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Review Article **Open Access**

Tuberculosis and Genetics of Sub-Saharan Africa Human Population

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Abstract

Sub-Saharan Africa has continued leading in the prevalence and incidence of tuberculosis (TB). The epidemiological triad of infectious diseases includes a susceptible host, pathogen/agent, and environment. Sub-Saharan Africa has the highest prevalence and incidence of TB. It is imperative that all aspects of vertices of the infectious disease triad are analysed to better understand why this is so. Many studies have been done to address this intriguing reality though these have mainly addressed pathogen and environmental components of the triad regarding TB infection. The host factors have not been exhaustively studied in this high TB burden region probably due to lack of the necessary expertise and technologies among African scholars yet three components of the triad interact to determine the disease outcome. Amongst host factors, genetic structure of the host greatly affects progression of disease following exposure. Studies have revealed that Africa is the most genetically diverse region of the world in addition to being the origin of modern humans therefore it would be important to study genetics of sub-Saharan African population in relation to TB. This review seeks to analyze contribution of host genetics to the observed variation in susceptibility to TB infection in this region.

Keywords: Pulmonary tuberculosis; Infectious diseases; Triad; Genetic

Abbreviations: TB: Tuberculosis, PTB: Pulmonary Tuberculosis, PMN: Polymorphonuclear Cells, IFN-γ: Interferon Gamma; IL: Interleukin

Introduction

Tuberculosis (TB) continues to devastate sub-Saharan Africa populations, a region with a total of 27 countries. In 2012, African region had approximately one quarter of the world's TB cases, and the highest rates of cases and deaths relative to population (255 incident cases per 100,000 on average, more than double the global average of 122). However, sub-Saharan Africa carried the greatest proportion of new cases per population with over 255 cases per 100,000 population [1]. Africa is thought to be the ancestral homeland of all modern humans, and is the more recent homeland of millions of individuals whose ancestors were brought to Europe and to the Americas as slaves [2]. There is much to learn from the genetics of sub-Saharan African populations regarding human origins, evolution as well as origin and nature of complex human diseases. At present, we have little understanding of the genetic structure of sub-Saharan populations and the genetic basis of complex disease in African populations because very few genetic studies have been conducted in African ethnic groups [2]. Research activity has traditionally been biased towards the study of non-African populations, and our knowledge of even the most fundamental information about the genetic basis of disease in Africa is quite limited [2].

Iam compelled to propose that modern humans who migrated away from sub-Saharan Africa encountered new environment and exotic pathogens in areas where they settled. We now know that infectious diseases have and will continue shaping the course of evolution of human species .In this antibiotic era, we should accept that drugs will equally act as a strong selective pressure on the human genome therefore the modern humans are under two important selective forces. The hypothesis whereby infectious diseases have been acting as a powerful selective pressure was formulated long ago, but it was not until the availability of large-scale genetic data and the development of novel methods to study molecular evolution that we could assess how pervasively infectious agents have shaped human genetic diversity [3]. Disease outcome is multifactorial process, requiring interplay of host-environment-microbial factors ultimately determine disease susceptibility. Genetic structures of the exposed human populations will determine the susceptibility patterns that are always observed in the herd population. Recent genome- wide analysis indicate that among the diverse environmental factors that most likely acted as selective pressures during the evolution of human species (climate, diet regimes, and infections), pathogen load had the strongest influence on the shaping of human genetic variability [4]. Possibly the indigenous pathogens in sub-Saharan Africa co-evolved with their hosts creating unique genetic profiles in these human populations. I propose that a form of Newton's third law of motion happens during an interaction between host and pathogen; action and reaction is equal and opposite.

This infers that there is a selective pressure exerted by these pathogens onto selected host genes and in response specific pathogen genes received similar pressure from the host driving host/pathogen diversity observed as unique genetic profiles in both host and pathogen accounting for co-evolution. I further propose that these unique genetic profiles created over time affect vaccine efficacy and of late we know that treatment outcome is also affected by the host genetic structures therefore these genetic variation will in future undermine use of universal vaccines and drugs. The unique genetic profiles created in these human populations can act as risk genetic factors for emerging pathogens.

