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Review

Emphasis on imperativeness of genomics related research in the areas of infectious diseases

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Sequencing of the human and other species genomes has generated a downstream of sciences that have taken advantage of this knowledge to generate vital links between diseases and genetic variants. Sub-Saharan Africa and many developing countries form the major epicenters for Infectious diseases. Here, the role that genomics may hold in the area of infectious diseases research is emphasized in five blocks: phenotype evaluation studies, evolutionary trends' studies across microbial and host genomes, idiopathic association or host susceptibility studies to disease, therapeutics or vaccine research insights, as well as the development of novel molecular diagnostics.

Key words: Genomics, infectious diseases, HIV/AIDS, malaria, tuberculosis.

INTRODUCTION

The completion of the sequencing of the human (International Human Genome Sequencing Consortium, 2004) has led to the emergence of downstream sciences that have taken advantage of this sequence information such as comparative genomics, transcriptomics, proteo-mics and metabolomics (Drazen and Phimister, 2007) . Consequently, many scientific journals have embraced and embarked on the publication of genome wide related studies. These articles are a major fruit of the human ge-nome and HapMap projects, and they report variants of specific genes, or narrow genomic regions, that are asso-ciated with the presence or severity of specific clinical conditions (Drazen and Phimister, 2007).

Majority of the studies published so far have dwelt on the association between genomic variants and various non-infectious diseases most prevalent in the North (Yates et al., 2007; Rennert et al., 2007, Robson and Offit 2007, Mann 2007, Samani et al., 2007; Dunckley et al., 2007; Orrel 2007 and The International Multiple Sclerosis Genetics Consortium, 2007). These studies have for instance elucidated the association between genomic variants and diseases such as Age-Related Molecular Degeneration (Yates et al., 2007), Breast Cancer (Rennert et al., 2007, Robson and Offit 2007), Heart failure (Mann, 2007), Coronary artery diseases (Samani et al., 2007), Sporadic Amyotrophic Lateral Sclerosis (Dunckley et al., 2007 and Orrel 2007), multiple sclerosis (The International Multiple Sclerosis Genetics Consortium, 2007) and periodic limb movement (Stefansson et al., 2007). In as much as related studies published here as well as elsewhere on part of the infectious diseases (Wormser, 2007; Moalem and Prince, 2007) . Breman, (2001) and Carmichael et al. (1996) have elucidated the vital role that genomics may play in the management, control and surveillance of infectious diseases; that emphasis has to an extent remained unfocused. This perspective presents how genomics and its related research may benefit the area of infectious diseases as a specialty.

The rationale for genome related research in the area of infectious diseases

In the period when sequencing of the human genome was on- going human (International Human Genome Sequencing Consortium, 2004), related sequencing of seve-ral microbial genomes preceded, paralleled or followed (National Centre for Biotechnology Information, 2007; HIV Sequence database, 2007; Cole et al., 1998; Hoff-

