عنوان المشروع باللغة العربية	
عنوان المشروع باللغة الإنجليزية	**Role of Angplt8 (Betatrophin) gene polymorphism in metabolic syndrome manifestations among Saudi subjects**
المشرف الرئيس	**Dr. Maha**
التخصص الدقيق للمشرف الرئيس	البيولوجية الجزيئية
المشرف المساعد	Dr. Majed Alokail
المدة المتوقعة لإنجاز البحث منذ الحصول على موافقة عمادة الدراسات العليا	12 شهر
Abstract or synopsis of the proposal (200 words or less):	It has been shown that components of the metabolic syndrome (MetS) (dyslipidemia, hyperglycemia, hypertension and obesity), individually and cumulatively, increase the risk of developing T2DM and cardiovascular diseases (1). The prevalence of MetS, a major public health issue, has been increasing steadily, resulting in a growing interest in developing drugs to correct dyslipidemia and hyperglycemia (2). Changes in lifestyle are clearly important, but genetic factors may also contribute to this increased risk. The angiopoietin-like (ANGPTL) genes encode a family of secreted proteins with pleiotropic effects on vascular cells (3) and lipid metabolism (4). ANGPTL8 has been shown to have a dual role in both lipid metabolism and glucose homeostasis (2). Multiple studies have identified ANGPTL8 sequence variations that are associated with lipid profiles in human genome-wide association studies (5). A nonsynonymous sequence variation in ANGPTL8 (rs2278426) is associated with reduced plasma levels of LDL-cholesterol and HDL-cholesterol (6) The SNP rs737337 has also been found to be associated with HDL-C levels, and the SNP, although located in a region upstream of the ANGPTL8 transcription start site, represents a synonymous variant in the DOCK6 gene (6).
Hypothesis or scientific	Based on the above findings, it will be interesting to study the impact

justification of the proposal	of ANGPTL8 and DOCK6 SNPs on MetS risk and to verify whether such SNPs could influence circulating lipid metabolism. The Polymorphism at specific loci in the ANGPTL8 and DOCK6 genes can serve as genetic contributors of metabolic disorder.
Specific objectives	1). To investigate the role of ANGPTL8 and DOCK6 variants in MetS phenotypes in a Saudi population. 2). To measure the serum levels of betatrophin in subjects with MetS and compare them with healthy controls. 3). To correlate ANGPTL8 and DOCK6 variants with serum glucose-lipid profile.
Methodology & Major Techniques to be used	Saudi MetS subjects between the ages 20-40 years (N = 100) and an equal number of age matched controls will be recruited for the study. Anthropometry including height (rounded off to the nearest 0.5 cm), weight (rounded off to the nearest 0.1kg), waist and hip circumference (centimeters), and mean systolic and diastolic blood pressure (millimeters of Hg) (average of 2 readings) will be measured. Body mass index (BMI) will be calculated as weight in kilograms divided by height in square meters. Diagnosis of MetS will be based on the International Diabetes Federation (IDF). Fasting blood samples will be collected and transferred immediately to a non-heparinized tube for centrifugation. Fasting glucose and lipid profile will be measured using a chemical analyzer (Konelab, Espoo, Finland). Serum betatrophin levels will be assessed using an enzyme-linked immunosorbent assay (ELISA). **Genotyping** Genomic DNA will be isolated from whole blood using the blood genomic Prep mini spin kit (GE healthcare Life Sciences, Piscataway, NJ, USA). DNA concentration and purity (260/280) will be checked using Nano-drop spectrophotometer. The two tagging SNPs (rs2278426, rs737337) will be evaluated by allelic discrimination Real-time PCR using pre-designed TaqMan genotyping assays from Applied Bio-systems (Foster City, CA, USA).

	<u>Major Techniques</u>: (i) DNA extraction (ii) Measurement of Biochemical parameters. (iii) SNP detection using allelic discrimination real-time PCR (iv) ELISA
Availability of Samples	Yes
Availability of Chemicals	Yes
Availability of Instruments	Yes
Availability of Ethical Approval (if needed)	Yes
Recent References	**1.** Alkharfy, K. M., Al-Daghri, N. M., Al-Attas, O. S., Alokail, M. S., Mohammed, A. K., Vinodson, B., ... & Draz, H. M. (2012). Variants of endothelial nitric oxide synthase gene are associated with components of metabolic syndrome in an Arab population. *Endocrine journal*, *59*(3), 253-263. **2.** Fu, Z., Berhane, F., Fite, A., Seyoum, B., Abou-Samra, A. B., & Zhang, R. (2014). Elevated circulating lipasin/betatrophin in human type 2 diabetes and obesity. *Scientific reports*, *4*. **3**. Camenish G, Pisabarro MT, Sherman, D, Kowalski, J, Nagel M, Hass, P, Xie MH, *et al* (2002). ANGPTL3 stimulates endothelial cell adhesion and migration via integrin alpha vbeta 3 and induces blood vessel formation in vivo. J Biol Chem, 277(19): 17281-90. **4**. Mattijssen F, Kersten S. (2012). Regulation of triglyceride metabolism by Angiopoitin-like proteins. Biochim Biophys Acta, 1821(5): 782-89. **5**. Quagliarini F, Wang Y, Kozlitina J, Grishin NV, Hyde R, Boerwinkle E, Valenzuela DM, Murphy AJ, Cohen JC, Hobbs HH (2012). Atypical angiopoietin-like protein that regulates ANGPTL3. *Proc Natl Acad Sci*, 109**:**19751-19756 **6.** Zhang, R., & Abou-Samra, A. B. (2014). A dual role of lipasin (betatrophin) in lipid metabolism and glucose homeostasis: consensus

	and controversy.*Cardiovascular diabetology*, *13*(1), 133.