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Review

An introduction to the role of immunology in medical anthropology and molecular epidemiology

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ABSTRACT

Medical anthropology is a multi-disciplinary approach to the medical sciences and humanities. Immunology is of the basic medical sciences dealing with anthropology as a science which involves in recognition of self and non-self. We performed this review paper to introduce the role of immunology in medical anthropology and molecular epidemiology. This narrative review was based on the authors' original experience and current literature. We discussed about human leukocyte antigens (HLA) and killer-cell immunoglobulin-like receptors (KIR) and their disease associations. Bioinformatics and biostatistics help us to use this topic in evidence-based medicine. Immunogenetics is an important part of the molecular anthropology being a part of medical anthropology in turn. There were different notions of the integration of immunology and medical anthropology including environmental, ecological and cultural effects, historical and philosophical approaches, immunological biomarkers in different patients, and immunogenetics. Such studies can be used in pharmacogenomics and personalized medicine especially for immunotherapy.

1. Introduction

Anthropology has dawned as a science in the British Association of Anthropology in 1878 through the attempts of Professor Huxley [1]. Anthropology had been defined at least from 1932 as "the study of the peoples of the simpler cultures in which attention is diverted from questions of the origin or form of institutions and directed to consideration of how they actually work and what is their meaning and significance in a given environment" in the word of Professor Radcliffe Brown's presidential address to the Anthropological Section of the British Association at its meeting reported by Mr. Driberg's [2].

Medical anthropology is a multi-disciplinary approach to the medical sciences and humanities which mainly consists of the history of medicine [3], the anatomical characteristics of individuals [4], physical anthropology [5,6], molecular variations in the immune systems of individuals [7,8], pharmacogenomics and personalized medicine [9,10], ecological and spatial studies on disease prevalence and associations [11], designing regional guidelines for management of disease [12], and so on in different ethnicities as well as the cultural, ethical and religious beliefs of the ethnicities through the lens of cognitive neuroscience called as neuroaesthetics [13].

Immunology is a basic medical science dealing with anthropology, because both of these sciences are involved in recognition of self and non-self [14]. So medical sciences are not alien to anthropology and offer an ethnographic international classification of ethnicities based on the immunological molecules [15] such as human leukocyte antigens (HLA) [7,8], Killer-cell Immunoglobulin-like Receptors (KIR) [7] and a variety of cluster of differentiation (CD) markers [15]. Other than immunologists, the mentioned biomarkers have attracted the viewpoints of developmental biologists because of a high level of genetic variations used in archaeology, ontology and paleopathology [16]. Thus the integration between immunology and anthropology as an example of integration between the medical sciences and humanities is a strategic way which enables us to create a biological information bank from different ethnicities in order to reach the aims mentioned in the present review such as bone marrow transplantation and finding the identity of persons not grown with their real parents [7,8], solid organ transplantation in different ethnicities [17], as well as infertility prediction

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Table 1
Founded papers in WOS.

Search in WOS core collection	Results	Time range of the results
TITLE: ("medical anthropology" AND immunology)	No result	–
TITLE: (anthropology AND immunology)	[22–24]	1990–2012
TOPIC: ("medical anthropology" AND immunology)	[14]	2012
TOPIC: (anthropology AND immunology)	[7,14,15,25–37]	1990–2017
TITLE: (anthropology AND HLA)	[38–43]	1993–2015
TOPIC: (anthropology AND HLA)	93 results	1991–2017
TITLE: (anthropology AND KIR)	[40,44]	2009
TOPIC: (anthropology AND KIR)	[40,44–48]	2006–2015
TITLE: (anthropology AND immunogenetics)	No result	–
TOPIC: (anthropology AND immunogenetics)	[25,37,45,47–56]	2001–2016
Total with exclusion of duplications + other than WOS papers	[7,14,15,22–48] (N = 30)	1990–2017

and treatment [18,19].