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man et al., 1997; Gardner et al., 1998; Bowman et al., 1999). As of today, several microbial genomes have thus been fully sequenced (National Centre for Biotechnology Information, 2007; Carrington et al 1999), inclusive of the pathogens responsible for the causation of the world's 3 leading infectious causes of morbidity and mortality: the Human Immunodeficiency virus (HIV) (HIV Sequence database, 2007 Casanova et al., 1991), Tubercle bacillus Mycobacterium (MTB) (Cole et al., 1998; Cease and Berzofsky, 1994) and plasmodium (Hoffman et al., 1997; Gardner et al., 1998; Bowman et al., 1999; Chen et al., 2000; Chun et al., 1997; Clerici et al., 1994). Approxima-tely 38.6 million [33.4 - 46.0 million] people worldwide were living with HIV by the end of 2005. An estimated 4.1 million [3.4 - 6.2] became newly infected, and 2.8 million [2.4 - 3.3 million] lost their lives to AIDS (UNAIDS 2006; Cohen, 1997). The Human Immunodeficiency virus (HIV) has posed one of the most demanding and yet stiffest challenge in the history of infectious disease vaccine research, mainly because although HIV transmission is in theory largely preventable, in practice, without the deve-lopment of an effective vaccine, HIV will continue to infect millions throughout the world (Johnson and Kalams, 1998; Graham and Wright, 1995; Cease and Berzofsky, 1994; Haynes, 1996; Cole et al., 1998; Cowman, 2001; Daniel et al.,1998; Dean et al., 1996). On the other hand, the disease tuberculosis (TB) has similarly still posed a great challenge to global human health, with about a third of the world's population, 2 billion carrying the TB bac-teria, tubercle bacillus, and 8 - 10 million catching TB dis-ease and 2 million dying from it annually (Snider, 1994; Desrosiers, 1994). The tubercle bacillus belongs to the genus Mycobacterium, which comprises a number of Gram -positive, acid-fast, rod-shaped aerobic bacteria and is the only member of the family *Mycobacteriaceae* of the order *Actinomycetales*. Despite the availability of effective short-course chemotherapy (DOTS) and the Bacille Calmette- Guérin (BCG) vaccine, the tubercle bacillus continues to claim more lives than any other single infec-tious agent. Diagnosis is also made cumbersome by the slow growth and dormancy of the bacillus. The combina-tion of genomics and bioinformatics has the potential to generate the information and knowledge that will enable the conception and development of new therapies and interventions needed to treat this airborne disease and to elucidate the unusual biology of its aetiological agent (Wheeler and Ratledge, 1994; Dorak et al., 2004). Apart from TB and HIV, approximately 40% of the world's popu-lation lives in areas where malaria is transmitted. There are an estimated 300 – 500 million cases and up to 2.7 million deaths from malaria each year. The mortality lev-els are greatest in sub-Saharan Africa, where children under 5 yrs of age account for 90% of all deaths due to malaria (Breman, 2001; Drazen and Phimister, 2007). Resistance to anti-malarial drugs and insecticides, the decay of public health infrastructure, population move-ments, political unrest, and environmental changes are contributing to the spread of malaria (Greenwood and Mutabingwa, 2002; Dunckley et al., 2007). In countries with endemic malaria, the annual economic growth rates over a 25 year period were 1.5% lower than in other countries. This implies that the cumulative effect of the lower annual economic output in a malaria-endemic country was a 50% reduction in the per capita GDP compared to a non-malarious country (Gallup and Sachs, 2001; Duraisingh et al., 2000). Recent studies suggest that the number of malaria cases may double in 20 yrs if new methods of control are not devised and implemented (Gallup and Sachs, 2001; Duraisingh et al., 2000). Despite more than a century of efforts to eradicate or control malaria, the disease remains a major and growing threat to the public health and economic development of countries in the tropical and subtropical regions of the world (Gallup and Sachs, 2001; Duraisingh et al., 2000).

The above pattern, coupled to the health challenges wrought by several other newly emerging (Wormser, 2007; Breman, 2001) and re-emerging pathogens (Moalem and Prince 2007; Carmichael et al., 1996) emphasizes why the area of infectious diseases is wanting for more, and better options; options that genomics and its related research promises to deliver.

How can genomics and genomics related research be explored to benefit the area of infectious diseases as a speciality?

While genomics may not be the solution to all the challenges posed on the scene of global health by infectious diseases, for now, it offers the key to a deeper understanding of the molecular mechanisms of disease; and thus insights into the development of novel therapeutics and diagnostics. The present focus will limit itself; without going in detailed methodologies, to five areas in which it is envisioned genomics related research to play a vital role: phenotype evaluation studies, evolutionary trends' studies across microbial and host genomes, idiopathic association or host susceptibility studies to disease, therapeutics or vaccine research insights, as well as the development of novel molecular diagnostics.

Phenotype evaluation studies and evolutionary trends' studies across microbial and host genomes

Within any microbial species capable of infecting and causing disease (pathogen) in man exist several subtypes with varying replicative and metabolic rates; immune evasion potential; drug resistance profiles and virulence patterns in various host species (Johnson and Kalams, 1998; Graham and Wright, 1995; Cease and Berzofsky, 1994; Haynes, 1996; Snider, 1994; Wheeler and Ratledge, 1994; Qijun et al., 2000; Robinson et al., 2003; Cole et al., 1998; Cowman, 2001; Daniel et al., 1993; Dean et al., 1996; Desrosiers, 1994; Dorak et al., 2004; Faure et al., 2000; Fidock et al., 2000). For instant-

