Summary

In the present study an attempt has been made to establish a link between the symptoms of depression, anthropometric measurements and genetic markers, to unravel the underlying association/s.

One hundred and fifty eight (158) adults with depressive disorder were recruited from the psychiatry unit of Badri Das Khaitan (BDK) Hospital, Jhunjhunu, Rajasthan, after obtaining an informed consent from them or their guardians (in cases of severe depression). Control group comprised of two hundred and forty five (245) unrelated healthy volunteers without any history of psychiatric disorders. The study was conducted within the norms of Declaration of Helsinki for human experimentation and with prior approval by the Institutional Human Ethics Committee at Guru Nanak Dev University and Birla Institute of Technology and Science (BITS), Pilani. All subjects were included in the study with help of trained psychiatrist working in BDK hospital Jhunjhunu, Rajasthan, using ICD-10 criteria, given by World health Organization. After a comprehensive survey of literature a suitable questionnaire was prepared to elicit the required information about demographic variables. During data collection personal interview was held with each subject and his/her guardian. Information about their socio-demographic background, personal history and other life style characteristics was collected from each subject. The anthropometric measurements like height, weight, hip and waist circumference were also recorded for each subject. Body mass Index and waist to hip ratio was calculated from the anthropometric markers with the standard formulas. About 5 ml venous blood was collected from each participant. Genomic DNA was isolated from peripheral white blood cells by the method described by Hammond et al. (1996). Repeat polymorphisms in Leptin gene and D2S2944 marker were detected using PCR-SSLP method, while PCR-RFLP based method was used to study the intronic polymorphism (A218C) in TPH1 gene. Chi-square ($\chi^2$) test and Odds Ratios (OR) with 95% Confidence Interval (CI) were used to test differences between the cases and controls. Student’s t test was applied for test of significance between means. Tests of
statistical significance were two sided. All statistical analyses were performed using SPSS v 16.0 (SPSS Inc, Chicago, III) and MedCalc (MedCalc Software, Mariakerke, Belgium).

The cases and controls did not differ significantly for the studied anthropometric indices i.e. BMI and WHR. Cases had higher mean values of triglycerides than controls. To study the role of genetic variants of LEP in depression, alleles of the Short Tandem Repeat (STR) marker (D7S1875) were examined in the upstream region of this gene. The alleles ranged in size from 196 to 226 bp in length and were divided into approximately equal groups, at 208 bp, according to their natural tendency for bimodal distribution as reported earlier and also evident from our results. Statistically significant difference between cases and controls for the <208 (short) allele of LEP gene was observed and this allele was prevalent in cases than in control subjects. Further, this association becomes even more robust at the genotype level after controlling for BMI (<30). A significant difference was observed in mean values of SBP and DBP among cases homozygous for either long or short allele of D7S1875. The results also show that the depressed obese or non-obese individuals have lower SBP and DBP in the presence of the short allele of LEP gene. The difference in SBP among non-obese cases (<30 BMI) with either short or long alleles of D7S1875 marker remained significant even after controlling for BMI. This suggests a probable role of LEP gene in regulation of blood pressure independent of obesity. This is the first study which provides molecular link for the relationship between depression and blood pressure. LEP was not found to be associated with weight loss and risk for suicide while a significant relation with addiction was observed in the present study.

Based on results of present study 124 bp allele of D2S2944 was found to be risk factor for depression. The alleleic distribution for 124 bp allele at D2S2944 locus differed significantly among cases and controls. When adjusted for gender the allele frequency for 124-bp allele was found to differ significantly among male subjects only while no such difference was seen in the females. Results also indicated some interesting potential
gender effects of this marker on depression. When analyzed for anthropometric markers the presence of a single or double copy of 124 bp allele doubled the incidence of being obese (BMI >30) in the cases. The risk of depression in individuals with BMI >30 was 1.6 times more than the controls, while risk was 3 times more in individuals with WHR >0.9 which is risk factor for metabolic disorders. The homozygous 124 bp depressive males were found to be more prone to smoking as compared to the subjects without 124 bp allele.

Distribution of TPH1 A218C genotypes were according to Hardy Weinberg equilibrium in cases and controls. When TPH1 genotypes were compared between cases and controls a significant lower representation of AA allele was seen in control subjects than the cases. Results showed that the CC genotype play a protective role in the etiology of depression. The multivariate logistic regression analysis also showed that presence of C allele plays a protective role against suicide ideation in depressed individuals. When data was controlled for BMI and WHR the association between the gene and disease remained statistically significant and showed the possible role of this gene in depression and obesity. It was found that the depressed individuals with ‘C’ allele of TPH1 A218C polymorphism have significantly low risk for suicide than the depressed individuals with ‘A’ allele. The TPH1 A218C was also found to be associated with higher risk of addiction among depressed individuals.

When the cases and controls were adjusted for LEP <208/<208bp genotype the risk for depression due to AC/CC genotype of TPH1 became extremely significant. Bonferroni correction was applied for these two genotypes and the risk for the depression remained significant. This shows that these markers together act as important factors in the etiology of both depression and obesity. Hence the polymorphism in CREB1 and TPH1 can synergistically affect the onset and progression of depression and obesity.

Present study also found the relation between socioeconomic factors and subsequent risk for depression. There were large number of depressed individuals losing weight in lower
socioeconomic class than the middle and higher socio-economic class. The observations of this study confirmed the earlier reports where low socioeconomic factors were found to be risk for depression. Present study is the first study which showed that genes (LEP and TPH1) also play critical role in the symptomatology of depression and are also influenced by the socio-demographic factors. Further research is needed to investigate the validity, causality and generalizability of these results.