Chapter 3

Toxoplasmosis and Public Health Genomics

Oymak Sibel, Hız Meliha Merve, Kılıç Sevilay,
Büyük Başak, Halil İbrahim Taş and
Ülken Tunga Babaoğlu

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Abstract

Toxoplasma gondii infection generally causes flu-like symptoms in healthy individuals; however, immunosuppression of the infected individual causes reactivation of the pathogen to its active form and relapse of the toxoplasmosis. Today it is known that toxoplasmosis triggers psychiatric disorders such as schizophrenia as well as behavioral changes such as suicide attempts. Although dermatological manifestations are very rare, the dermatological lesions are not unique. In addition, previous toxoplasma infection also causes congenital infections because of placental infection and causes birth defects and spontaneous abortion. *T. gondii* strains are mainly divided into three main clonal lineages, yet higher recombination rate causes unusual population structure and heterogeneous distribution of the pathogen. Both genetic variations, of the pathogen and the patients, are important for virulence property and success of the therapies. The scientist focuses on the genetic variations of the pathogens and individuals to achieve effective treatment and developed tailor-made medicines. Thus, understanding the molecular basis of the disease and the link of molecular mechanism with host immunity is important to fully know the disease and related disorders. In this chapter, we would like to evaluate the current knowledge on genetic, molecular characteristics of toxoplasmosis in view of public health genomics.

Keywords: *Toxoplasma gondii*, schizophrenia, public health genomics

1. Introduction

Toxoplasma gondii is a life-long infectious protozoan parasite and thus understanding the immunological and molecular pathways during toxoplasmosis is important for effective treatment and vaccine development. *T. gondii* infection and related neurological, behavior,

dermatological, and ocular manifestations are an important area of current research. In addition, the molecular life cycle of the pathogen, immunologic, and genetic changes during the infection is also important to diagnose and improve new treatment strategies. The other important research area related to toxoplasmosis is development of safe and efficient diagnostic assays for early detection of pathogens during pregnancy period.

It is thought that *T. gondii* has a role in the etiology of schizophrenia and that parasites have special genes that can be inherited. However, there are some limiting factors. In schizophrenia, it is difficult to show the cause of toxoplasmosis in brain tissue. *T. gondii* can also be found in brain tissue in immunocompetent individuals. Moreover, not all of the *T. gondii*-infected individuals develop schizophrenia. Increased risk of exposure to *T. gondii* has been shown in schizophrenic patients, but the exposure relationship is often studied by case-control studies. Despite the cohort-type studies that show the best relationship between the etiologic agent and the disease, researchers prefer to work in case-control type because of the latent course of the disease, not being a common disease in society, and difficulties in follow-up. It should be kept in mind that genetic factors as well as environmental exposures may increase the risk of this disease and that the presence of the agent before disease development may better explain the causal relationship.

We need a perspective of public health genomics to better understand the relationship between schizophrenia and toxoplasma, which is one of the most frequently used topics in recent years, and also in order to better understand the public health effects of parasites. The clear understanding of the histological, biochemical, and genetic characteristics of parasites can also explain the mechanisms of disease development. For this purpose, in this chapter, genotypic features of *Toxoplasma gondii*, other molecular changes, and mechanisms of schizophrenia development are discussed and suggestions are given in terms of public health.

2. Molecular basis of toxoplasmosis

The first line of defense against *T. gondii* compose of dendritic cells (DCs), monocytes, and macrophages, and *Toxoplasma* induces toxoplasmosis-specific $CD4^+$ and $CD8^+$ T cells, which are the secondary defense systems. The ligands expressed by *T. gondii are* recognized by toll-like receptors (TLR) [1–3] and stimulate IL-12 production via MyD88 signaling [4, 5]. GPI-anchored proteins of *T. gondi* is important for both adhesion to host and regulate host immune system via TLR2 and TLR4 on macrophage surface [2, 3] aside profilin that secreted from *T. gondii* binds to TLR11 on dendritic cells [5]. Pro-inflammatory IL-12 secretion triggers IFN-γ production by NK cells; thereafter, $CD4^+$ and $CD8^+$ T cells join to release IFN-γ [6], and then IFN-γ binds to a receptor tyrosine kinase (IFN-γ-R) and activates the JAK/STAT1 cascade by JAKs phosphorylation (**Figure 1**).

