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عنوان المشروع باللغة العربية - Title of the proposed project in Arabic	تعدد الأشكال الجينية لجينات IL-6 and TNFα وخطر الإصابة بمرض الزهايمر في المجتمع السعودية
Title of the proposed project in English	Association of IL-6 and TNFα gene polymorphisms with the risk of Alzheimer's disease in Saudi subjects
المشرف الرئيس - PI	Saba Abdi
التخصص الدقيق للمشرف الرئيس - Specialty of PI	Nucleic acid immunology
المشرف المساعد - Co-PI	Amani Alghamedi
المدة المتوقعة لإنجاز البحث منذ الحصول على موافقة عمادة الدراسات العليا (بالشهور) - Expected time in month to finish	12 months
Abstract of the proposal (No more than 200 words)	Alzheimer's disease (AD), is the most common form of dementia and approximately one in eight people over 65 years old are at risk worldwide. It is a degenerative brain disease characterized by the development of amyloid plaques and neurofibrillary, or tau, tangles; the loss of connections between nerve cells in the brain; and the death of these nerve cells. The intricacies of the

	mechanism of AD have not yet been clearly defined. The risk factors for dementia and AD are age, female gender, diabetes mellitus, hypertension and cerebrovascular diseases. Among the Saudi population the risk factors thought to be associated with the onset and pathogenesis of AD are not exactly identified. Genome-wide associated studies (GWAS) have identified lipid metabolism, inflammatory response and endocytosis as the three main pathways involved in AD risk. Thus, we propose to validate various inflammatory blood biochemical markers of AD including ,Interleukin-6 (1L-6) , Tumor necrosis factor(TNF-α) and C-reactive protein (CRP). Furthermore we intend to investigate the genetic polymorphisms in genes belonging to inflammatory response (IL-6 and TNFα) in relation to AD and its measured biochemical markers in samples from Saudi Arabia
Hypothesis of the proposal	Influence of the Single nucleotide polymorphisms of IL-6and TNF-α gene on risk of AD in Saudi population
Specific objectives	1. To investigate the relationship of the serum levels biomarkers for inflammation Interleukin-6 (1L-6) ,Tumor necrosis factor(TNF-α) and C-reactive protein (CRP)with outcome of the disease. 2. We will determine the association between genetic variants in 1L-6 (rs1800795, rs1800796) and TNF-α (rs 1799724 and rs1800629) and biochemical parameters (measured in objective 1) and its association with the occurrence of AD in samples from Saudi ethnic population.
Methodology & Major Techniques to be used	Methodology : 1. Collect detailed information from the patients and age matched control subjects with a particular focus on the family history ofAD/Demintia, medications, diet, chronic disorders, and lifestyle habits Ethical approval will be obtained from the Ethics Committee of the Research Center, College of Science, King Saud University prior to the study. Written consent will also be obtained from the subjects prior to their inclusion in the study. Saudi subjects between the ages 65-90 years (N =100) with a confirmed diagnosis of AD and no treatment of any kind and an equal number of age matched controls will be recruited for the study. Subjects with malignancy, endocrine, cardiac or lung disease will be excluded from the study.The subjects will be recruited from King Khalid Hospital ,Riyadh.with the help and coordination of physicians with proven expertise in the field. AD will be diagnosed in the subjects following the NINCDS-ADRDA and the

	DSM-IV criteria A generalized questionnaire seeking the details of present and previous medications dietary habits, chronic disorders, lifestyle activities including cigarette smoking, and exercise and a family history of AD will be obtained from the subjects. Subjects with a history of Dementia or AD treatment and those currently receiving any medications such as steroids that are known to interfere with metabolism and patients with documented disease, and malignancies and will be excluded from the study. Clinical and anthropometric parameters will be collected from both the patients and the controls by trained and experienced personnel. Subjects with normal NINCDS-ADRDA and the DSM-IV scores that are free of any metabolic bone diseases based on the medical history provided in the structured questionnaire will be considered as controls. The anthropometry included height, weight, waist and hip circumference utilizing a standardized measuring tape in cm; systolic and diastolic blood pressure measurements; and body mass index(BMI) (calculated as kg/m2). Blood will be collected in EDTA tube for genomic DNA analysis. For collection of serum, blood will be transferred immediately to plain a non-heparinised tube and kept undisturbed for some time at room temperature to allow clotting, the clot will be removed by centrifugation. The resulting serum will be transferred to pre-labelled plain tubes and stored at -20°Cuntil analysis 2. Measuring the levels of the biochemical markers of inflammation Interleukin-6 (1L-6) ,Tumor necrosis factor(TNF-α) and C-reactive protein (CRP)in subjects as well as in age matched controls. Enzyme-linked immunosorbent assay (ELISA) will be used to measure plasma concentrations of both these markers, according to manufacturers instructions. 3. Analysis of polymorphisms in the IL-6 and TNFα genes. High quality genomic DNA will purified from the whole blood by using the All Prep DNA mini kit according to manufacturer's instructions and will be quantified spectrophotometrically. Two SNPs in 1L-6 (rs1800795, rs 1800796)and two in TNF-α (rs 1799724 and rs1800629) gene will be evaluated using allelic discrimination Real-time PCR using pre-designed TaqMan ® Probes from Applied Bio-systems, Foster City, CA, USA. Major Techniques used: 1. ELISA 2. Real-time PCR
Availability of Samples	Yes

Availability of Chemicals	Yes
Availability of Instruments	Yes
Ethical Approval	In the process
Recent References	1. Mun MJ, Kim JH, Choi JY, Jang WC.Meta.Genetic polymorphisms of interleukin genes and the risk of Alzheimer's disease: An update meta-analysis. Gene. 2016 Jun; 8:1-10.Epub 2016 Jan 11. 2. Laws SM, Perneczky R, Wagenpfeil S, Müller U, Förstl H, Martins RN, Kurz A, Riemenschneider MTNF polymorphisms in Alzheimer disease and functional implications on CSF beta-amyloid levels..Hum Mutat. 2005 Jul;26(1):29-35 3. Guanglin Cui, HaoranWang,RuiLi,Lina Zhang, ZongzheLi,Yan Wang, Rutai Hui, Hu Ding,and Dao Wen WangPolymorphism of tumor necrosis factor alpha (TNF-alpha) gene promoter, circulating TNF-alpha level, and cardiovascular risk factor for ischemic stroke.J Neuroinflammation. 2012; 9: 235. 4. O'Bryant S.E., Waring S.C., Hobson V., Hall J.R., Moore C.B., Bottiglieri T. Decreased C-reactive protein levels in Alzheimer's disease. J Geriatr Psychiatry Neurol. 2009;23:49–53