2. Objectives

Omics and genome wide association studies (GWAS) are the future of medicine. In GWAS single nucleotide polymorphisms (SNP) as well as uncommon and emerging mutations are investigated [20]. Medical anthropology is the theme of such studies. The results of such studies will be used in pharmacogenomics and personalized medicine [21]. According to this rationale, we performed this review paper to introduce the role of immunology in medical anthropology.

3. Evidence acquisition

The present work is a narrative review based on the authors' experience and current literature. The search strategy was using key words and phrases such as "anthropology AND immunology", "anthropology AND HLA" and so forth.

Through searching in web of science core collection (WOS) relevant papers were founded in the time period of 1983-2017. The search was performed on 1 April 2017 (Table 1). In order to find older papers we used PubMed, Google and Google Scholar.

As the search result, we found few exactly related records that most of them had been published in *Nature* and other nature publishing group journals. The oldest one was for 1901 entitled "anthropology" published in *Scientific American* [1] and the latest one is an article published in *Nature* in 2016 about anthropology [57]. However, the oldest well-related article was for 1949 under the title of "Systematics, Evolution, and Anthropology in the Light of Immunology" published in *The Quarterly Review of Biology* [22]. The situation and impact of the term "medical anthropology" in global scientific production is not acceptable; because this term has been repeated in titles of just 263 WOS papers at the time of our search (Table 2).

4. Narrative review of the literature

Sanchez-Mazas et al. introduced immunogenetics as a tool in anthropological studies. They accounted ABO blood grouping system (in 1900) as the history of role of immunology in anthropology [48]. William Clouser Boyd was a well-known American biochemist (1903–1984) [58]. In 1949 he published a paper under the title of "Systematics, Evolution, and Anthropology in the Light of Immunology". In that paper he believed that taxonomy is associated with cellular antigens like blood group related molecules [22]. Then in 1958, he and Isaac Asimov wrote a book entitled "races and people". This book consisted of Mendelian genetics, inheritance patterns, basics of blood transfusion, language families, and a lot of things known today [59]! Based on search in PubMed, the term "medical anthropology" was firstly used in 1952 by Gomez [60]. In 1962 Roney as another pioneers of this term believed that medical anthropology play its role through 1) giving insights to the participants of medical fields, 2) altering behavior in order to control disease, and 3) predicting the direction and rate of culture change. As well history of medicine had been accounted as another part of medical anthropology [61].

In 1990 Emily Martin in a paper entitled "Toward anthropology of immunology" compared immune system with a nation state. In other words body cells were like citizens of a city, and since anthropology was a study on individuals of a region, immunology would be an anthropological study on immune cells. The key concept of this similarity from her viewpoint was "self and non-self" distinguish [24].

In 1993 human genome project was reminded as an example of using genetics and immunology in medical anthropology. It had been suggested that technologies such as polymerase chain reaction (PCR) could be used in bio-politics [28]. Parham as another pioneer of this topic published a paper entitled "HLA, anthropology and transplantation". He believed that HLA typing using PCR with sequence specific primers (PCR-SSP) was more accurate than serology [41].

In 1996 Petrov and Ulyankina wrote an essay about E. Metchnikoff (1845–1916) a Russian biologist and winner of Nobel Prize in 1908. His fame was for discovery of macrophages (1882). He had published an essay about anthropology and proposed the theory of orthobiosis [34]. Orthobiosis is a multidisciplinary approach to lifestyle and well-being [62,63].

Molecular study on burnt bone fragments had been an approach to immunological anthropology. In 1999 Cattaneo et al. published a study because they believed that finding out human or non-human origin of such bones are not possible through morphology and gross anatomy. They were trying to extract human albumin and human mitochondrial DNA from powder of the bones burnt at 800–1200 °C [26].

In 2000 Sharp had an anthropological approach to body parts commodification and then discussed about its genetics and immunology [35]. In another paper published in 2000, Sumara mentioned that complexity theory can be used in ecology, psychology, neurology, anthropology and immunology [36].