Activation of JAKs phosphorylates the tyrosine residue of STAT1 and cause dimerization of the molecule hence translocate the nucleus [7] then binds to IFN-γ-responsive gamma-activated site (GAS) consensus sequence and initiate the transcription of IFNγ-inducible genes Irf-1 and Lrg47 [7, 8]. In addition to T-cell mediated immunity, STAT1 induces nitric oxide (NO) and reactive oxygen species (ROS) production in monocytes and macrophages [9]. Lüder et al. [10]

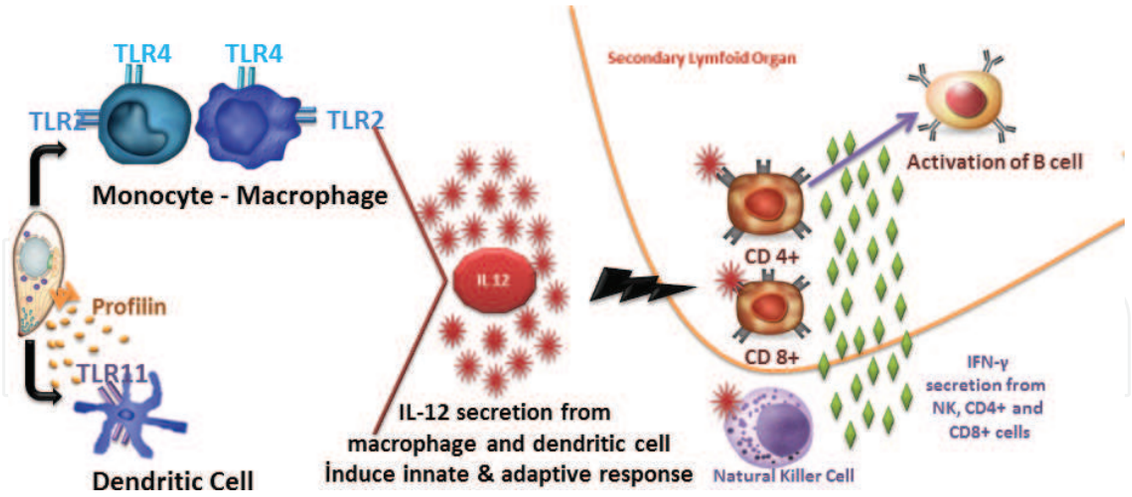

Figure 1. Immune response to *Toxoplasma gondii* infection in humans.

have reported the toxoplasma IFN-gamma-induced gene expression via STAT1 pathway. In addition, STAT4-dependent IFN-γ has been reported in dendritic cells and macrophages [11]. Many reports have been shown the *T. gondii* success of toxoplasma's immune evasion strategies [10, 12, 13]. The molecular basis of parasite-host interaction is important in understanding the disease mechanism and developed successful treatment strategy (**Figure 2**).

