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Parallel Journeys: The birth and growth of molecular genetics and its influence on a career spanning three decades

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PARALLEL JOURNEYS

The birth and growth of molecular genetics and its influence on a career spanning three decades

Michèle Ramsay

INTRODUCTION:

Good evening ladies and gentlemen. It is a great honour to be presenting my inaugural lecture this evening. Thank you for the kind introduction:

- Helen Laburn (Dean of the Faculty of Health Sciences)
- Yunis Ballam (DVC - Academic)
- Ahmed Wadee (Head of the School of Pathology)
- Sagie Pillay (CEO of the NHLS)
- Trefor Jenkins (Emeritus Professor in Human Genetics)
- My family here this evening: my mother Una, my husband Andre, our children Michiel and Emma and my sister, June. You are an inspiration to me and I truly appreciate your support throughout my career
- Colleagues, students and friends

In the early 18th century Isaac Newton (1642-1727) summed up the process of scientific research when he said: "I keep the subject of my inquiry constantly before me, and wait till the first dawning opens gradually, by little and little, into a full and clear light."

For me this speaks to a journey of scientific discovery. The concept of parallel journeys arose from my reflection on the extraordinary developments in the field of molecular genetics over the past three decades and how this has shaped my career as a scientist.

This journey has been possible because of the people who have walked with me or crossed my path at critical times during my development and I dedicate this lecture to them. Nature's guide to mentors (June 2007) states: "Having a good mentor early in your career can mean the difference between success and failure in any field." My exceptional mentors and role models will emerge as this talk progresses.

My parallel journeys this evening will be described in three stages:

- Stage 1: The beginnings of molecular genetics and translational science – Eighties and Nineties
- Stage 2: The challenge of complex questions – 21st Century Science
- Stage 3. Building projects for the future

Stage 1: The beginnings of molecular genetics in translational science

In 1980, on completing an MSc in recombinant DNA technology and microbial genetics, I arrived in the office of Trefor Jenkins at the South African Institute for Medical Research with the objective of starting a PhD project. This was my first introduction to population genetics and the notion that human genetics could be pursued at a molecular level. **Trefor Jenkins** is a remarkable man and therefore a great inspiration as a mentor. He has opened many doors to me during my career and I thank him for his unstinting support and for sharing his vision of building a DNA diagnostic laboratory that would compare to the best in the world.

In the late seventies and early eighties, recombinant DNA technologies were developed for the first time. It became possible to isolate DNA and to cleave it at very specific positions using restriction enzymes isolated from a variety of bacteria. We could manipulate the DNA and clone fragments into vectors, usually bacterial viruses or plasmids and put them in bacteria and grow lots and lots of copies. This was referred to as cloning DNA fragments. We could use these to interrogate human DNA sequences and genetic variation using a technique called Southern blotting, named after Ed Southern who developed it.

In the early eighties the structure of the globin genes and the two gene clusters on chromosomes 11 and 16 were elucidated and it became possible to discover DNA mutations that were responsible for a myriad of electrophoretic haemoglobin variants. One of our first studies was to show that Haemoglobin J Cape Town that was caused by an amino acid substitution at position 92 (Arg>Gln) occurred on a chromosome that had a deletion of the other alpha globin gene.

Knowledge of globin DNA related mutations meant that we could study them on a population basis and could also apply them to diagnostic tests. My PhD studies focused on both aspects. I was exposed to the enriching experience of field trips with Professor Jenkins to the small village of Tsumkwe in Bushmanland in the then South West Africa. With appropriate permits and verbal consent, we approached several communities of San and enlisted their participation in our studies. Some of these samples are still used for research today, with permission from our ethics committee. I was fortunate to attend the Namibian independence celebrations in 1990 when I happened to be in Windhoek during one of our field trips. Our work on these and other African populations demonstrated that a mild form of alpha thalassaemia was relatively common among the African populations we studied and that the sickle cell mutation was very rare or absent from many South African black populations.

The knowledge gained was translated into diagnostic tests in the early eighties when we established our DNA-based diagnostic testing laboratory. We started with tests on families with thalasaemia or sickle cell anaemia in order to detect carriers and to do prenatal testing for fetuses at risk for these serious genetic

conditions. The first prenatal test by DNA analysis for sickle cell anaemia was also the subject of my first scientific publication in 1984. Such studies were publishable because they were so novel at that time.

