African Society of Human Genetics

2003 First Annual Meeting

La Palm Royal Beach Hotel, Accra, Ghana

8th – 10th December 2003

Discussion Notes

The aim of these notes is to give a flavour of the discussion stimulated by the talks which will be posted on the website. They are by no means comprehensive as I did not manage to get everything down, or fully hear or understand some of the points being made. However they could form the basis for web-based discussion that people could add their comments/corrections to, or get matched up to the individual talks that will be posted.

8th December 2003

Impact of the human genome project on the future of higher education in Africa. **Clement Adebamowo, MD**

Comment: Many countries do not have science and technology policies, so how can African countries get involved?

Response: to develop centres of innovation and growth

C: This talk was very frank and I feel exposed as an African. However, it tells us we have to be open. We have had poverty and oppression for so long from governments, so why rely on them? There is a need for ways beyond looking to government or policy makers. Think about what we can do individually. E.g. link up together and exchange students. Start with small things so as not to completely miss the boat and thing may then rollercoaster. Avoid long communiqués.

C: How can you forget the government and succeed when you have no power?

R: An example was given of how governments decided it was not economical to treat hypertension and comparison made – the digital revolution will allow the development of an infrastructure at both the individual and institutional levels. Think about how to manage meagre resources and cross fertilise.

C: What do you recommend as the short-term aim of the AfSHG in terms of education and training?
R: People need to look and see who is where, what resources they have, however meagre, and look at what they can do. Those with resources can train people, others identify individuals who could be trained.

C: At what level should curriculum development occur?
R: A curriculum for web-based education could be developed. The experience of African people who are using distance-based learning might be valuable. It is $200-300 to get a functional computer and there are many free web resources – find out what is available and how to access.

C: Not only are the numbers of publications low for Africa, the journals are often low impact so situation may be worse than portrayed in the talk. Also need to develop the infrastructure to support individuals who do get trained elsewhere to prevent the brain drain.

Genomic Variation in the African Diaspora: Implication for understanding differential distribution of diseases. Georgia M. Dunston, PhD

General introduction regarding how good it is that this meeting is happening after all the talking and planning, and congratulations and thanks to Professor Charles Rotimi for his efforts to this end. Also praise for first speaker (Dr Adebamowo) and the focus on education and seeking truth.
'The darkest dark is just before dawn and truth is dawning in the hearts and minds of people all over the world'.
'We are at the beginning of the knowledge revolution'.
'Today is an historic occasion – everyone come here with a history but at the individual and the collective level. We will leave with a sense that something has happened'.
'Our time has come and we are ready'.

Discussion:
C: Is it a question of the definition of getting from genotype to phenotype? What is changing is not what we are looking at, but how we are looking?

R: The genotype is now a phenotype. When interrogating the genome, we need to shift from looking at a medical model to a biological model i.e. get away from the what is wrong and how doesn't it work, to how it does work and then we can understand disorder and dysfunction
C: Yes, and phenotype variation is not disease: disease is an arbitrary definition.

Bio-banking in Africa: The Gambia National DNA Collections. **Giorgio Sirugo, MD, PhD**

C: What are the implications of biodiversity between ethnic groups, for example could it lead to ethnic conflict?
R: To illustrate the value of this diversity, an example was given as to how variation between ethnic groups underlies susceptibility to malaria and the insights derived from understanding this.

C: Are there formal legal procedures to prevent against breach of anonymity? What is the official documentation of the guidelines and the involvement of the people and government?
R: The name of the bank includes National and Gambian to demonstrate the involvement of the people and the guidelines were written with government input. They are to be submitted soon for publication in a scientific journal, but there is no legislation, or moves towards this at present.

C: Two logistical points were raised – the shipment of samples and the problems with continuous electrical power in many African countries.
C: The MRC Labs in The Gambia have a generator and therefore continuous power. Samples are shipped in dry ice and several thousand samples shipped to collaborators this year. For his talk, Scott Williams brought in one of his dry shippers to demonstrate his way of shipping samples from Ghana to the USA.

Ethical Challenges in Genomic and Genetic Research in Africa: Implications for Informed Consent and IRB Protocol Review. **Patricia A. Marshall, PhD**

C: You can do things by the book yet people still behave unethically: what does informed consent really mean, and how can it be informed if the researcher does not know what the results will be?
R: Yes, and most participate because they believe they will benefit e.g. by getting better access to medical care or there is a misconception that participating will lead to a cure of their disease.