ce, *Plasmodium falciparum* related malaria is associated with more complications than that caused by other *Plasmodium sp*, and exhibits more resistance to the available drugs options. Phenotypes can include various drug resistances and differences in parasite growth and development, virulence, metabolism, gene expression, efficiency of red blood cell invasion and transmission (Robinson et al., 2003; Su and John, 2004; Fidock et al., 2000; Flori et al., 2004), These variations are really a physical expression of a genetic variation, and may be traced and identified with the apparent subtype(s) infecting a patient using genomics related methods: genetic crosses and linkage mapping (Walliker et al., 1987; Smith, J.D., 2004; Gallup and Sachs, 2001; Galvani and Slatkin, 2003), gene association or expression studies (Cowman, 2001; Hayton and Su, 2004; Peterson, 1988; Duraisingh, 2000; Gardner et al., 1998; Gonzalez et al., 2005; Gonzalez et al., 2005; Goudsmit et al., 1991), as well as genome wide population association studies using comparative genomics and DNA microaarays (Mann, 2007; Fidock, 2000; Anderson, 2004; Graham and Wright, 1995). The most studied genes using candidate gene association are probably *pfdhfr*, *pfmdr1* and, more recently, *pfcrt* (Walliker et al., 1987; Gardner et al., 1998). Association of *pfdhfr* mutations with resistance to PY and proguanil in parasite isolates was reported in the late 1980s. Potential association of *pfdmr1* with CQR was described in 1990 (Schwarzer, 1998; Greenwood and Mutabingwa, 2002) but studies from additional field isolates have been controversial, with some declaring a strong association (Duraisingh, 2000; Goudsmit et al., 1997).

Idiopathic association or host susceptibility studies to disease

Several studies have of late emerged demonstrating the association between certain genetic variants and infectious diseases (Fidock et al., 2000; Schwarzer et al., 1998; Paterson et al., 1998; Flori et al., 2003; Casanova et al., 1991; Dean 1996; Frederick et al., 1996; Stephens, 1998; Greenwood, and Mutabingwa, 2002; Haas, 2006; Haynes, 1996; Hayton and Su, 2004; HIV Sequence database 2007; Hoffman et al., 1997; Hu et al., 1996; International Human Genome Sequencing Consortium 2004) . For instance, phagocytosis of the Malarial Pigment, hemozoin, Impairs expression of Major Histocompatibility Complex Class II Antigen, CD54, and CD11c in Human Monocytes (Fidock et al., 2000; Greenwood, and Mutabingwa 2002). Major histocompatibility complex (MHC) variations have also been associated with juvenile survival and parasite resistance in a large unmanaged unregulated population, meaning that parasites such as *Plasmodium* are likely to play a major role in the maintenance of MHC diversity in this population (Schwarzer et al., 1998; Haas, 2006). In particular, various clinical pictures of malaria have been associated with variations in MHC, and T cell receptor genes in a series of class I major histocompatibility complex-restricted cytotoxic T lymphocyte clones specific for a Plasmodium berghei nonapeptide (Paterson et al., 1998; Flori et al., 2003; Haynes, 1996; Hayton and Su, 2004). On t he other hand, individuals who are homozygous for a 32-bp deletion in the chemokine-cell receptor gene (*CCR5)* are highly resistant to becoming infected with HIV-1 (Casanova et al., 1991; Dean, 1996; HIV Sequence database, 2007; Hoffman et al., 1997). This *CCR5* "Δ32" variant became established in Europe centuries ago, likely under selective pressure from some other pathogen for example *Yersinia pestis* (Frederick et al., 1996; Hu et al., 1996) or smallpox (Step-hens et al., 1998; Galvani and Slatkin, 2003; International Human Genome Sequencing Consortium. 2004; Johnson et al., 1997) . Additional human genetic variants reported to influence HIV-1 transmission, viral replication, and/or disease progression include those of the major histocom-patibility complex (MHC) genes (Kaslow, 1996; Saah et al., 1998; MacDonald et al., 1998; Carrington et al., 1999; Tang et al., 1999; Keet, 1999 ; Karacki, 2000 ; Tang et al., 2002; Liu et al., 2003 ; Dorak et al., 2004; Johnson and Kalams, 1998; Karacki et al., 2001 ; Kaslow et al., 1996; Keet et al.,1999 ; Liu et al., 2003; MacDonald et al., 1998; Mann, 2007; Martin et al., 1998; Martin et al., 2002; Mazzoli et al., 1997), as well as other variants, in the chemokine receptors *CCR5* (Martin et al., 1998; Micahel et al., 1997; Ping et al., 2000; Tang et al., 2002; Tang et al., 2002; McLean and Blower 1993; Michael et al.,1997; Michel et al., 1996; Misaki, 2007; Moalem and Prince, 2007), *CCR2* (Saah, et al., 1998; Karacki et al., 2001), and *CX3CR1* (Faure et al., 2000; Modi et al.,2003), the chemokine-receptor ligands (*CCL5*-RANTES)(An et al., 2002; National Centre for Biotechnology Information (NCBI), 2007) , *CCL2 (MCP1)* (Gonzalez et al., 2002; Modi et al., 2003; Orrell, 2007; Peterson et al., 1988), *CCL3L1 (MIP1αP)* (Gonzalez et al., 2005; Paterson et al., 1998), and *CXCL12 (SDF-1*) (Winkler et al., 1998; Perelson et al.,1996), the cytokine *IL10* (Shin et al., 2000; Pinto et al., 1995), a killer immunoglobulin–receptor *(KIR)* gene (Martin et al., 2002; Robson M and Offit 2007), and *APOBEC3G* (Valcke et al., 2004; Robertson et at., 1995). Understanding of these genetic associations in light of clinical disease manifestation, as has been demonstrated for several non-infectious diseases may be well demon-strated and understood using genome wide association studies (International Human Genome Sequencing Con-sortium, 2004; Drazen and Phimister, 2007; Yates et al., 2007; Rennert et al., 2007; Robson and Offit 2007; Mann, 2007; Samani et al., 2007; Dunckley et al., 2007; Orrel, 2007; The International Multiple Sclerosis Genetics Con-sortium, 2007; An et al., 2000a; An et al., 2000b; An et al., 2002; Almond et al., 2005; Anderson, 2004; Baba et al., 1995; Blaak et al., 1998; Blower and McLean, 1994; Bolognesi, 1994; Bowman et al., 1999). “Moreover, per-sonalised medicine is increasingly taking advantage of pharmacogenomics to avoid adverse effects. For instance, in the area of HIV care, by way of genomics