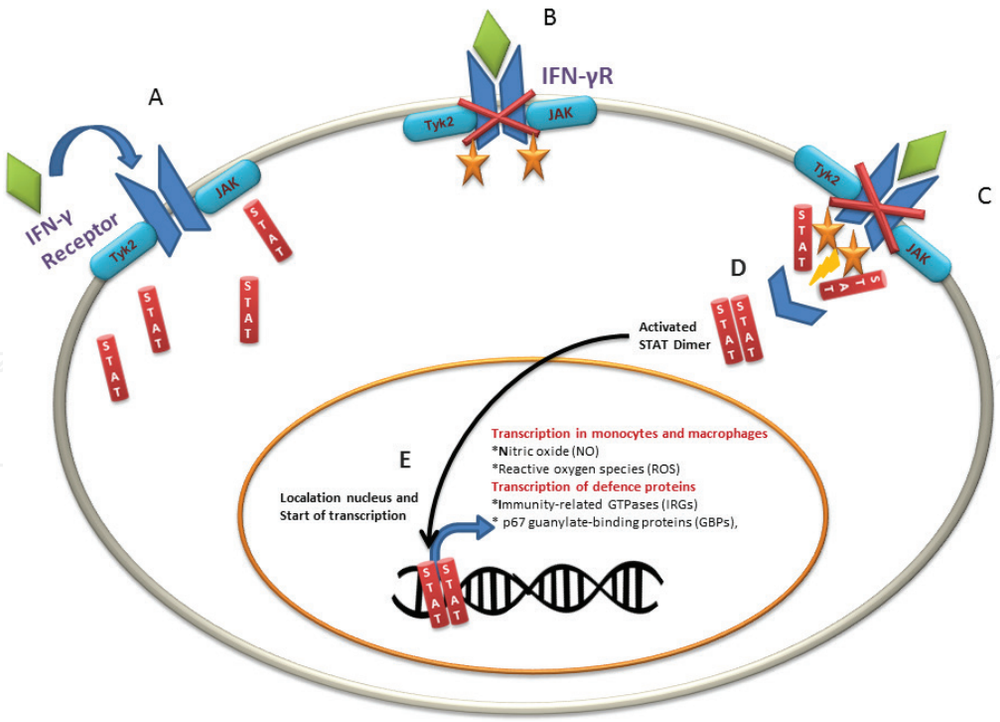

Figure 2. JAK-STAT pathway is important to induce toxoplasma-related response genes. INF-γ binds to its receptor (A) and activates the tyrosine kinase activity of receptor (B) and hence the phosphorylate SH2 domain of the STAT (C). Phosphorylation of the STAT triggers dimerization of the molecule (D) and conformational changes cause nuclear localization of the STAT which then binds to the nuclear response sequence on promoter region (E) to induce expression of target genes.

3. Genetic variation of *Toxoplasma gondii*

The complexity of an organism is directly related to its genome, and the variation on parasite genome is crucial for their success during evolution. In addition to natural selection, the pharmacy industry also forces parasites for evaluation; thus, genomic diversity also means successful pathogenicity.

Toxoplasma gondii consists of three main clonal lineages (types I, II, and III) among North America and Europe [14], and type II is the major strain that causes human infections in North America [14] and Europe [15, 16]. Early studies that performed multilocus enzyme electrophoresis (MLE) had limitations to show biological and epidemiological diversity [17].

Nowadays, high throughput technologies allow the scientist to understand the genetic diversity of *T. gondii*. In contrast, genetic analyses that were performed by multilocus markers have been shown that isolated samples from South America were highly diverse from each other and also from European and North American strains [15–18] due to a higher recombination rate [19]. The recent researchers have been shown that *T. gondii* has unusual population structure with different growth rates [20], frequency of differentiation, motility [21] virulence, persistence, and migration capacity [15, 21–23]. Recent developments in molecular tools allow enhancing their success to identify the genetic diversity of the parasite [24, 25]. Su et al. [25, 26] have analyzed the nuclear and plastid genome of 950 isolates from all over word and reported six major clades dividing 15 haplotypes with 138 unique genotypes. Ning et al. [22] have reported that toxoplasma dense granule protein 20 (GRA20) may be useful for intraspecific phylogenetic analyses. Wang et al. [27] have reported that rhoptry protein 47 may be used as a genetic marker for a phylogenetic relationship. In contrast, genes with low sequence variation such as superoxide dismutase (SOD) are not useful for variation analyses [28, 29].

4. Importance of human genetic variation for toxoplasmosis infection

Nowadays, researches are focused on the personalized medicine by using genetic variations of the patients to develop tailor-made therapeutics for appropriate and optimal therapies. The most important part to develop tailor-made therapeutics understands the relation between molecular basis of the disease and phenotypic screening. In addition, genomic variation is also important to understand personal immune response to a specific disease or therapeutic efficiency.

Toll-like receptor (TLR) is a single-pass transmembrane, non-catalytic receptor family, which is crucial for an early innate immune response during evolution. TLR expression differs in the stage of pregnancy, and a different subtype of TLR is activated or deactivated in placental tissues during pregnancy period [30, 31]. Nishimura and Naito have shown that TLR3 expression was the highest in placenta [32]. TLR is linked to infertility [33], pregnancy disorders, and placental dysfunction [34]. In toxoplasmosis TLR2, TLR4, TLR9, and TLR11 have been found important for recognition of ligands expressed by *T. gondii* [1, 35–37]. Andrade et al. [38] have demonstrated *TLR7 and TLR9 sense T. gondii*-associated nucleic acids (DNA or RNA) while TLR11 and TLR12 sense Toxoplasma profiling. Thus, understanding genomic variations in TLR is important to highlight immune defense against *T. gondii* [30, 39, 40]. NOD-like receptor

(NLR) families are important for immediate responses against structures that are present in *T. gondii* like TLR receptors. Dutra et al. [41] have reported that NOD2 gene polymorphism (rs3135499) increases the ocular toxoplasmosis by its effects on IL-17A production. Witola et al. [42] have reported that NALP1, a member of the NLR family of proteins, is crucial for immune responses to *T. gondii* infection and pathogenesis. Variation in immunity-related genes is also associated with toxoplasmosis. Shimokawa et al. [43] have shown that HLA-DQA1 and DQB1 alleles are increasing the risk of congenital toxoplasmosis. In conclusion, human genomic variation influences the defense against *T. gondii* as well as its manifestations of congenital infection and ocular toxoplasmosis.