Role model: Renee Bernstein

Renee Bernstein was the head of the cytogenetics division at that time and she was responsible for encouraging me to go to my first international congress on my own. The theme was on the molecular investigation of the haemoglobinopathies and took place on the Greek island of Crete. There I had the opportunity to mix with about eighty international scientists and to experience the collegiality of the international science community. Renee and I subsequently worked and published together on Y chromosome anomalies and true hermaphroditism. She inspired me with her enthusiasm, attention to detail and rigorous research ethic. No doubt she would have enjoyed discussing the extraordinary case of Caster Semenya.

Toward the late eighties, the era of gene hunting for genes that cause Mendelian traits began in earnest with groups chasing the cystic fibrosis gene, the Huntington disease gene and myotonic dystrophy, among many others. Cystic fibrosis (CF) is a condition that affects mainly the lungs and gastrointestinal tract. The production of thick viscous secretions in the lungs encourages the growth of bacteria, like Pseudomonas aeruginosa. Repeated infections would cause the death of the patient at a very early age, were it not for aggressive antibiotic treatment. CF patients also failed to thrive because of a lack of pancreatic enzymes that promote digestion and absorption of nutrients and this problem is now effectively treated using enzyme therapy.

In the mid eighties the cystic fibrosis gene was localized to the long arm of chromosome 7 through the technique of linkage mapping in extended families. It was at this time that I left South Africa to do a post-doctoral fellowship in London with **Bob Williamson** at the St Mary's Hospital Medical School. I chose to work with the CF group in chasing down the gene and journeyed throughout the UK, to Portugal, Austria and Spain, as well as the US. There I listened and presented talks about our research work and the novel technologies of pulsed field gel electrophoresis and yeast artificial chromosomes and right towards the end of my stay the cystic fibrosis transmembrane conductance regulator (CFTR) gene was identified through the joint efforts of three research groups working in Canada and the USA. The CF gene was shown to encode a chloride transport protein which regulated the flow of water and ions across epithelial membranes, elegantly explaining the pathophysiology of the viscous secretions in CF patients. On my return to the SAIMR and under the watchful eye of Trefor Jenkins, we started to investigate the molecular mutations in South African patients and their families. Firstly in the CF clinics of Johannesburg and later in pursuit of black patients with CF; this despite the fact that generations of medical students had been taught that CF did not occur in black Africans. Our research uncovered a

common black mutation known as 3120+1G>A. We developed diagnostic tests for sets of mutations tailored to specific South African ethnic groups.

Role Model: **Mireille Claustres**

While in London as a postdoctoral fellow, I was assigned the task of teaching a French scientist-clinician the Southern blotting technique and this triggered a lifelong friendship. Mireille Claustres has since become a world expert on the molecular basis of cystic fibrosis and she and her team have recently constructed the most detailed genotype-phenotype database for cystic fibrosis. This database will be used by scientists and clinicians to gain insight into the potential clinical manifestations of cystic fibrosis. We have published together on CF many times. Mireille's research interests also include the molecular basis of deafness and Marfan's Syndrome, among other conditions, and she is the head of one of only three preimplantation genetic diagnostic laboratories that are certified in France. She has taught me the value of nurturing research teams in order to do the best science and fighting for important improvements in laboratory infrastructure and for necessary expansion of her group in order to provide an exceptionally good diagnostic service. She recently hosted the International Human Genome (HUGO) meeting in her home town, Montpellier.

DNA diagnostic testing has been significantly simplified by the development of the polymerase chain reaction technique, PCR, which became automated in the early nineties. We bought out first PCR machine at that time and it was so robust that we are still using it twenty years later. With these and other technological developments, like automated DNA sequencing, it was possible to accelerate the pace of gene discovery. This was also the time at which the international Human Genome Project was initiated. Its main purpose was to sequence the entire human genome and to make it available to scientists around the world to use for their research studies.

There was an exponential growth in the discovery of the genes which, when mutated, cause Mendelian genetic disorders. The Mendelian Inheritance in Man catalogue was established single-handedly by Victor McKusick in 1960 and since the information could not longer fit comfortably into a book, it evolved into OMIM (Online Mendelian Inheritance in Man) in the mid eighties. It is a source of electronic information used and accessed across the world with useful links to genomic resources including annotated genome databases, gene expression databases and protein structure, among others.

