association of clinical endocrinologists' guidelines for management of dyslipidemia and prevention of atherosclerosis. *Endocr Pract.* 2012 Mar-Apr;18(Suppl 1):1–78. [PubMed: 22522068]
9. Mitchell AJ, Delaffon V, Vancampfort D, Correll CU, De Hert M. Guideline concordant monitoring of metabolic risk in people treated with antipsychotic medication: Systematic review and meta-analysis of screening practices. *Psychol Med.* 2012 Jan; 42(1):125–47. [PubMed: 21846426]
10. Morrato EH, Newcomer JW, Kamat S, Baser O, Harnett J, Cuffel B. Metabolic screening after the american diabetes association's consensus statement on antipsychotic drugs and diabetes. *Diabetes Care.* 2009 Jun; 32(6):1037–42. [PubMed: 19244091]
11. Morrato EH, Druss B, Hartung DM, Valuck RJ, Allen R, Campagna E, et al. Metabolic testing rates in 3 state medicaid programs after FDA warnings and ADA/APA recommendations for second-generation antipsychotic drugs. *Arch Gen Psychiatry.* 2010 Jan; 67(1):17–24. [PubMed: 20048219]
12. Colton CW, Manderscheid RW. Congruencies in increased mortality rates, years of potential life lost, and causes of death among public mental health clients in eight states. *Prev Chronic Dis.* 2006 Apr;3(2):A42. [PubMed: 16539783]
13. Ferno J, Raeder MB, Vik-Mo AO, Skrede S, Glambek M, Tronstad KJ, et al. Antipsychotic drugs activate SREBP-regulated expression of lipid biosynthetic genes in cultured human glioma cells: A novel mechanism of action? *Pharmacogenomics J.* 2005; 5(5):298–304. [PubMed: 16027736]
14. Brown MS, Goldstein JL. A proteolytic pathway that controls the cholesterol content of membranes, cells, and blood. *Proc Natl Acad Sci U S A.* 1999 Sep 28; 96(20):11041–8. [PubMed: 10500120]
15. Horton JD, Goldstein JL, Brown MS. SREBPs: Activators of the complete program of cholesterol and fatty acid synthesis in the liver. *J Clin Invest.* 2002 May; 109(9):1125–31. [PubMed: 11994399]
16. Gimpl G, Burger K, Fahrenholz F. A closer look at the cholesterol sensor. *Trends Biochem Sci.* 2002 Dec; 27(12):596–9. [PubMed: 12468222]
17. Le Hellard S, Muhleisen TW, Djurovic S, Ferno J, Ouriaghi Z, Mattheisen M, et al. Polymorphisms in SREBF1 and SREBF2, two antipsychotic-activated transcription factors controlling cellular lipogenesis, are associated with schizophrenia in german and scandinavian samples. *Mol Psychiatry.* 2010 May; 15(5):463–72. [PubMed: 18936756]
18. Kristiana I, Sharpe LJ, Catts VS, Lutze-Mann LH, Brown AJ. Antipsychotic drugs upregulate lipogenic gene expression by disrupting intracellular trafficking of lipoprotein-derived cholesterol. *Pharmacogenomics J.* 2010 Oct; 10(5):396–407. [PubMed: 19997082]
19. Raeder MB, Ferno J, Vik-Mo AO, Steen VM. SREBP activation by antipsychotic- and antidepressant-drugs in cultured human liver cells: Relevance for metabolic side-effects? *Mol Cell Biochem.* 2006 Sep; 289(1–2):167–73. [PubMed: 16718372]
20. Bartzokis G. Neuroglialpharmacology: White matter pathophysiology and psychiatric treatments. *Front Biosci.* 2011 Jun 1;16:2695–733.
21. Takahashi N, Sakurai T, Davis KL, Buxbaum JD. Linking oligodendrocyte and myelin dysfunction to neurocircuitry abnormalities in schizophrenia. *Prog Neurobiol.* 2011 Jan; 93(1):13–24. [PubMed: 20950668]
22. Saher G, Brugger B, Lappe-Siefke C, Mobius W, Tozawa R, Wehr MC, et al. High cholesterol level is essential for myelin membrane growth. *Nat Neurosci.* 2005 Apr; 8(4):468–75. [PubMed: 15793579]
23. Spitzer RL, Williams JB, Gibbon M, First MB. The structured clinical interview for DSM-III-R (SCID). I: History, rationale, and description. *Arch Gen Psychiatry.* 1992 Aug; 49(8):624–9. [PubMed: 1637252]
24. Lahiri DK, Nurnberger JI Jr. A rapid non-enzymatic method for the preparation of HMW DNA from blood for RFLP studies. *Nucleic Acids Res.* 1991 Oct 1;19(19):5444. [PubMed: 1681511]
25. Salek L, Lutucuta S, Ballantyne CM, Gotto AM Jr, Marian AJ. Effects of SREBF-1a and SCAP polymorphisms on plasma levels of lipids, severity, progression and regression of coronary