pre-screening, the associations that have been replicated in multiple studies between HAART and Genetics can be identified on individual level and the regimens appropriately adjusted to avoid the adverse effects. These include, for example those between (1) abacavir-hypersensitivity reaction and HLA-B*570 (2) efavirenz and nelfinavir pharmacokinetics and the CYP2B6 516G T47, and CYP2C19 681G A polymorphisms, respectively; (3) indinavir- and atazanavir-induced hyperbilirubinemia and a UGT1A1 polymorphism; and (4) nucleoside analogue–associated lipoatrophy and a TNF- polymorphism.

Elucidating novel therapeutics or vaccine research insights

Although the transmission of several infectious diseases is in theory largely preventable, in practice, without the development of effective vaccine, Infectious diseases will still pose a global health threat. For instance, HIV sequence diversity (Valcke et al., 2004; Haas, 2006; Robertson et al., 1995; Perelson et al., 1996; Hu et al., 1996; Goudsmit et al., 1991; Carmichael et al., 1996; Clerici et al., 1994; Pinto et al., 1995; Mazzoli et al., 1997; Blaak et al., 1998; Robertson et al., 1995; Robinson et al., 2003; Samani et al., 2007; The International Multiple Sclerosis Genetics Consortium, 2007; Stefansson et al., 2007; Wheeler and Ratledge 1994; Saah et al., 1998; Schwarzer et al., 1998; Shin et al., 2000; Stephens et al., 1998; Smith et al., 2000), which is a major determinant of antigenic variation, is the biggest of all scientific challenges inclusive of uncertainities surrounding the humoral and mucosal protective immunities (Almond et al., 1995; Johnson et al., 1997; Chun et al., 1997; McLean and Blower, 1993; Blower and McLean, 1994; Desrosiers, 1994; Snider et al., 1994; Su and Wootton 2004; Tang et al., 1999; Tang et al., 2002a; Tang et al., 2002b; Tang et al., 2002c), in-vitro latency or switch off potentials (Daniel et al., 1992; UNAIDS. 2006), safety of trail vaccine candidates (Wyand et al., 1996; Bolognesi, 1994; Valcke et al., 2004; Walliker et al., 1987) and a scarcity ideas for of efficacious options (Bolognesi, 1994; Baba et al., 1995; Wyand et al., 1997; Cohen J, 1997; Walliker et al., 1987; Wyand et al., 1996; Wyand et al., 1997; Wootton et al., 2002). Its has now become apparent that an effective HIV vaccine must be representative in terms of immune elicitation to all the antigenic subtypes present within the population its intended for-thus the principle of multivariate vaccines; besides rendering some sort of restriction to the erratic error prone nature of the reverse transcriptase as well as rapid HIV replication rate, in a way arresting the diversity in viral progeny-the basis for recombinant DNA vaccines(Cowman, 2001; Danie et al., 1992). Moreover, newer approaches exploring regenerative strategies such as immune modulation and reconstitution are increasing become promising for an effective anti-HIV vaccine and microbicide (Misaki, 2007; Wormser, 2007) . Understanding of the molecular mechanisms of other infectious diseases like Malaria has in the past been explored to elucidate novel vaccination approaches (Qijun et al., 2000; Robinson et al., 2003; Su and John, 2004; Wal liker et al., 1987; Faure et al., 2000; Fidock et al., 2000; Flori et al., 2001; Gallup and Sachs, 2001). The sequencing of several microbial genomes, as was the case for the sequencing of the human (International Human Genome Sequencing Consortium, 2004) must led to the emergence of downstream sciences that will take advantage of this sequence information such as comparative genomics, transcriptomics, proteomics and metabolomics (Drazen and Phimister, 2007; An et al., 2000) to elucidate novel therapeutic and vaccination strategies on the part of infectious diseases.

Development of novel molecular diagnostics

The characteristic features of the tubercle bacillus include its slow growth, dormancy, complex cell envelope, intracellular pathogenesis and genetic homogeneity (Haynes, 1996; Snider, 1994; Dean et al., 1996; Desrosiers, 1994). The generation time of *M. tuberculosis*, in synthetic medium or infected animals, is typically 24 h. This contributes to the chronic nature of the disease, imposes lengthy treatment regimens and represents a formidable obstacle for researchers. The state of dormancy in which the bacillus remains quiescent within infected tissue may reflect metabolic shutdown resulting from the action of a cell-mediated immune response that can contain but not eradicate the infection. As immunity wanes, through ageing or immune suppression, the dormant bacteria reactivate, causing an outbreak of disease often many decades after the initial infection (Snider, 1994; Wheeler, and Ratledge, 1994; Desrosiers, 1994; Dorak et al., 2004). The molecular basis of dormancy and reactivation remains obscure but is expected to be genetically programmed and to involve intracellular signalling pathways (Wheeler and Ratledge, 1994; Desrosiers, 1994). Yet, despite the availability of effective short-course chemotherapy (DOTS) and the Bacille Calmette-Guérin (BCG) vaccine, the tubercle bacillus continues to claim more lives than any other single infectious agent. This is in part due to the evolution of drug resistance, the high prevalence of HIV associated TB, and partly due to this pattern of dormancy adapted by the tubercle bacili in-vitro (Wheeler and Ratledge, 1994; Dorak et al., 2004). Daignoses is also made cumbersome by the slow growth and dormancy of the bacillus. The combination of genomics and bioinfor-matics has the potential to generate the information and knowledge that will enable the conception and develop-ment of new therapies and interventions needed to treat this airborne disease and to elucidate the unusual biology of its aetiological agent (Cole et al., 1998; Wheeler and Ratledge, 1994; Cease and Berzofsky 1994; Dorak et al., 2004). The combination of genomics and genomics related research offers hope to the development of novel diagnostics such as DNA microarray, and resistance testing

through gene expression studies as well as linkage disequilibrium (LD) (Wootton et al., 2002; Winkler et al., 1998) and genome wide association studies (Fidock, 2000; Graham and Wright, 1995).

Conclusion

Conclusively, it is widely accepted that genomics and its related sciences has more to offer to infectious diseases especially that which is yet to be explored, but whose exploitation will generate new knowledge vital to reducing the burden of Infectious diseases.

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