One of our contributions to the list of identified genes is the gene for lipoid proteinosis (LP), a skin condition that is particularly common among Afrikaners as a result of a founder effect. This study led us on a journey to Namaqualand to find the families that were first described by Heimi Gordon, a physician from Cape Town, who emigrated from South Africa to the USA (Mayo Clinic) and as his health deteriorated, he urged Professor Jenkins to investigate LP further. Gordon handed over his thesis, copious notes and pedigrees. True to his word,

Trefor Jenkins produced the goods. Together with a group in London, the LP gene was identified as the extra cellular matrix 1 (*ECM1*) gene. We showed that the carrier frequency for LP in Namaqualand is 1 in 9, making this a community at very high risk for this condition.

This work had a poignant added benefit for me. It led me to the small Coloured town of Concordia where Michael Dönges was a Rhenish missionary and built the stone church in 1875 which continues to serve the community worship even today. Michael Dönges is a great grand father of my mother on her paternal side. A few years after our research studies, my mother, her sister and our family visited the graves of Michael Dönges' young children in Concordia.

For no particular reason, other than through association, much of my research has been related to the genetic basis of skin diseases. Albinism is no exception. It is particularly common among Africans occurring in about 1 in 4000 black births in South Africa. This is interesting, considering that albinism is a particularly deleterious condition in areas of high sunshine with an increased risk for early onset skin cancer and decreased visual acuity and photosensitivity.

Role model: Jennifer Kromberg has become a recognized world expert on albinism. She is a social worker by training and published her first papers, together with Trefor Jenkins, on albinism. They explored the impact on mother child bonding, the prevalence among black South Africans and the cancer rates among individuals with different forms of albinism. Jennifer has inspired a generation of students in genetics and particularly genetic counseling, with her energy, her rigour, her generosity and her practical attitude to life and genetics.

I was delighted to have the opportunity to add to the molecular understanding of albinism together with an extended group of students. Our work demonstrated that the common form of albinism among South African blacks is caused by mutations in the P gene (named after the pink eyed dilute locus in the mouse). We proceeded to characterize the mutation profile in this very large gene. There is a single common mutation that deletes exon 7 and a whole spectrum of other mutations that occur more rarely. The work of Prashiela Manga, a former PhD student, showed that the rufous form of albinism is caused by two specific mutations in a gene called the tyrosinase related protein 1 (*TYRP1*) gene. This knowledge was once again translated into a diagnostic service, however, the fact that albinism is a manageable condition, means that it is seldom taken up for the purposes of prenatal testing for at risk fetuses.

What is important is that we better understand the molecular basis of albinism in Africans and can use this information to assist in dispelling myths about albinism. In the time of David Livingston newborn babies with albinism were killed at birth. The myth that tissues from people with albinism have magical properties has sadly lead to the murder of many individuals with albinism on the sub-continent, and particularly in Tanzania.

One of several intriguing questions that remain, is why the carrier rate of such a condition is so high in Africans, at about 1 in 36 individuals. Is this is just chance or is there perhaps a heterozygous carrier advantage as a result of an unknown natural selection phenomenon?

This stage of the journey can be summarized as follows:
In the seventies and early eighties it was possible, for the first time, to isolate and manipulate DNA. With the advent of the Southern blot technique we could interrogate particular genes in individuals and make inferences about the inheritance of Mendelian disorders like sickle cell disease. The nineties saw the beginning of big science projects in biology, the most notable being the human genome project.

Stage 2: The challenge of complex questions – 21st Century Science

By the turn of the century many of the genes which cause Mendelian disorders had been identified. Research efforts turned to understanding the proteins, their functions and their mechanisms of action, specifically as they relate to health and disease. The time had come to tackle the challenging questions about how to effectively identify the genetic contributions to complex multifactorial traits. How do we begin to understand gene-gene and gene-environment interactions?

The first decade of this century has been characterised by big projects in the biological sciences. In 2001 the first draft of the human genome was published, and 2003 heralded the completion of the Human Genome Project. This was followed by an unprecedented rate of discovery of genetic variants and their study in vast numbers of individuals. At this time microarray technology was beginning to mature and hundreds of thousands of genetic markers could be detected in singe experiments. These experiments can identify different types of genetic variants including single nucleotide polymorphisms and copy number variations.