Human host genetic diversity and infectious diseases

The high levels of genetic diversity in African populations and their

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demographic history make these populations particularly informative for the fine mapping of complex genetic diseases [5] as well as known complex infectious and emerging diseases. Studies using human mitochondrial DNA and nuclear DNA markers consistently indicate that Africa is the most genetically diverse region of the world [6]. Historically, human population genetic studies have relied on one or two African populations as being representative of African diversity, but recent studies show extensive genetic variation among even geographically close African populations, which indicates that there is not a single 'representative' African population [3]. TB was introduced in Africa by probably early settlers, sailors, colonialists, missionaries and traders. The environment in this region plus the TB naïve host genetic structures of the region may have account for the rapid spread of the disease. Studies now indicate that different strains of TB have geographical preferences.

The immunological responses to MTB are due to the interaction between the human host immune system (host genetics), bacterial and environmental factors [7]. Genetics as well as acquired defects in host immune response pathways greatly increase the risk of progressive disease [8]. Furthermore, host genetics is inherent and relatively constant for an individual but acquired defects may arise from mainly the environment and antibiotic use. Results from genome wide linkage studies suggest that TB disease susceptibility is highly likely to be polygenic, with contributions from many minor loci [9] and a large number of TB susceptibility markers have been identified from candidate gene studies as 'disease-causing' genes which include TIRAP, HLA DQB1, VDR, IL-12β, IL12Rβ1, IFN-γ, SLC11A1 and MCP-1. However, to date the greatest evidence to support an underlying genetic basis for TB has come from the discovery of single gene defects

Gene Name	Symbol	Disease Type	Result	Population	Reference
Arachidonate 5-lipoxygenase	ALOX5	PTB	+	Ghana	[32]
Butyrophilin-like 2 (MHC class II associated)	BTNL2	PTB	−	South Africa (Mixed)	[33]
Cathepsin Z	CTSZ	PTB	+	The Gambia, Guinea-Bissau, Republic of Guinea, South Africa (Cape Town and Malawi)	[34]
CD40 molecule, TNF receptor superfamily member 5	CD40	PTB	−	The Gambia, Guinea-Bissau, Republic of Guinea	[35]
CD209 molecule (DC-SIGN)	CD209	PTB	+	The Gambia, Guinea-Bissau, Republic of Guinea, South Africa (Cape Town and Malawi)	[36-38]
			−	South Africa (Cape Town), Tunisia†	[39,40]
Chemokine (C-C motif) ligand 2 (Monocyte chemoattractant protein-1, MCP1)	CCL2	PTB	+	Ghana, Zambia	[41,42]
			−	South Africa (Cape Town)	[43]
Chemokine (C-C motif) ligand 3	CCL3	PTB	−	South Africa (Malawi)	[44]
Chromosome regions: 1p31 (15 Mb from IL12RB2), 21q22 (containing IFNGR2); 2p22-2p16, 8p12-8q11, 8q21-8q23, 9p21-9q12, 11q14-11q23, 19p13-19q12, 22p13-22q11 (no candidate genes)		TNF levels	+	Uganda	[45]
Chromosome regions: 2p13-2q11 (containing the IL1 complex of genes), 3q23 (containing IL12A), 6p21 (containing MHC complex and TNF); 1p21-1q24, 8p12-8q11, 10q24-10q24, 11p15, 22p13-22q11 (no candidate genes)		PTB	+	Uganda	[45]
Chromosome regions: 7p22-7p21 (containing IL6), 20q13 (containing MC3R and CTSZ)		PTB	(+)	Uganda	[45]
Chromosome regions: 2q27 (17 Mb from SLC11A1); 2q14, 7q35-7q36, 8p22, 8p12-8q11, 14p13-14q11, 14q21-14q24 (no candidate genes)		Resistance to infection	+	Uganda	[45]
Chromosome regions: 2q21-2q24, 5p13-5q22 (no candidate genes)		Resistance to infection	(+)	Uganda	[45]
Chromosome region 8q12-q13 (gene not found)		PTB	(+)	Morocco†	[46]
Chromosome 15q microsatellite markers		PTB	(+)	The Gambia, South Africa	[47]
Chromosome Xq microsatellite markers		PTB	(+)	The Gambia, South Africa	[47]
Complement component (3b/4b) receptor 1 (Knops blood group)	CR1	PTB	+	South Africa (Malawi)	[44]
C-type lectin domain family 4, member M (LSIGN)	CLEC4M	PTB	−	South Africa (Cape Town)	[39]
Cytotoxic T-lymphocyte-associated protein 4	CTLA4	PTB	+	Ghana	[48]
Fucosyltransferase 2	FUT2	PTB	−	The Gambia	[49]
Group-specific component (vitamin D binding protein)	GC (DBP)	PTB	−	South Africa (Xhosa, Cape Coloured)	[50]
Intercellular adhesion molecule 1 (CD54)	ICAM1	PTB	−	South Africa (Malawi)	[44]
Interferon, gamma	IFNG	PTB, TB meningitis	+	The Gambia, Guinea-Bissau, Republic of Guinea, South Africa (Mixed)	[51,52]
		PTB	−	South Africa (Malawi)	[44]