5. Immunohistochemistry of toxoplasmosis

Toxoplasmosis can cause severe fetal conditions during pregnancy, and this fetal influence is related to the trimester of pregnancy. *Toxoplasma gondii* infection in the first trimester of pregnancy (4th week) can cause serious neurological and ophthalmological damage as well as spontaneous termination of pregnancy [44]. Infection of the nervous system leads to central nervous system injuries including hydrocephalus, microcephaly, motor mental retardation, and intracranial calcifications. Microphthalmia can also be observed in the first trimester. *Toxoplasma gondii* infection in the second and third trimester may result in chorioretinitis, visual defects, and mild neurological sequelae [45]. Dermal symptoms of *Toxoplasma gondii* in fetus are nonspecific and differs in each trimester.

Histopathological report attracted attention to especially parasitic infiltration and also inflammatory cell infiltration in affected tissue during toxoplasmosis. Immunosuppressive patients because of reduced inflamatory response due to immunne suppressive agents. Thus, immunohistochemically staining with appropriate antibodies will be helpful in these cases [46, 47]. Pathologic changes especially visible in skin lesions are pseudoepitheliomatous hyperplasia and perivascular lymphohistiocytic infiltration. Parasites can be seen in macrophages by hematoxylin eosin staining or as its single parasitic form by basophilic staining. Bradyzoites form that contains tissue cysts can be visualized by hematoxylin-eosin, Giemsa, Mallory, Biondi, and PAS reagent [48]. Parasites can also be visualized immunohistochemically by marking them with antigen-specific antigens inside the host tissue [49]. Tachyzoites are able to be visualized by light microscopy from samples taken from infected tissues [48, 50]. In addition to light microscopy, immunofluorescence methods can be used to detect parasites and to show them microscopically in samples taken from infected tissues with parasites [50].

6. Toxoplasmosis and psychiatric patients

6.1. Behavioral changes and toxoplasmosis

Kozar has shown the relationship between toxoplasma infection and psychiatric disorders for the first time [51] *T. gondii*, present in one-third of the world's population, may be associated with an increase in suicide rate [52]. *T. gondii*, a neurotrophic parasite, plays a role in the

development of schizophrenia and causes behavioral changes, suicide attempts, and neuropathological degenerations in the brain tissue [53–56, 74]. *T. gondii* has a role in the development of behavioral disorders via changes in neuroimmunomodulation and neurotransmission, yet pathophysiological mechanisms are not fully understood by scientists [57, 58].

6.2. Schizophrenia and toxoplasmosis.

Several studies and later metaanalyses have been reported the association between *Toxoplasma gondii* infection with schizophrenia [55, 59, 60]. It has been shown that *T. gondii*-infected individuals increase the risk of schizophrenia when compared to healthy individuals, yet these relationships were only examined by case-control studies. Epidemiologically, the best way to show the relationship between the agent and the disease is to work in cohort type. In contrast, the researchers prefer to work in case-control type studies because of the latent course of the disease, the difficulties encountered in the follow-up, and the life cycle pathogen and rare nature of disease. It should be kept in mind that genetic factors as well as environmental exposures may increase the risk of this disease. Previous toxoplasma infection before neurological disease development may better explain the causal relationship.

Schizophrenia susceptibility genes are associated with life cycle of *T. gondii* [61]. The factors that play a role in the etiology of the disease time of infection, genetic variation of *T. gondii*, and strain of the parasite [60]. In addition to the genetic characteristics of infected individuals, immigration or being the offspring of immigrants is also related with schizophrenia among *T. gondii*-infected humans [62].

T. gondii and schizophrenia relations have been linked in many studies [63], and generally it's accepted that *T. gondii* triggers psychiatric disorders via affecting neurotransmitter secretion [54]. It is known that the *T. gondii* genome contains two aromatic amino acid hydroxylases that can directly affect dopamine and/or serotonin biosynthesis [64]. It is unclear how *T. gondii* increased dopamine levels; however, the dopamine is released during inflammation due to the increase of cytokines such as interleukin-2 (IL-2) [65, 66]. Hence, dopamine imbalance in the mesolimbic and mesocortical regions of the brain may play a role in the development of schizophrenia [67].