- atherosclerosis and response to therapy with fluvastatin. *J Mol Med (Berl)*. 2002 Nov; 80(11):737–44. [PubMed: 12436350]
26. Fiegenbaum M, Silveira FR, Van der Sand CR, Van der Sand LC, Ferreira ME, Pires RC, et al. Determinants of variable response to simvastatin treatment: The role of common variants of SCAP, SREBF-1a and SREBF-2 genes. *Pharmacogenomics J*. 2005; 5(6):359–64. [PubMed: 16158080]
27. Salek L, Lutucuta S, Ballantyne CM, Gotto AM Jr, Marian AJ. Effects of SREBF-1a and SCAP polymorphisms on plasma levels of lipids, severity, progression and regression of coronary atherosclerosis and response to therapy with fluvastatin. *J Mol Med (Berl)*. 2002 Nov; 80(11):737–44. [PubMed: 12436350]
28. Rudolph MC, Monks J, Burns V, Phistry M, Mariani R, Foote MR, et al. Sterol regulatory element binding protein and dietary lipid regulation of fatty acid synthesis in the mammary epithelium. *Am J Physiol Endocrinol Metab*. 2010 Dec; 299(6):E918–27. [PubMed: 20739508]

EXECUTIVE SUMMARY

- The sterol regulatory element binding transcription factors (SREBF) have been shown to upregulate sterol regulatory binding protein (*SREBP*) gene expression which is ultimately responsible for the coding of proteins that facilitate the uptake and synthesis of TGs, cholesterol and unsaturated fatty acids.
- Genetic variation within the *SREBF1* and *SREBF2* genes, have been shown to have a relationship with the illness schizophrenia.
- Antipsychotics used to treat schizophrenia upregulate *SREBP* and in general disrupt lipoprotein trafficking, thus adding to the cholesterol hypothesis of schizophrenia.
- Schizophrenia subjects who were receiving statin medications and also had the *SREBF1* T allele exhibited higher total cholesterol ($p < 0.0001$) when controlling for gender differences compared to those taking statins and carrying the *SREBF1* CC genotype.
- For schizophrenia individuals with the *SREBF1* rs11868035 T allele incomplete response to statin medications may be seen.

Figure 1.

Differences in lipid levels based on *STREBF1* genotype and statin medication while controlling for gender

*This figure represents subjects who were currently taking a statin stratified by the *SREBF1* CC genotype or T allele.

**The regression model for TC was significant (<0.0001) based on the interaction between genotype and statin use. All other lipid levels were not significant when controlling for gender (all >0.05) however differences in lipid levels within these non-significant findings may still be of clinical interest.