Interferon gamma receptor 1	IFNGR1	PTB, TNF levels	+	The Gambia, Guinea-Bissau, Republic of Guinea, Uganda	[51,53]
		PTB	−	The Gambia	[54]
Interferon gamma receptor 2	IFNGR2	PTB	−	The Gambia, Guinea-Bissau, Republic of Guinea	[51]
Interleukin 1, alpha	IL1A	PTB	+	The Gambia	[49]
Interleukin 1, beta	IL1B	PTB	+	The Gambia	[55]
			−	The Gambia	[49]
Interleukin 1 receptor antagonist	IL1RN	PTB	+	The Gambia	[49]
			−	The Gambia	[55]
Interleukin 8	IL8	PTB	−	The Gambia	[12]
Interleukin 10	IL10	PTB, IL10 levels, TNF levels	+	Ghana, South Africa (Malawi), Uganda	[44,53,56]
		PTB	−	The Gambia, Ghana	[49,56]
Interleukin 12 receptor, beta-1	IL12RB1	PTB	+	Morocco†	[57]
Lymphotoxin alpha	LTA	PTB	−	South Africa (Malawi)	[44]
Major histocompatibility complex	HLA	PTB	+	South Africa (Venda)	[58]
Mannose-binding lectin (protein C) 2, soluble (opsonic defect)	MBL2	PTB	−	The Gambia, South Africa (Malawi), Tanzania	[44,59,60]
Melanocortin 3 receptor	MC3R	PTB	+	The Gambia, Guinea-Bissau, Republic of Guinea, South Africa (Cape Town and Malawi)	[34]
Nitric oxide synthase 2, inducible	NOS2	PTB	+	South Africa (Cape Town)	[43]
Nucleotide-binding oligomerization domain containing 2	NOD2	PTB	−	South Africa (Cape Town)	[61]
Pentraxin-related gene	PTX3	PTB	+	Guinea-Bissau	[37]
Protein tyrosine phosphathase, non-receptor type 22 (lymphoid)	PTPN22	PTB	+	Morocco†	[62]
Purinergic receptor P2X, ligand-gated ion channel, 7	P2RX7	PTB	+	The Gambia	[63]
Solute carrier family 11, member 1	SLC11A1	Clinical TB, IL10 production, PTB, TB meningitis	+	The Gambia, Republic of Guinea, South Africa (Cape Town and Malawi), Tanzania	[44,60,64-67]
		PTB	−	The Gambia, Morocco†	[68,69]
Solute carrier family 11, member 2	SLC11A2	PTB, TB meningitis	−	South Africa (Cape Town)	[67]
SP110 nuclear body protein	SP110	PTB	+	The Gambia, Guinea-Bissau, Republic of Guinea	[70]
			−	Ghana, South Africa	[71,72]
Surfactant, pulmonary-associated protein A1	SFTPA1	PTB	+	Ethiopia	[73]
Surfactant, pulmonary-associated protein A2	SFTPA2	PTB	+	Ethiopia	[73]
Toll-interleukin 1 receptor (TIR) domain containing adaptor protein	TIRAP	PTB, TB meningitis	+	Algeria†, The Gambia, Guinea-Bissau, Kenya, Republic of Guinea, South Africa (Mixed)	[74,75]
		PTB	−	Ghana	[76]
Toll-like receptor 2	TLR2	PTB, TNF levels	+	Tunisia†, Uganda	[53,77]
		PTB	−	Guinea-Bissau, South Africa (Malawi)	[37,44,53]
Toll-like receptor 4	TLR4	PTB, TNF levels	+	Uganda	[53]
		PTB, development of TB in HIV patients	−	The Gambia, Guinea-Bissau, South Africa (Malawi), Tanzania	[37,44,78,79]
Toll-like receptor 9	TLR9	PTB	−	Guinea-Bissau	[37]
Tumor necrosis factor	TNF	PTB	−	South Africa (Malawi)	[44]
Tumor necrosis factor receptor superfamily, member 1A	TNFRSF1A	PTB, TNF levels	+	Uganda	[53]
Tumor necrosis factor receptor superfamily, member 1B	TNFRSF1B	PTB, TNF levels	+	Ghana, South Africa, Uganda	[53,82]
Ubiquitin protein ligase E3A	UBE3A	PTB	+	The Gambia, Republic of Guinea, South Africa (KwaZulu-Natal)	[80]
Vitamin D (1,25- dihydroxyvitamin D3) receptor	VDR	PTB	+	The Gambia, Guinea-Bissau, Republic of Guinea, South Africa (Venda)	[18,19,37,58]
			−	South Africa (Cape Town and Malawi), Tanzania	[44,60,81]