The International HapMap project was started in 2002 with the aim of describing the common patterns of human genetic variation and the structure of the genome. We define this through the concept of haplotypes and linkage disequilibrium and this varies from population to population as a result of several processes. These include new mutation, recombination, natural selection and random genetic drift. To capture some of the variation, four populations were studied, the Yoruba from Nigeria, individuals of northern and western European descent, Chinese and Japanese. Phase three of the project was completed in 2009 and this initiative has produced a vast wealth of knowledge that scientists dip into on a regular basis when designing experiments.

The 1000 genomes study was launched in January 2008. It is an international effort to establish the most detailed catalogue of human genetic variation and the project is already well underway. The aim is to sequence the entire genome of at least 1000 anonymous participants from a number of different ethnic groups within a three year period. They use next generation sequencing technologies that are becoming faster and less expensive. Several African populations have been included: the Yoruba from Nigeria and the Luhya and Maasai from Kenya.

These projects provide vast amounts of data and aim to discover over 95% of genetic variants (SNPs and CNV) with frequencies as low at 1%. With this information has come the application to understanding genetic variation that underlies disease states in different populations. This is done by genome wide association studies (GWAS) on very large case-control cohorts, of tens of thousands of individuals, in order to identify highly significantly associated genetic variants. The Wellcome Trust Case Control Consortium was one of many such endeavours and more recently hardly an issue of Nature Genetics is published without at least one GWAS study.

However, despite the large sample sizes and high statistical power, highly significant associations seldom point to markers which have good predictive power for the disease under scrutiny. Unfortunately there are many companies worldwide and several in South Africa that offer genetic testing for multifactorial traits like heart disease and diabetes. These tests have very little predictive power and the advertising is almost invariably misleading. Examples include the DNA diet and wellness tests.

The lack of predictive power is exemplified by large studies on obesity. Obesity has a heritability of 40 to 70% and for which a dozen or so highly significant associations have been found. However, together as a group, they account for less than 2% of the heritability of obesity. Importantly, out of the more than 150 GWAS studies published to date over 95% have focused only on populations of European origin.

If there is one message I would like you to take from this presentation it is the fact that indigenous Africans harbour the greatest degree of genetic diversity of any population worldwide, yet they have been neglected in studies towards understanding the role of genetics in health and disease.

The vast source of untapped genetic variation was illustrated by a study which appeared in nature earlier this year with the publication of genome sequences of Emeritus Archbishop Desmond Tutu and four San individuals. This led to the discovery of 1.4 million novel single nucleotide variants, not previously documented in any databases.

To stimulate genomic research locally, we built a medium throughput genotyping facility at the NHLS as a joint initiative between the NRF, Wits and the NHLS with the capacity to investigate candidate genes in large cohorts with a view to understanding the potential contribution of genetic variation to disease states. Zane Lombard, my former PhD student and present colleague, and many of our students have now set up collaborations to explore the genetic variation in common disease states in indigenous southern Africans. These include studies on autoimmune diseases (Mohammed Tickly), obesity in the Birth to Twenty study group (Shane Norris and Nigel Crowther) with a planned replication study in another Johannesburg-based group of black Africans (Gavin Norton and Angela Woodiwiss), bone mineral density (John Pettifor and Shane Norris) and glaucoma (Sue Williams).

Genetic variation does not, however, fully explain the causality of disease and we are increasingly becoming aware of the important role of non-traditional mechanisms of transmitting information across generations. Many of these factors influence gene expression. They include cytoplasmic inheritance, mosaicism, uniparental disomy and genomic imprinting.

Role model: Judith Hall

In 1989, when I was a postdoc in London, Judith Hall visited from Vancouver and gave a lecture on non-traditional or non-Mendelian inheritance and I am embarrassed to admit that I did not even attend the lecture as the title seemed to suggest the impossible. I have now come to appreciate just how visionary Judith's research was. She was one of the first scientists of our generation to explore the highly significant impact of the environment on states of disease, hinting at the now widely studied field of epigenetics.

Others have aptly described it as follows: DNA (the genetic code) is like a book with all the words in place, neutral on a page. Epigenetics, however, happens when you read that book and in so doing experience and give it your own interpretation. This can be done in many different ways. So one book can give rise to multiple interpretations. Epigenetics therefore refers to signals superimposed on the DNA sequence that contribute to regulating gene expression.