In 2001 Antonio Arnaiz-Villena as a pioneer of HLA typing, published a paper about association of languages and *HLA* genetics. He and

Table 2
The impact of medical anthropology in global science production.

Search in WOS core collection	Results	Time range of the results	*h* index
TOPIC: ("medical anthropology")	770 results	1983–2017	44
TITLE: ("medical anthropology")	263 results	1983–2017	20

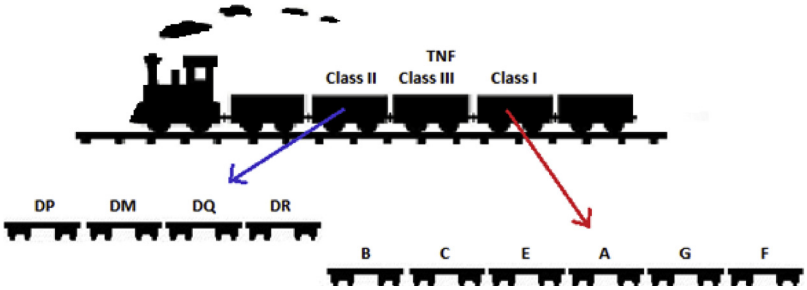

Fig. 1. Choromosome 6P21.3, *HLA* loci. Tumor necrosis factor (*TNF*) is another polymorphic gene in this loci. Each of these genes can have allelic polymorphisms in turn. Centromeric end is at the left (short arm of the chromosome) [originally designed].

his coworkers used HLA profile (*-A*, *-B*, *-DRB1* and *-DQB1*) in order to design neighbor-joining tree. Evaluation of HLA class I alleles (*-A* and *-B*) were low resolution and HLA class II alleles (*-DRB1* and *-DQB1*) were high resolution [25].

In 2003 McDade believed that mechanisms such as development, plasticity and adaptation were central concepts of biological anthropology; on the other hand such concepts were associated with immunology. As well he had an ecological approach to immunology. For example ecology of nutrition, ecology external diseases and molecular ecology of microorganisms affect immune system of human [31].

In 2004 Helmberg et al. in a conference paper mentioned HLA typing data as an example of medical anthropology [39].

In 2006 Frassati et al. mentioned that KIR typing both at content level (loci) and at allelic level (locus) can be used in genetic association and anthropological studies [46].

In 2007 on the occasion of investigation of *HLA* gene diversity in two ethnic groups of southeast of Iran, it was announced that HLA typing studies can be used both in anthropology and clinical practice [30].

In 2009 Hollenbach and Middleton reported an abstract from 15th international histocompatibility workshop about anthropology of KIR [40,44]. Buhler et al. performed a study on polymorphism of *KIR2DL4* locus [*KIR* genes have loci and each locus can be polymorphic in turn]. They believed that *KIR2DL4* polymorphism can be a good candidate for anthropology [45].

In 2011 milk synthesis in primates was investigated from the viewpoint of nutrition, biology and anthropology. Although this paper was not directly about immunology and medical anthropology, but on the occasion of immune-factors existence in milk, the immunological and anthropological approaches were discussed inside each other [29]. Thorsby mentioned that HLA can be used in pharmacogenomics of vaccination, transplantation and autoimmune diseases. The author mentioned that anthropological role of HLA had been shown in the 5th international histocompatibility workshop (1970–1972). High resolution genomic typing resulted in advances in this field during recent years [37].

In 2012 Moulin added a comment on the paper of Napier entitled "NONSELF HELP: How immunology might reframe the enlightenment" [14]. In this note, she suggested "selfhood" instead of "self / non-self" paradigm [32]. Parker et al. design a review on the role of modern immunology in pandemics of non-infectious diseases in this industrial world. According to biological, anthropological and ecological approaches, they account this pandemics as a consequence of "loss of human biome" especially helminthes depletion and vitamin D deficiency [33].