T. gondii modulates host gene expression by secretion of effector molecules [68] or cause post-translational modification such as acetylation of protein residues in neurons and glial cells [69]. The success of the pathogen is its virulence ability to cross biological barriers such as the blood brain barrier [70]. In a study, Du et al. [68] demonstrated that *T. gondii* terminates the NF-κB pathway by its rhoptry protein that causes p65 ubiquitination for proteasomal degradation. In a study, it has been shown that *T. gondii* changes lysine acetylation in astrocytes [69].

TOXO-specific IgG and IgM antibody levels are elevated in schizophrenia [71–75]. In a study in which other demographic variables might affect age, race, sex, and mortality, it was found that the risk of death in serologically positive individuals was five times higher than *Toxoplasma gondii* seronegative ones [75]. Toxo-specific IgG antibody level was found four times higher in patients with schizophrenia than in individuals without [76].

Torrey has shown that *Toxoplasma* seroprevalence in individuals with schizophrenia is 2.73 times higher than the control population [60]. In a study, Emelia et al. [77] have shown significant sero-intensity rates of anti-*T. gondii* IgG antibody in schizophrenic patients when compared to psychiatrically healthy volunteers. Tamer et al. [78] have shown that IgG *T. gondii* antibodies were higher in patients with schizophrenia when compared with controls, and in contrast, Karabulut et al. [79] have reported that there is no association between *T. gondii* IgG positivity and schizophrenia.

7. Toxoplasmosis and dermatological disease

Dermatological manifestations are rare and diagnosis of lesion is difficult. Skin lesions in congenital infections are usually exfoliative lesions and hemorrhagic and necrotic papules (small papules in the shape of 'blueberry muffins'). These lesions tend to hold the body. But it can be seen in the entire body, except in the palmoplantar region and face. The skin findings of toxoplasmosis are very varied: the dermatological lesions are reported as roseola, erythema multiforme [80], papular urticaria [80, 84], urticarial, hemorrhagic eruptions, formation of nodules and bullae [81, 82] on palms, soles, hands, legs, trunk, face and chest [83, 84]. Jeffrey and Pollock have shown a 12-year-old boy patient with dermatomyositis and polymyositis and offered to use sulfadiazine, pyrimethamine, and folinic acid for treatment [85]. Fong et al. [81] have reported a 49-year-old HIV-positive Chinese male with hard and painful nodular lesions. Ivanova et al. [86] described a case of 46-year-old male patient with acute toxoplasma lymphadenitis, similar to malignant cervical lymphadenopathy. In another study performed by Marina et al. [87], scientists reported a case of a 43-year-old immunocompetent man who has several erythematous papules and nodules on the body and extremities.

Histopathologic features are common for both acquired and congenital forms. Lymphocytes, macrophages, plasma cells, and superficial and deep perivascular infiltration, which is composed of eosinophils, are seen in the dermis. Tissue forms of *T. gondii* may not always be seen in specimens of biopsy taken from the lesion.

It is important that congenital toxoplasmosis is distinguished from the TORCH group of infectious diseases. Acquired toxoplasmosis may be confused with inflammatory diseases such as viral exanthema, meningococcemia, syphilis, urticarial vasculitis, and erythema multiforme associated with herpes simplex and autoimmune collagen tissue diseases. If active acute infection occurs in organs such as the skin or the eye, or congenital infection occurs, or immunosuppressed patients need treatment, the most effective treatment method is pyrimethamine (from 25 to 50 mg per day followed by 100 mg loading) and sulfadiazine (2–4 mg per day oral, divided into four doses). Patients allergic to sulfonamides may be given clindamycin (300 mg, four times a day).

8. Toxoplasmosis and pregnancy

T. gondii is an important, warm-blooded pathogen that causes congenital infection during pregnancy which results in cardiovascular, cerebral, and ocular damage in newborns by

transplacental infection [87, 88]; *T. gondii* infection also causes birth defects and spontaneous abortion [89–92].