Generally it is pragmatism not altruism that motivates an individual to participate. The issue of trust was raised – if people are asked by someone they trust, or by a representative of an institution they trust, they are more likely to agree to participate.

C: Consent forms now protect the institution not the individual.
R: Yes, whose interests are being served? Is it the lawyers (certainly in the US), it is the institutions in many cases and not necessarily the study participants. Forms should be easily understood by 6th graders but are now so convoluted and any conceivable risk, however remote is included.

C: What is the federal judiciary responsibility of the Institutional Research Boards?
R: To ensure the individual who participates in research is protected. It is voluntary and so there should be mechanisms to protect them. Traditionally IRBs are not well supported.

C: Should members of IRBs be paid?
R: Some get honorariums for their efforts e.g. if the study is submitted from a non-University Institution or from overseas for example. Consultants may also be hired.

C: Regarding biobanking, we cannot anticipate all research questions and where they will end up, so how can you protect the interests of the individual for example if the research leads to some kind of profit?
R: PM referred to the fiction of consent – it is impossible to predict the results or possible developments and technologies that result from the research. It is maybe time to shift from consent and set up other mechanisms to protect individuals and communities involved by anticipation – e.g. has the community already got a system for sharing benefits. A gradual approach is needed – consent is never a one-off moment and should be regarded as an opportunity to establish a dialogue which is two way and ongoing.

Ethics in the curriculum of biomedical and related programs in Africa: Past, present and future. Olayemi Omotade, MD

C: The idea of training individuals from the African Diaspora from within the cultures is appealing.

C: Speaker commended for presenting a framework of importance. The relationship between ethical conduct and economic status was explored. The common situation in Africa of unemployment and lack of job opportunities after training was compared with a developed country like the USA where student leave training in significant debt.

C: Everyone has something to bring to the table whatever their background. What is the African perspective on the consent (individual) form, where the issue may not be how to protect myself?
R: In Africa we are our brother's keeper i.e. we have a responsibility towards each other. There is a challenge to come up with a proper consent process.

C: There are aspects of globalisation that are not necessarily bad – e.g. democracy, ethics, but other challenges occur – e.g. in Sudan there are over 100 languages to translate a consent form into (compared to say 3 in the USA), and the idea of individualism came with colonialism.
C: Yes, and in Nigeria there are maybe 200 groups, 400 languages plus all kinds of religious and social variations to consider.

C: How realistic is the idea of putting things (e.g. educational resources) on the web when it can be impossible to access?
R: This approach is working well for Bioinformatics at the University of the Western Cape (UWC, Raphael Isokpehi) but perhaps many strategies are required – recognise diversity in all its forms. Provide different levels of access that are appropriate to the surroundings and people can aspire to improve to the next level.

C: What is the US experience of teaching ethics to medical students and what strategies are required to implement curriculum change?
R (PM): Models have been developed and ethics teaching is part of the curriculum in the US. There were many challenges to begin with and some of these will be there for Africa. For example getting time in the curilculum devoted to teaching ethics. It may be necessary to be creative in the beginning and start with something small that can evolve. Also collaborate with colleagues and involve them. Trust and transparency are important.

C: There can be problems relying on field assistants to translate: for example they may be other factors influencing their behaviour such as performance rewards.

C: Things have been done the wrong way round – we have informed consent because we did not train people in ethics. It should not be just for medical students/doctors, but all researchers.

PM: Yes and transparency and training is key here.

C: Dealing with the unknown in terms of where the research might lead has led to a paradigm shift – all limitations and uncertainties should be disclosed and this transparency increases trust. AfSHG must not lose sight of its goal: to conduct genetic research in communities, and the relationship with them is crucial.

Bioinformatics. Rafael Isokpehi PhD

C: This talk was pure hope, the inspiration that high quality research can be led by Africa.
R: the power of the computer – it is more than for email and internet access!

C: How can people get training starting from scratch – it seems if you are already working or have some training you can go further but what of people with no training at all?
C: There are masters and PhD programmes at UWC and a curriculum under development, with information on the web. There are established strategies developed at UWC that could be modified for other countries. For the undergraduates lectures on bioinformatics are being included to give them a feel for what is out there. South Africa National Bioinformatics Institute (SANBI) is a regional; training centre and already collaborates with other centres Africa – e.g. in Tunisia. They are ready to help.

