Translational Genomics in Low- and Middle-Income Countries: Opportunities and Challenges

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Abstract

Translation of genomic discoveries into patient care is slowly becoming a reality in developed economies around the world. In contrast, low- and middle-income countries (LMIC) have participated minimally in genomic research for several reasons including the lack of coherent national policies, the limited number of well-trained genomic scientists, poor research infrastructure, and local economic and cultural challenges. Recent initiatives such as the Human Heredity and Health in Africa (H3Africa), the Qatar Genome Project, and the Mexico National Institute of Genomic Medicine (INMEGEN) that aim to address these problems through capacity building and empowerment of local researchers have sparked a paradigm shift. In this short communication, we describe experiences of small-scale medical genetics and translational genomic research programs in LMIC. The lessons drawn from these programs drive home the importance of addressing resource, policy, and sociocultural dy-

namics to realize the promise of precision medicine driven by genomic science globally. By echoing lessons from a bench-to-community translational genomic research, we advocate that large-scale genomic research projects can be successfully linked with health care programs. To harness the benefits of genomics-led health care, LMIC governments should begin to develop national genomics policies that will address human and technology capacity development within the context of their national economic and sociocultural uniqueness. These policies should encourage international collaboration and promote the link between the public health program and genomics researchers. Finally, we highlight the potential catalytic roles of the global community to foster translational genomics in LMIC. © 2015 S. Karger AG, Basel

Introduction

The ultimate goal of translational genomic research is to use knowledge gained from genomic research to improve the precision of the practice of medicine at an individual level and to inform public health strategies at a population level. Thus, proper implementation of ge-

nomic-driven insights into the pathobiology of diseases and therapeutics promises to contribute to better health in all human populations. Advances in genomic research are enabling the implementation of next-generation sequencing (NGS) in 21st-century western medical care, particularly in areas of tumor screening, family health history (FHH)-directed decision support, pharmacogenomics-driven treatment, complex disease risk advice, and diagnostic genome sequencing [1]. In contrast, genome-based decision support for public health is absent or inadequate in most low- and middle-income countries (LMIC). Of 603 international laboratories offering genetic testing registered in GeneTests, none are in low-income countries and only 20 are found in middle-income countries (www.genetests.org). The hurdles encountered by LMIC in the move towards genomic medicine include inadequately equipped research and clinical laboratories, shortage of scientifically skilled personnel, lack of awareness of the importance of genomics to guide public health, and lagging public health policy framework. Recent initiatives such as the Human Heredity and Health in Africa (H3Africa), the Qatar Genome Project, and the Mexico National Institute of Genomic Medicine (INMEGEN) are fostering genomic research capacity of LMIC by funding locally initiated research and empowering local researchers to lead genomic research projects [2]. Successful examples include the African Genome Variation Project [3] and the Mexico Genomic Variation Project [4] that are documenting the striking landscape of genetic structure of diverse ethnic groups with the goal of facilitating genomic medicine in Africa and Mexico.

Low-cost precision medicine driven by genomic research and technological advances presents tremendous promise for LMIC because the morbidity and mortality cost of common diseases is disproportionately high in resource-limited settings. Therefore, early investment in genomic research has the potential for returning long-term benefits to LMIC. Sequencing and genotyping costs are decreasing by at least ten-fold per year (www.genome.gov/images/content/cost_per_megabase2.jpg) thanks to technological advances. In the near future, NGS-based screening programs are anticipated to be more cost-effective than conventional clinical tests currently in use in LMIC. This is good news to LMIC in terms of affordable genomic research and clinical practice. Moreover, LMIC can maximize the impact of available resources by pooling funds to establish and strengthen regional research centers instead of working in isolation.

Communicable Diseases: Lessons from Pharmacogenomics

In the field of communicable diseases, research on host immunogenetics of HIV-1 has led to the development of maraviroc, the first FDA-approved oral CCR5-receptor antagonist in clinical use [5]. In developed countries, screening for HLA-B*5701 genotypes is performed before initiation of abacavir (a nucleoside reverse transcriptase drug used to treat HIV) to predict the risk of drug hypersensitivity [6]. HIV treatment guidelines of some African countries have included abacavir as an alternative regimen [7, 8]; therefore, these guidelines should stress the importance of HLA-B*5701 allele screening as a prerequisite for high-risk populations [9]. *IL28B* genotypes are associated with a significant difference in response to pegylated interferon (Peg-IFN)-based treatment for hepatitis C virus (HCV). The *IL28B* (rs12979860) TT genotype associated with reduced response to treatment is more common in African- than in European-ancestry populations (64 vs. 32%) [10]. This polymorphism provides an explanation for part of the lower response to Peg-IFN-based treatment observed in Africans [10] and for about half of the observed difference in response rates between African- and European-ancestry HCV patients [11]. This disparity in response to treatment as well as the toxicity and limited efficacy of Peg-IFN-based therapy has necessitated an increase in global access to direct-acting antiviral (DAA) regimens (www.who.int/selection_medicines/committees/expert/20/reviews/overview-new-treatments-HEP-C_13-Apr-15.pdf). Clinical trials have shown that patients with the *IL28B* TT genotype experienced more improvement from triple therapy when DAA regimens were added to Peg-IFN/ribavirin [12]. Consequently, some LMIC, including Egypt, which has the highest prevalence of HCV in the world (14.7%), are making a transition from IFN-based to triple therapies and DAA-based regimens [12, 13]. Given the high cost of DAA-based regimens, LMIC could use *IL28B* genotypes of patients to develop a more precise and cost-effective DAA-based treatment protocol.