In 2015 Rey et al. preformed an HLA typing study in Turkmen population of northwest of Iran bordering Turkmenistan. The theme of the article was based on transplantation, pharmacogenomics and anthropology. This work was reported in 2 congresses as well [38,42,43]. Gonzalez-Galarza et al. reported 2015 update allele frequency net database (AFND) [AFND is available from http://www.allelefrequencies.net]. AFND had been established in 2003. It can be used in pharmacogenomics and anthropology; e.g. in adverse drug reaction database [47].

In 2016 Gilbert and Tauber had a philosophical approach to immunology. They believed that historically, immunology had been previously affiliated with biology of individuals, and nowadays has become a science concerned with the biology of communities. As well they believed that the balance of immune rejection and immune tolerance plays an important role in interaction of individuals with other organisms and their surrounding ecosystem [27].

In the most recent article having both keywords of immunology and medical anthropology AFRIBIOTA project was discussed. This project is a large study in Africa about pediatric environmental enteropathy. Their anthropological approach was related to environmental factors. The authors believed that gastrointestinal diseases are associated with imbalance of gut immune system and normal microbial flora [64].

5. HLA and medical anthropology

In mankind, *HLA* gene is located on chromosome 6p21.3 with the length of 3600 kb and has 239 antigenic loci that approximately 40% of them are immunogenic [65]. There are 2 classes of HLA. The class I in turn falls in two categories of classical (HLA-A, -B and -C) expressed in all the nuclear cells of body and non-classical (HLA-G, E and F) expressed on the surface of specific cells like trophoblasts (Fig. 1) [19]. The main role of HLA class I is acting as the identifying cards of self-cells causing immune-tolerance. In order to do that, some of these biological molecules perform the function of identifying card for nuclear cells of body to be proposed for the KIRs expressed on the surface of natural killer (NK) cells (CD56CD16). Different polymorphic receptor-ligand interactions in different individuals and ethnicities result in different useful, harmless and harmful outcomes. Some other HLA class I molecules (A and B) play their role through interaction with cytotoxic T lymphocytes (CTL). Both NK cells and CTL monitor nuclear cells of body dynamically [66].

Since some alleles of *HLA* are commonplace in specific ethnicities, the alleles are used by anthropologists as biomarkers to detect genetic interactions in that populations. Clinically, being acquainted with HLA distribution is necessary for forensic medicine, transplantation and bone marrow donating centers [67,68], and studies of HLA related diseases (whether infectious agents [69–72] or autoimmune diseases [73]).

HLA is inherited as haplotype form (Fig. 1). All genes of this haplotype are necessary for survival. Each gene has allelic polymorphism in turn (Fig. 2). Individual variations are in such alleles (not in presence or absence of the very genes unlike *KIR*).

There are different research and clinical methods for evaluation of *HLA* genotypes and HLA typing including serology, PCR-SSP, and sequencing methods including next generation sequencing (NGS), Sanger and high resolution melting (HRM). Each method has pros and cons. Serology is the less accurate method, however it can show the current clinical phenotype of patients. For example in ankylosing spondylitis HLA-B27 seropositivity is investigated, however genetic investigation

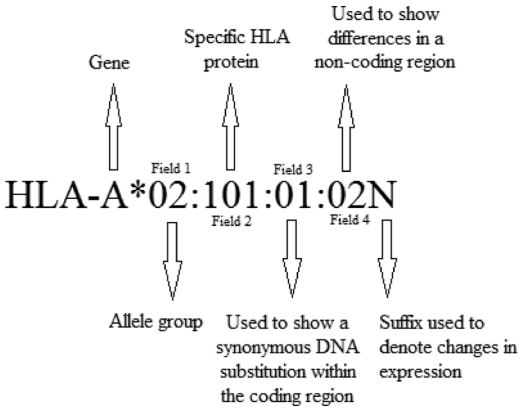

Fig. 2. Nomenclature of *HLA* allelic polymorphisms [Adapted from [47] and originally redesigned].