In 1999, on Professor Jenkins' retirement as head of the Department, Denis Viljoen joined us and brought with him his interest in fetal alcohol syndrome. Fetal alcohol syndrome (FAS) has been attributed to *in utero* alcohol exposure affecting the development of the fetus. It results in stunted growth, behavioural and cognitive disability and unusual facial features. Denis succeeded in interesting me in this condition for several reasons. Firstly, it is a devastatingly common occurrence is several communities in the Western and Northern Cape, with a prevalence of over 70 per 1000 children of school going age. Secondly, there appears to be some genetic contribution to whether a fetus develops the condition or not. For example, not all mothers who drink during pregnancy have

children with FAS and in dizygotic twin pairs, they are often discordant for FAS, with one being affected and the other not. Thirdly, although an extremely difficult study in humans, for obvious reasons, there are excellent animal models to study the deleterious effects of alcohol exposure.

After some initial genetic studies in collaboration with Denis and his team from the Foundation for Alcohol Related Research, a postgraduate student, Philip Haycock, suggested that epigenetic mechanisms may be important in the teratogenic effects of alcohol. Neither of us was familiar with the field and it was early days on the road to understanding the nature of epigenetic signatures and their implications. Together we tackled the literature and after much iteration settled on a project involving a mouse model. This work was followed by further studies by a post doctoral fellow, Lillian Ouko, and another student, Jaysen Knezovich. Currently more studies by several students are aimed at understanding the role of epigenetic alterations in children with FAS. In addition, since there is much evidence to support the effect of alcohol on gametes, we are also looking at epigenetic effects on sperm DNA that could have an impact on the offspring even in the absence of maternal alcohol exposure.

Briefly discuss mouse models

This stage of the journey can thus be briefly summarised as follows: The twenty first century is about a more in depth molecular understanding of function and process. It is also about high-throughput biology. It is emphasising the complexity of science and multi-disciplinary approaches that are now necessary to conduct meaningful research.

Stage 3. Building projects for the future

It has become abundantly clear that detailed biological scientific enquiry is no longer possible for individuals working in isolation. To gain an understanding of the biological causes and processes of disease now requires groups of scientists with complementary skills and knowledge. Judith Hall and her Canadian colleagues have made a compelling argument for why institutions and governments need to better support and reward interdisciplinary health research. They wrote: "…IDHR is directly linked to translational research, which is the application of basic research to clinical practice and the generation of scientific questions through clinical observation" (Hall JG et al. CMAJ 2006)

My father, Ralph Ramsay, was an engineer who built tractors, designed a new gear to improve traction, and who set up a factory for building tractors just outside Mexico City in the early 1970s. He knew about the value of building effective teams to achieve big goals and within a short three years he could hand over the factory to the Mexican team.

Addressing the big questions in health related science is about collaboration between individuals with diverse skills and about building strong teams and networks of scientists and clinicians.

Sometimes it is necessary to build the skills-base, especially when it is in a new discipline where there is very little capacity worldwide. Since high-throughput biology has come of age and massive amounts of data are being generated in single experiments, we needed to build the discipline of bioinformatics at Wits. Bioinformatics is the development and construction of databases and tools to store, organize, select, retrieve, compare and analyse biological information. Wits Bioinformatics was therefore established in 2005 with the objective of building capacity in the discipline here at Wits.

To nurture interdisciplinary research at our University we have established Research Thrusts to heighten awareness of the research being conducted at Wits and to alert scientists to potential collaborative possibilities. I am delighted to be an active member of two Research Thrusts: Molecular Biosciences and Diseases of Lifestyle, and to be alerted to the possibilities of interdisciplinary research projects. The Sydney Brenner Institute for Molecular Bioscience, founded at Wits in 2009, has been placed at the intersection between the research activities of these groups and aims to provide an enabling research environment where excellent research on the molecular understanding of health and disease in African populations can flourish.

This reminds me to mention the well supported concept that our species, Homo sapiens, originated in Africa and that small groups left the continent in waves, taking only a subset of the genetic variation of the parental populations with them. There is now ample evidence that the greatest genetic diversity remains on the African continent in the genomes of its extant populations.