Determination of *T. gondii* infection is crucial during pregnancy to decrease congenital toxoplasmosis [91] and thus companies try to develop new commercial tests. The serologic screening of IgM, IgA, and IgG is important to determine current or past infections of the pregnant women [88, 93]. In addition to serological methods, ELISA IgG avidity is also found safe, efficient, and easy to determine *T. gondii* infection in the first trimester of pregnancy in routine diagnostic treatment [94, 95]. PCR is an effective diagnostic tool to determine the pathogen in a tiny amount of sample with high specificity [96–98]. The scientist's efforts to develop efficient and safe methods to alternates of ELISA, IFA, or modified agglutination test (MAT [88] or to develop these commercial ones to eliminates limitations of previous ones are ongoing [99, 104]. Armengol et al. [100] have compared different commercial assays which use anti-Toxoplasma IgG seroconversion in pregnant women and efficiency of the assays differs.

Pomares et al. [101] have developed new multiplexed *T. gondii* IgG and IgM tests which allow determining the pathogen in ~1 microliter of the serum sample. Mahmoudi et al. [102] have developed ELISA-based interferon-gamma release assay for the early detection of the pathogen. Mohammadpour et al. [103] have been reported that tachyzoites form of *T. gondii* able to detect via its soluble crude antigens by ELISA. Robert-Gangneux et al. [104] have been developed efficient toxoplasmosis assay which able to diagnose from non-cell-rich or non-hemoglobin-rich samples by real time PCR.

The development of diagnostic tests is particularly important in addressing the difficulties encountered during routine follow-ups by the population. Common guidelines are needed to guide both patients and clinicians in the subsequent processes, especially when toxoplasmosis is diagnosed in pregnancies. Sensitive tests to be developed for definite diagnosis are very important because there are problems related to diagnosis in pregnancy. *T. gondii* scans should be done serologically in cats and dogs at the same time. There is a need for regional studies on toxoplasmosis, especially in developing countries because socio-cultural features play a role in the development of the disease. As in many countries, studies in Turkey are continuing. There are studies on seroprevalence of toxoplasmosis and schizophrenia reported from the University and State Hospital in our research area Canakkale [105–108].

9. Conclusion

Attention should be paid to veterinary basic health services in combating and protecting zoonoses, which are thought to be an important risk factor in schizophrenia etiology such as *T. gondii*. While the risk of being infected with *T. gondii* by individuals living in urban centers increases risky behaviors such as cat feeding, cleaning of cat external feces, and contact with street cats; these risks are the factors such as contamination of animal products, consumption of raw meat and meat products, general hygiene conditions and inadequate

water hygiene in the people living in rural areas and living with agriculture and animal husbandry. Therefore, it is more effective and useful to plan the health trainings and surveys that are to be carried out, considering the socio-demographic and environmental characteristics of these target groups.

Data obtained in screening studies should be recorded with geographic information systems, and risky areas should be identified and individuals at risk (primarily pregnant women, children, people with psychiatric health problems) living in these areas should be regularly monitored. Trainings should be given on healthy lifestyle behaviors, such as personal and environmental hygiene. In clinical practice, in order to prevent *T. gondii* from being missed, in-service trainings should be made to raise awareness and responsibility for health personnel.

In order to overcome the question marks in the schizophrenia mechanism, a gene pool can be created on serum samples obtained from regional and national studies, and the present and changing immunogenetic structure of parasite can be monitored. This important point of public health and genetics is that infectious agents are monitored in a large pool of genes to monitor the changes they show and to help them analyze the distribution of health problems caused by infectious agents in their populations and risk factors. We also believe that the molecular monitoring of parasites such as toxoplasma will help to improve the early diagnosis and treatment of parasitic infections, which are the most important of public health problems, and the prevention and control of these infections.

Author details

Oymak Sibel[1]*, Hız Meliha Merve[2], Kılıç Sevilay[3], Büyük Başak[4], Halil İbrahim Taş[5] and Ülken Tunga Babaoğlu[6]

*Address all correspondence to: sibeloymakpublichealth@gmail.com

1 Department of Public Health, Faculty of Medicine, Çanakkale Onsekiz Mart University, Canakkale, Turkey

2 Department of Medical Biology, Faculty of Medicine, Çanakkale Onsekiz Mart University, Canakkale, Turkey

3 Department of Dermatology, Faculty of Medicine, Çanakkale Onsekiz Mart University, Canakkale, Turkey

4 Department of Histology and Embriology, Faculty of Medicine, Çanakkale Onsekiz Mart University, Canakkale, Turkey

5 Department of Psychiatry, Faculty of Medicine, Çanakkale Onsekiz Mart University, Canakkale, Turkey

6 Department of Public Health, Faculty of Medicine, Ahi Evran University, Kırsehir, Turkey

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