More generally, the disproportionate paucity of pharmacogenomic research in LMIC has limited our knowledge of clinically relevant variants in non-European-ancestry populations [14]. This picture is beginning to change with the growing pool of pharmacogenomic research [15–17] and supportive programs such as the Pharmacogenomics for Every Nation Initiative (PGENI) that aims to integrate pharmacogenetics with the public health system of LMIC by constructing a resource for rel-

evant polymorphisms using DNA samples from major ethnic groups that represent at least 10% of the population in LMIC (www.pgeni.org).

Noncommunicable Diseases: Potential Genomics Applications

Noncommunicable diseases impose an additional burden on LMIC. For example, the number of people with diabetes in sub-Saharan Africa is projected to rise from 7.2 million in the year 2000 to 18.7 million in the year 2030 [18]. Genomic research has provided novel insights into the pathogenesis of type 2 diabetes. For example, a recent report linking insulin secretion to variants in a gene encoding a zinc transporter protein (SLC30A8) has illuminated the role of zinc in islet function and inspired public health interest in using dietary zinc to prevent type 2 diabetes [19, 20].

Another example of translation of genomic research to stratify patients for more effective targeted interventions in LMIC has come from studies on asthmatic children in Mexico City. The studies showed that asthmatic children with the *GSTM1*-null genotype are more susceptible to the adverse effects of ozone on lung function than those with the *GSTM1*-positive genotype. Antioxidant supplementation (vitamins C and E) improved forced expiratory flow levels more strongly among children with the high-risk genotype (i.e. *GSTM1*-null-null), demonstrating the effectiveness of genomics-informed stratification for interventions in noncommunicable diseases [21, 22].

A third striking example is the reported relationship between the African-ancestry-specific *APOL1* gene variants (G1 and G2) and increased risk for several forms of kidney disease [23]. Despite the increased risk for kidney diseases, the prevalence of the risk genotype is 13% among African Americans and virtually absent among non-African-ancestry populations [23]. It is hypothesized that *APOL1* renal disease risk variants evolved in sub-Saharan Africa about 10,000 years ago to confer protection against the regionally endemic trypanosome parasite, the cause of African sleeping sickness [2, 23]. Published studies demonstrated that the frequency of the risk variants as well as the prevalence of chronic kidney disease are much higher in west Africa (Yoruba, 28%; Igbo, 23%) where the trypanosome parasite is endemic as compared with the nonendemic region of Ethiopia (~1%) [24–26]. Furthermore, kidney transplant failure is higher in recipients of donor kidneys from African-ancestry individuals with

APOL1 risk variants. These data call for screening of *APOL1* risk variants in kidney donors or recipients of west African ancestry [27]. A validation of the functional role of these variants and a comparative evaluation of the clinical utility of screening for these variants in ethnically diverse populations are warranted before integration into clinical practice and public health policy.

Community Genetics Programs: Success Stories and Challenges

The World Health Organization's (WHO) recent Consultation Report indicated that the availability of community genetics services in LMIC is inadequate. However, the report noted the success of community genetics programs implemented by LMIC through newborn and carrier detection screening and environmental control [28]. Valuable lessons can be learned from existing small-scale medical genetics services in LMIC. For example, newborn screening (NBS) for congenital hypothyroidism, which can be inexpensively treated with oral thyroxine, has been implemented in the Middle East and North African countries [29]. In South Africa, medical genetics services are provided for prenatal genetic diagnosis, predictive and carrier testing, and genetic counseling at secondary and tertiary care levels. The ophthalmic genetic service in South Africa illustrates that translational research programs can successfully be run in an academic medical setting in Africa. A system has been designed for the identification of individuals affected with retinal degenerative disorders, and protocols are in place for processing referral, informed consent, pre- and post-test counseling, and result delivery [30]. Similarly, breast cancer genetic services provided in South Africa involve mutation screening and counseling for test-positive individuals and family members. Women with hereditary breast cancer who meet protocol-driven criteria are tested for targeted sequence-based *BRCA1* and *BRCA2* mutations. A primary care physician or a genetic counselor conducts pre-test counseling, a multidisciplinary team involving a geneticist/genetic counselor reviews the test results, and the genetic counselor provides post-test counseling and screening to family members [30]. In Cameroon, a small-scale, yet promising, medical genetics service has recently been established. The presence of a trained medical geneticist and strong links with an established collaborative center in Geneva are anticipated to contribute to the success of this service [31]. In summary, these small-scale genetic services provided in research

Fig. 1. Factors for the effective translation of genomics to health care practice in global settings. Integration of genomic research with clinical and public health care, and the cycle of bench-to-clinic-to-community in global settings is influenced by three key factors: local and global policy and governance (public health policy and ethical guidance), resource (infrastructure, funding, and technology), and sociocultural factors.

and clinical programs demonstrate that genomic medicine can be successfully implemented in LMIC.