C: Lack of intellectual power is not a problem here! It's a natural resource. Bioinformatics (BI) represents democracy and knowledge. The dissemination of knowledge using BI allows connectedness.

C: Brazil, not a first world country, has sequencing projects and BI – i.e if the political will is there is should develop in African countries. Some link to colonial history was made here.

C: 'It is not us against them' and we must be careful not to send wrong message. The spirit should be of a human diaspora, not African. People don't want to cut you out, but they don't have the patience if you are slowing them down. You need a voice to say I may slow things

down but I am important. Difference voices are needed for a comprehensive discussion and genomics is not forgiving – if you are not comprehensive you will fail.

Tuesday 9th December

Genomics and genetics of infectious diseases. Melanie Newport, MD PhD

C: How common are these protein truncation disorders?
R: Very rare, but they tell us so much about the pathways, in the same way that knockout mice do. Also there is a spectrum of severity of mutations in the genes within the IFN/IL-12 pathway that correlates with phenotypic severity suggesting that more subtle variants of these genes may be important in complex phenotypes.

C: Infectious diseases (ID) are stigmatising, and knowing someone has an ID susceptibility genotype could cause problems with stigma too.

R: This is an important point and applies to other disorders such as neurodegenerative disease, and other implications such as for insurance. My interest as a clinician seeing patients with ID is to use genetics as a tool with which to identify the major pathways of disease pathogenesis that can be targeted for drugs and vaccines that will be useful for everyone regardless of individual genotype. Also, to get infection you need a pathogen contact too, so there is not a 100% relationship between genotype and the development of disease. Knowing you have a susceptible genotype could be beneficial e.g. get vaccinated, take prophylaxis, and the phenotype of ID is probably more stigmatising that the genotype, especially if genotype information is confidential.

C: Information on environmental factors such as nutritional status should be collected in addition to detailed clinical phenotyping as this is also going to contribute to the phenotype.
R: Absolutely, and the relatively disappointing results from genetic studies in ID probably result from poor study design where such factors are not considered.

C: Is it likely we will see a rise in allergic disease as lifestyles change and become 'cleaner'?
R: Yes, there is evidence that the balance between the immune responses required to control infections such as tuberculosis and those involved in the immune response to helminths and the

development of allergy can be modified by many things and there is the hygiene hypothesis that allergy has increased in the West as a result of less exposure to infections, and the dampening down of one arm of the immune response allowing the other to become dominant. There is a study from Guinea Bissau that suggests that BCG, which drives the other arm of the immune response, reduces the risk of allergy if given in early life.

African Diaspora: An opportunity to study gene-environment interaction. **Charles Rotimi, PhD**

C: Why does the body 'choose' one gene over another in the development of these diseases?
R: There is more than one gene involved, and the concept of disease genes should be reviewed. There is more likely a continuous phenotypic variable and disease may occur at the extremes.

C: Why do genes vary between populations?
R: We should resist the temptation to compare populations as it unlikely to be one gene in one population and another in another population, more likely that it is allele frequencies for the same genes that are the variables between populations.

C: Is there a connection between non-communicable disease (NCD) and infection in terms of the genetics. For example is there an association between sodium channel genes that influence the red blood cell sodium levels and may have been selected for by malaria, and hypertension?
R: The systems we study have been perfected in the harsh environment in Africa and there are many lines of evidence that inflammatory responses are involved in the pathogenesis of NCD. However, the studies to investigate the relationship between ID and NCD genetics are generally hard to fund and therefore have not been done.

C: Will it be possible to use candidate genes to assess the risk of developing diabetes in an individual before they get disease and it's too late?
R: This is in progress and a panel of diabetes susceptibility genes is under development. Meanwhile, the strong epidemiological evidence that eating less, keeping fit and stress reduction is the best public health strategy, even if hard to follow this advice!

Genomic science and cardiovascular disease research in Africa and the Diaspora. **Scott Williams, PhD**

C: How do you identify disease genes and interpret findings in different populations, when study design depends on what we already know? As all genes are characterised and annotated individualised medicine becomes a possibility.
R: Treatment is currently empirically based on what we know about pathophysiology of hypertension but there are unknown pathways, which can be missed at present when we screen for the usual suspects. Individualised medicine will come but not for a long time.