Table 1

Reaction Conditions for PCR

SNP	Forward Primer	Reverse Primer	Pyrosequencing Primer	PCR Reaction Conditions*
SREBF1 rs11868035	5' biosig-CACAACAGGTCCTGGAAAGTCA-3'	5' -TTGGGGCTGTGTCAACCCCTTA-3'	5' -CCCAGCTCTGTCCCC-3'	95°C × 5 minutes
				95°C × 30seconds
				57°C × 30seconds
				68°C × 30seconds
				68°C × 5 minutes
SREBF2 rs1057217	5' biosig-TGGCAGGGAGGTCTGAGT-3'	5' -GCCGGTACTGCAGCGTGA-3'	5' -AGCCGGTACTGCAGCGTAG-3'	4°C
				95°C × 5 minutes
				95°C × 30seconds
				62°C × 30seconds
				68°C × 30seconds
				68°C × 5 minutes
				Final Extension
				Hold
				Initial Denaturation
				45 Cycles
				Final Extension
				Hold
				Initial Denaturation
				45 Cycles
				Final Extension
				Hold

* 25ul volume with 1.8mM Mg^{2+} and 10pmol of both the forward and reverse primer

Table 2
Demographic characteristics of the entire study population followed by a breakdown based on *SREBF 1* and *SREBF2* genotypes.

Mean value $\pm$ SD,	Schizophrenia Cohort (n=157)	SREBF1 T allele (n=75)	SREBF1 CC genotype (n=79)	SREBF2 A allele (n=89)	SREBF2 GG genotype (n=66)
Age (years)	46.6 $\pm$ 11.0	46.8 $\pm$ 11.0	46.1 $\pm$ 11.2	45.9 $\pm$ 11.0	47.8 $\pm$ 11.2
Gender (% males)	64	64	65	61	67
Race-Caucasian (%)	59	59	60	63	53
Race-African American (%)	32	33	30	27	39
Body Mass Index (BMI) (kg/m ²)	32.9 $\pm$ 8.0	33.2 $\pm$ 8.0	32.8 $\pm$ 8.2	32.7 $\pm$ 8.0	32.3 $\pm$ 8.1
Current smokers (%)	55	53	54	51	59
Statin users (%)	30	32	28	26	35
Atypical Antipsychotic (AAP) users (%)	86	84	89	87	85
Total Cholesterol (mg/dl)	169.9 $\pm$ 42.5	171.5 $\pm$ 41.0	169.2 $\pm$ 43.8	172.1 $\pm$ 43.4	167.4 $\pm$ 42.0
Triglycerides (mg/dl)	138.1 $\pm$ 100.5	154.7 $\pm$ 109.1	122.9 $\pm$ 91.3	145.9 $\pm$ 107.6	128.6 $\pm$ 91.2
Low Density Lipoproteins (mg/dl)	101.1 $\pm$ 31.6	102.0 $\pm$ 31.1	100.8 $\pm$ 32.7	101.0 $\pm$ 32.4	101.8 $\pm$ 31.2
High Density Lipoproteins (mg/dl)	50.4 $\pm$ 16.1	48.8 $\pm$ 14.6	52.0 $\pm$ 17.3	51.1 $\pm$ 16.2	49.1 $\pm$ 16.1

-Comparing demographic characteristics based on genotype yielded no significant differences

Table 3

Genotype distribution based on Race

Genotype	Caucasian	African-American	American Indian	Asian	Hispanic Latino	Other or not listed	P-value*
SREBF1 rs11868035	CC	47	24	4	1	2	0.8
	T allele	44	25	2	0	3	
SREBF2 rs1057217	GG	35	26	3	0	1	0.4
	A Allele	56	24	3	1	4	

* using chi-square test with p<0.05 considered significant

Table 4

Lipid Levels based on Gender

	Male	Female	p-value
Total Cholesterol (mg/dl $\pm$ s.e.)	164 $\pm$ 4.2	181 $\pm$ 5.7	0.01
Triglycerides (mg/dl $\pm$ s.e.)	140 $\pm$ 10.1	133 $\pm$ 13.7	0.6
Low Density Lipoproteins (mg/dl $\pm$ s.e.)	98.5 $\pm$ 3.17	106 $\pm$ 4.30	0.1
High Density Lipoproteins (mg/dl $\pm$ s.e.)	46.4 $\pm$ 1.53	57.6 $\pm$ 2.07	<0.001