may result in detection of a genetic positivity not having serological manifestation (Of course many researchers consider this feature of genetic evaluation as an advantage for prediction of the disease [74]). Conventional PCR with restriction enzyme is not useful, because *HLA* genes are highly polymorphic. PCR-SSP is accurate enough, however it is moneys-taking and times-consuming for complete HLA typing due to a large number of specific primers. Among sequencing methods NGS and Sanger can be used for complete HLA typing as well as using for GWAS, however for detection of some previously selected variants (such as *HLA-B13:01* and *-B31:01* in pharmacogenomics of adverse drug reaction [75,76]) HRM is an economical, rapid and simple technic using NanoDrop spectrophotometer and real-time PCR [77].

6. KIR and medical anthropology

KIRs are receptors of NK cells. These cells are a subset of lymphoid progenitor comprising about 10–15% of peripheral blood total lymphocytes [78]. NK cells mainly perform their function in innate immunity as well as adaptive immune responses by killing their target cells and production of different cytokines [79]. Among NK cell subsets, there are mainly $CD16^{+}CD56^{dim}$ and $CD16^{-}CD56^{bright}$ NK cells; the dim form has further cytotoxic capacity called as "cytotoxic NK cell", and the bright form performs its function in secretion of inflammatory cytokines called as "immune-regulatory NK cell". Both of them express KIR, but the dim form express more. Bright NK cells are also called as uterine or decidual NK cells [18,19,78].

KIRs are one of the markers on NK cell surface proteome, and similar to HLAs, they are inherited as haplotype form [79]. *KIR* gene cluster is located on chromosome 19q13.4 within the leukocyte receptor complex (LRC). This cluster has a centromeric and a telomeric region [80]. *KIR* gene cluster has 14 genes and 2 pseudo-genes in which 8 of them encode inhibitory proteins and 6 of them encode activating proteins [18]. The encoded proteins expressed on surface of NK cells interact with the HLA class I (especially -C, -G, and Bw) existing on surface of the other nucleated cells of human. In inhibitory interactions, the result is immune tolerance if the target cells be healthy, and otherwise they result is cytotoxic activity of NK cells against the cancerous or viral infected target cells (called as the "missing-self hypothesis" which is due to down regulation HLA molecule expression). Unlike to HLA, having all of these genes are not necessary for survival, and every individual can have some of them [81]. Considering that *HLA* is the most polymorphic loci in human genome and as well KIR has different types of alleles for each gene, different interactions of KIR-HLA can be associated with different diseases (susceptibility or protection) like autoimmune diseases and cancers among different ethnicities and populations; this, is called "disease association" in medical anthropology [7].

Such associations are not necessarily cause-effect associations. For example, *KIR2DS4* is an activating gene existing also in inhibitory haplotypes. Hence its associations with some variables may be due to the accompanied inhibitory genes. From the viewpoint of biostatistics, it can be a kind of alpha error. In addition, none of these genes are not specific for any specific disease. From the view point of philosophy of medicine, although such genes may have high amounts of odds ratios and relative risks with some diseases, but they have not necessarily enough amounts of absolute risk or positive predictive values.

Based on the number of extracellular immunoglobulin domains, KIRs are categorized in two groups (2D and 3D). The two functional types of KIR, i.e. inhibitory and activating, are distinguished depending on the length of their intracellular domains. Inhibitory KIRs (iKIRs) are characterized by their long intra-cytoplasmic tail (distinguished by an 'L' in their name) and presence of at least one immunoreceptor tyrosine-based inhibitory motif (ITIM). Activating KIRs (aKIR) are characterized by their short intra-cytoplasmic tail (distinguished by an 'S' in their name) and absence of ITIM. ITIM is a protein triggers inhibitory cascade in cytoplasm [82]. iKIRs are 2DL1-2DL5 and 3DL1-3, and aKIRs are 2DS1-2DS5 and 3DS1. The pseudogenes are of *KIR2DP1* and *KIR3DP1* that do not encode any functional KIR molecule. *KIR2DL4* exists in all individuals with both inhibitory and activating functions, but more of inhibitory. The genes *3DL3* and *3DL2* are always located at centromeric and telomeric tails of this cluster respectively. These genes are called frame work genes (Fig. 3) [81].