The success of genomics in transforming the health of a population demands more than the availability of diagnostic or screening tests (fig. 1). Several lessons have accumulated from screening programs for sickle cell disease (SCD), a blood disorder that occurs when a person inherits two abnormal copies of the hemoglobin beta gene (*HBB*). Unlike emerging applications of genomics for which consensus on clinical validity and utility is yet to be established, there is compelling evidence showing that SCD screening improves patient care. To mention some, neonatal screening for sickle hemoglobin has contributed to dramatic increases in survival and quality of life of patients in the US and Europe [32]. Similarly, the NBS and early-life intervention program for SCD in Jamaica has resulted in a substantial decline in child mortality – a successful model that can be replicated in LMIC [33]. Although sub-Saharan Africa bears 75.5% of the estimated 312,302 babies born with SCD globally each year [32],

neonatal screening for SCD and supportive care are limited in the region. No country in sub-Saharan Africa has a national universal NBS program for SCD. As a consequence, most children with SCD die during the first years of their life, and those who survive suffer serious clinical complications during adulthood [32]. Recent small-scale or pilot SCD screening projects in several African countries are showing promising results with respect to the feasibility of establishing SCD NBS and follow-up programs for SCD in Africa. Some of the challenges encountered by African countries with SCD screening programs include: inadequate number of equipped laboratories with a capacity to screen a large number of newborns, poorly coordinated health management information system to track babies that test positive to do a confirmatory test and to initiate early medical management, and limited resources allocated to SCD in the public health system [34–37].

It is perhaps timely to ask if genomics could help bring the needed attention to the establishment of more comprehensive NBS programs in LMIC. The anticipation that NGS-led NBS will provide cheaper, faster, and more robust medical information is welcome news to LMIC. However, proper integration of NGS as part of a routine NBS program raises new challenges and controversies (reviewed in [38]). Some of the potential challenges discussed include the burden of whole genome sequence data on the public health system, psychosocial and legal consequences of reporting the findings revealed by sequencing, and unresolved issues in the interpretation of the scientific validity, clinical utility, and actionability of whole genome sequence results. LMIC should begin to explore these issues and other challenges surrounding NGS-led NBS within their unique economic, public health, and cultural contexts.

Family Health History: Readily Available Genomics Tool

Another inadequately utilized genomic application with proven validity and utility is FHH. FHH captures genetic and environmental factors that influence risk of disease shared by family members [39]. In the US, FHH has been shown to be a valuable tool to target an intervention to high-risk families [40], and Web-based FHH tools are being piloted [41, 42]. Although inquiry about FHH – the simplest and most readily available genomic tool – is a long-standing medical practice globally, documented examples of its use in LMIC are scarce. One reproducible

example of the use of FHH to target resources to high-risk individuals in LMIC can be drawn from a genomic research program that led to a FHH-driven public health strategy for preventing podoconiosis [43, 44]. In southern Ethiopia, children at high genetic and environmental risk for podoconiosis were identified using FHH and were targeted for distribution of shoes [45]. The effectiveness and sustainability of such programs depend on understanding community perceptions about heredity [46] and addressing them using strategies that bolster healthier lifestyles inspired by a concrete understanding of genetic and environmental risk.

Conclusions and Future Directions

Translation of genomics to health care is becoming a reality in the developed economies around the world. We advocate for a more robust engagement of LMIC in genomic research and technological innovations to enable them to fully harness the benefit of genomic discoveries for improving the health of their people. The role of new initiatives such as H3Africa and INMEGEN in promoting genomic research capacity and infrastructure development is an excellent example of early preparations to make genomic medicine equitable to the world populations. Existing medical genetics services in LMIC provide lessons about resources, policy, and sociocultural dynamics that need to be addressed to realize genomic medicine to the public. In order for LMIC to have functional ge-

nomics medicine programs, they must invest in biotechnology and train a cadre of medical geneticists, genetic counselors, genetic-epidemiologists, bioinformaticians, and computational biologists. Local context-driven ethical and legal frameworks should be established. In parallel, a global community of government agencies, the private sector, and philanthropy should be engaged in the process. Global approaches propelled by the WHO can foster translocal replication of successful models by offering a platform for developing guidelines for incorporation of low-cost high-impact genomic technologies into the health care system.

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Disclosure Statement

The authors declare that they have no competing interests.

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