C: Much higher resolution is required before we can think in terms of individualised medicine and it will anyway depend on fully understanding the environmental interactions, which are more difficult to quantify. We should be moving away from a 'good/bad' gene model of diseases but think in terms of natural genetic variation working in combination with a certain environment to create a phenotype, the extreme of which may be considered to be disease.

C: The multilocus approach to data mining has its advantages, using multiple genes in a single smaller sample, (such as cost implications for large scale cohort studies) but is there a risk of becoming discouraged if results are negative? What is the physiological relevance of what you find?
R: Yes and replications are required to check for spurious findings and more detailed pathway dissection is required. At present the addition of a new gene might change the whole terrain.

C: Linkage disequilibirum has been show to exist over shorter distances in African people, and this is related to recombination but in fact there are no meiotic maps for any African population. Are haplotype blocks random or are there recombination hotspots?
R: This is a complex issue and it is difficult to even agree on what constitutes a haplotype block. But points of reference (meiotic maps for example) are crucial.

C: Cardiovascular disease is different phenotypically in Africa – hypertension and strokes are more common that coronary artery disease and in diabetic patients peripheral vascular disease is rare while neuropathy is relatively more common.

R: This research focuses on blood pressure mainly which is a continuous trait and hypertension is an expression of an extreme phenotype. The clinical phenotype is more complex and results from many different pathways.

C: What would your advice be to someone setting up a genetics project now?
R: It is hard to find single gene effects and a concerted effort between the epidemiologist (environment) and geneticist is required.

C: Clinicians are moving the goal posts e.g. the cut of for hypertension and geneticists cannot always agree – what impact does this have on the attempt to relate phenotype and genotype?
R: If we investigate continuous traits such as blood pressure, rather than an extreme for which a cut off then has to be defined we can avoid this problem.

C: Is this model a priori or a postori?
R: This approach is hypothesis-generating rather than hypothesis-driven– i.e. data driven. It is looking for models to predict the phenotype from the multilocus genotypes. Hypotheses may then be tested in other populations

Muntaser Ibrahim

C: Regarding work on differences between ethnic groups, the problem becomes one of boundary definitions – for example susceptible and resistant is not a clear boundary and reflects differential allele frequencies between groups – i.e. a spectrum.
R: Ethnicity and language differences will disappear in the near future so it is important to study population substructure now and know the history of both populations and genes.

C: Selection is not the only explanation for genetic variation between populations and it is important to consider the complexity of the 'phenome'. Gene flow and drift can also influence allele frequencies. It is not a question of does substructure have an impact, but how much does substructure influence interpretation of findings.
R: Is it possible anyway to predict an ethnic group from genetics data, and should we be thinking in terms of 'Gambian' or 'Sudanese'?

C: Are we losing track here of what the goal is – to bring health. We make the definitions we then operate on. We need to question our assumptions look at whether the problem exists within the group or is it being imposed by others looking for it.
R: Some problems are political – for example showing the genetic history of the population is important but dangerous if used in the wrong way.

C: Africa is often treated as one group without any reference to the huge diversity within the continent. We need to get data on variation between groups to then decide if this issue matters and how much. Many phenomena affect allele frequencies including inflow – how much do we actually know about substructure?
R (CR): Very little. The definition of an ethnic group may be dynamic and there are national, social and political boundaries too. There is no uniqueness – just differential allele frequencies. We are observing chronic manifestation of poor research design.

C: The question here is 'research to what end?' We are trying to find solutions to human problems and there is no single answer. Problems will arise from interpretation as long as there are limitations to interpretation. It is therefore critical to understand all variations (e.g. ethnic, population and family specific). In Africa it is important to keep an open mind, to find teachable moments – is there something to flush out for public health and education that will benefit populations?

C: There is the potential here for genetics to influence ethnic conflict. The identification of the precise site of the origin of man is also a potential problem with a number of groups claiming this distinction. Genetics has the potential to unravel the history and interpretation and study design are so important.

C: Some cautionary remarks.
Humans are complex and changing. There is a need to understand that outcomes are complex and many variables contribute to the outcome. Only looking at one thing misses the point. An interdisciplinary approach is required and people should work as a group to reinforce arguments.
Regarding ethnicity and race, the social construction of these concepts is important. We all came from Adam and Eve and evolution has brought differences. We need a holistic approach to get a better picture.

Issues of study design with internal and external validity matter, otherwise we make conclusions that are subject to general criticism even if they serve our purpose.

CR cites the Fusion study here as living proof to reinforce these comments.