As we mentioned, although KIRs are inherited as haplotype forms, but unlike HLA, having all of them is not necessary for survival. There are four main groups of *KIR* haplotypes which are defined based on gene content termed as haplotypes *A* (centromeric *A* and telomeric *A*) and *B* (centromeric *B* and telomeric *B*) (Fig. 3). Uncommon haplotypes are named with *X*. Patients with *AA* genotypes have uniform in gene content which is composed of five inhibitory genes (*KIR2DL1*, *2DL3*, *3DL1*, *3DL2* and *3DL3*), one activating gene (*KIR2DS4*), and the *KIR2DL4* which may have both inhibitory and activating capacity. Interestingly, many *A* haplotypes possess null variants of both *KIR2DS4* and *KIR2DL4* that are not expressed on the cell surface. Such individuals may have not any functional *aKIR* gene. The *B* haplotypes contain variable numbers of both activating and inhibitory genes and are the primary contributors to the extraordinary differences in *KIR* gene profiles observed in distinct ethnicities across the world [83].

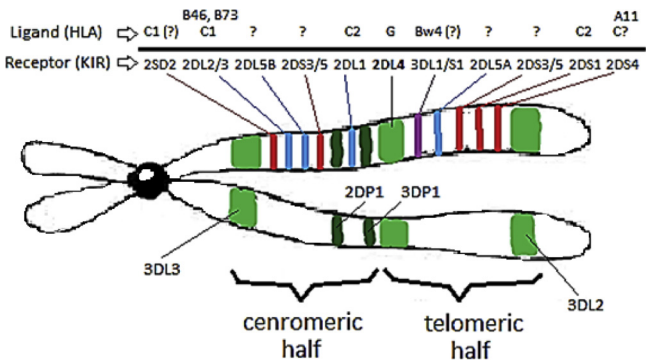

Fig. 3. Chromosome 19q23, *KIR* loci. The green genes are present in all people (except 2DP1); therefore they have not anthropological value at gene level (however 2DL4 is polymorphic at allelic level). Blue genes are inhibitory and red genes are activating. In the purple locus, 3DL1 is inhibitory and 3DS1 is activating. The ligand of 2DS2 is unknown, but seems to be HLA-C1 (or C1 associated) [84,85]. The ligand of 3DL1 is HLA-Bw4, but the ligand of 3DS1 in unknown (in some papers HLA-Bw4 is considered) [85]. The sizes are not real [originally designed]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

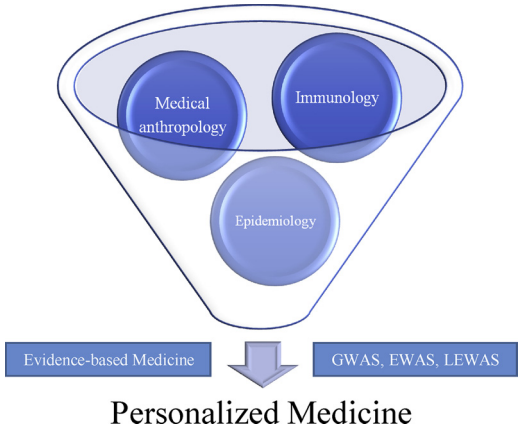

Fig. 4. Immunology, medical anthropology and epidemiology are integrated and imported to GWAS, EWAS and LEWAS. Using evidence-based medicine, the results will be used in personalized medicine [originally designed].