+ indicates a genetic association or linkage was reported (p ≤ 0.05), (+) indicates a suggestive linkage was reported,

− indicates no genetic association was detected

† Country outside sub-Saharan Africa

Table 1: Genetic Associations with Tuberculosis in Africans

Source: http://chgr.mc.vanderbilt.edu/files/library/TB%20Table_December%202009.doc predisposing to disseminated and often lethal mycobacterial disease [10]. I can assert that the indigenous infections like malaria created unique genetic structures in these mixed ethnic populations which can be risk factors for exotic infectious diseases like tuberculosis, HIV/AIDS and other emerging diseases. A notion that exposure to indigenous pathogens/parasites in these areas shaped the genetic structures of these native human populations resulting in the observed inter-ethnic disparities in susceptibility to new infectious agents is undisputable.

Tuberculosis susceptibility genes in sub-Saharan Africa population

A lot of attention has been given to study the importance of the *Mycobacterium tuberculosis* (MTB) pathogen and the genetic constitution of the host largely ignored especially in the most affected regions like sub-Saharan Africa. It is estimated that only 10% of those who become infected with TB will ever develop clinical disease [11]. A growing body of evidence suggests that host genetics play a role in the predisposition to TB disease, in addition to pathogen, environmental, and socioeconomic factors [12,13]. Genetic factors contributing to TB susceptibility include variants of the human leukocyte antigen (HLA) class II complex [14-17] and the vitamin D receptor gene (*VDR*) [18-21] among others. HLA alleles are found to be associated with susceptibility and resistance to infectious diseases including HIV/AIDS, tuberculosis, and malaria that impose huge public health burdens in sub-Saharan Africa [22]. HLA studies have also yielded important insights into the role of pathogens in driving HLA polymorphism. For example, a study that analyzed 61 human populations across the world showed that populations that have a greater burden of pathogens show higher HLA diversity and those populations farther from Africa (geographic distance measured through land masses from Ethiopia) are characterized by lower HLA diversity [23].

Tuberculosis was a major selective force in the evolution of western European populations, whereas malaria served a similar role in Africa [24,25]. The subsequate introduction of TB in the malaria endemic by early Europeans may now account for the observed status of TB infections since these were TB naïve populations. Genes involved in protective immunity against diseases are always under greater selective pressure, showing greater variability than other genes [24,25]. For a disease to be a selective pressure in the evolution of a human population, the gene must have a significant impact for long periods of time, influencing morbidity and mortality before reproductive age [24,25]. Tuberculosis is currently a world-wide pathogen, and archeologic evidence indicates a great prehistoric prevalence for the disease in crowded cities of Europe and North Africa [26,27]. It appears, however, that this organism was once completely absent from several isolated areas [28,29], the largest of which was Africa [30]. Recent observations strongly suggest a significant role for genetic factors in innate resistance to infection by *Mycobacterium tuberculosis* [30]. This relation was discovered in a study of tuberculosis in Arkansas nursing homes and was supported by data from three outbreaks of tuberculosis in two prisons [30]. A person's resistance level was found to correlate with the region of his or her ancestry [30]. Ancestors of persons' in the more resistant group tended to derive from densely populated areas and cities rife with tuberculosis, whereas the ancestors of persons in the more susceptible group tended to derive from areas once free of tuberculosis [30] like the pre-colonial Africa (Table 1). With the completion of Human Genome Project and advances in genotyping technology, Genome-wide Association (GWA) Study has been one powerful tool for the study of genetic susceptibility in human complex diseases [31].

Conclusion

Infectious diseases remain an important component of human survival and continue to present a major threat for human populations world-over and consequently, shape their genetic diversity of. Tuberculosis remains very prevalent in sub-Saharan Africa despite the continued efforts to eradicate it through reforms in the environmental factors impelling its spread. In this antibiotic era, we continue to notice increase in the prevalence and incidences of TB especially in this region. The explanation to this intriguing conundrum may be masked in the host genetics.

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