7. Enviromics in molecular anthropology

Eviromics is a study of the envirome and exposome which are a set of different internal and external factors affecting genetic and immune system. Immune cells can be affected by many of such factors including food and nutrition. Like GWAS, there are studies known as longitudinal epigenome-wide, evirome-wide and exposome-wide association studies (LEWAS) [86]. Such interdisciplinary works provide the needed materials for personalized medicine. Global changes and human-associated microbes affect early life development of immune system. Adulthood health is correlated with the childhood health affected by early metabolic programming and early immune programming. Food and nutrition, antibiotics, vaccination, sunlight exposure and vitamin D status (as described by Parker et al. [33]) and so on influence on early metabolic and immune programming. Primary microbial exposure results in development of pattern recognition receptors (like toll-like receptors) and T helper cells. All of these together show the role of anthropology in development of immune system [87]. Environment wide association studies (EWAS) are also notable in human health. Association of food web with human health and children development is discussed in this field [88]. The final phenotype of each individual is made up of all of the factors investigated in GWAS, EWAS and LEWAS [89,90].

8. Molecular pathological epidemiology

Molecular pathological epidemiology (MPE) is a term used to integrate epidemiology and health sciences with immunopathological basis of diseases. Such studies are also named immunology-MPE research. Other than pure genetic basis of disease, nutrition, diet and environmental factors influence genomics and epigenomics of immune cells. In MPE research biostatistics and bioinformatics are used in immunology and pathology. The results of such researches can be used in precision (personalized) medicine. In immunology-MPE model of research immunological biomarkers (including receptors, ligands and secretory factors) such as programmed cell death 1 (PD1) and its ligand (PD-L1), CD markers, KIR and HLA subtypes, interleukins and other cytokines are investigated. The results will be used in immunotherapy and targeted therapy [91,92].

9. Evidence-based medicine in molecular anthropology

It needs a way to link molecular anthropology to clinical practice. Bioinformatics and biostatistics help us to reach this aim as the tools of evidence-based medicine (EBM). From the viewpoint of philosophy of medicine, basic medical sciences (based on causation relationship) and clinical medical sciences and practice (based on EBM), both help each other [93–97]. Molecular anthropology is an example of this integration [98,99]. A controversy is that molecular anthropology is used in personalized medicine, but on the other hand EBM is based on epidemiology (not a single person). The question existed is that how personalized medicine can be evidence-based. The answer is that the pieces of evidence obtained from epidemiological studies are subjected to be used in per case decisions. This controversy is currently resolved (Fig. 4) [92].

The way of using medical anthropology in clinical practice, starts from international and regional bioinformatics databases. The raw data can be used for disease association and pharmacogenomics study. Such observational studies are performed according to the guideline strengthening the reporting of observational studies in epidemiology (STROBE) (available from https://www.strobe-statement.org). In genetic association studies, other than STROBE, another guideline entitled strengthening of genetic association studies (STREGA) should be regarded [100]. If in a genetic association study, the gene is *HLA* or *KIR* (immunogenetic studies), another guideline should also be regarded entitled strengthening the reporting of immunogenetic studies (STREIS) [101]. These guidelines help researchers to unify their studies as a check list; because these studies are supposed to be used in meta-analyses. At the next step, the results of observational studies as raw pieces of evidence can be used in interventional studies. Finally the results of clinical trials (or meta-analyses of clinical trials) can be used in clinical practice.

10. Conclusion

Immunology is an important part of the molecular anthropology being a part of medical anthropology in turn. There were different notions of the integration of immunology and medical anthropology including environmental, ecological and cultural effects, historical and philosophical approaches, the molecular fingerprints of immune system, immunological biomarkers in different patients, and immunogenetics. Such studies can be used in pharmacogenomics and personalized medicine especially for immunotherapy.

Conflicts of interest

We declare that there is no personal, commercial, cultural and governmental conflicts of interest. There may be potential conflict of interest for the named journals, websites and persons; however we deny any relationship.

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