As the African diaspora has populated the world, so have we in South Africa been training scientists and a significant proportion has left the continent to explore their science in other places. This map shows the contribution from our molecular genetics laboratory to populating geneticists around the world. We are proud of the contributions they are making. We do, however, wish to attract some of them back and encourage others to stay by providing a strong research environment. I am therefore delighted that many of our graduates remain close to home.

Acknowledgements:

It is appropriate for me to thank my colleagues and collaborators and to acknowledge two institutions that have supported me throughout the past three decades and provided me with great opportunities and support to pursue my research: The South African Institute for Medical Research which became the National Health Laboratory Service in 2001 and the University of the Witwatersrand. At these institutions I have been immersed in a collegiate fellowship of mentors, role models, colleagues, talented young scientists and inspiring students.

I wish to acknowledge the dedicated molecular laboratory diagnostic team led at different times by Debbie Morris, Andy Goldman, Robyn Kerr and currently by Fahmida Essop. They have flourished due to the extraordinary commitment, supervision and oversight by Professor Amanda Krause.

Research cannot be done without funding and I have been the grateful recipient of funds from the following: SAIMR/NHLS, Wits, MRC, NRF, March of Dimes (US) and more recently the NIH (US) and DST.

CONCLUSON:

My journey is about knowledge discovery and understanding genetic variation and its implications for the health of the peoples of the African continent. It is therefore gratifying to participate in the unfolding of two new projects, the Southern African Human Genomes Project and the Human Heredity and Health in Africa Project (H3Africa).

John Dewey, an American philosopher and educational reformer said: “Every great advance in science has issued from a new audacity of the imagination.”

I therefore encourage our young scientists to think and to dream. However, they must do so with scientific rigour and a sound knowledgebase.

PARALLEL JOURNEYS

The birth and growth of molecular genetics and its influence on a career spanning three decades



NATIONAL HEALTH
LABORATORY SERVICE



Michèle Ramsay

Division of Human Genetics

NHLS & University of the Witwatersrand

30 August 2010

Stage 1
The beginnings of molecular genetics and translational science



Stage 2
The challenge of complex questions



Stage 3
Building projects for the future

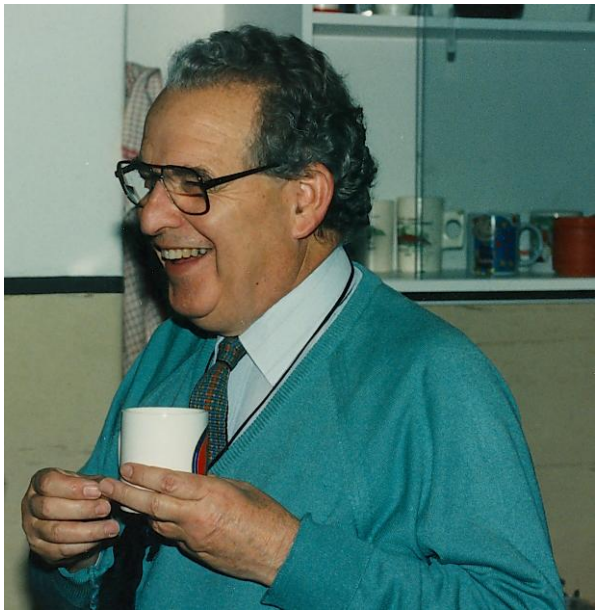


Stage 1
The beginnings of molecular genetics and translational science

Eigthties and Nineties

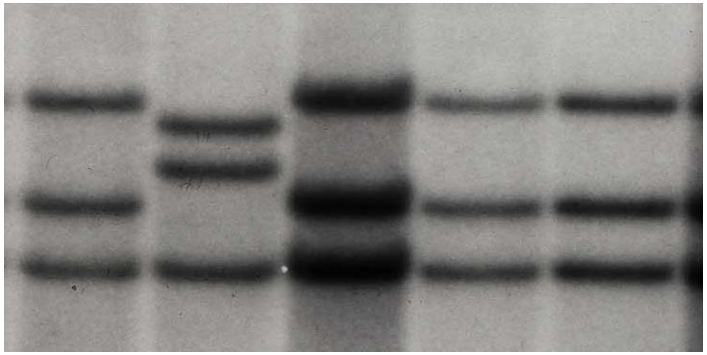


Trefor Jenkins









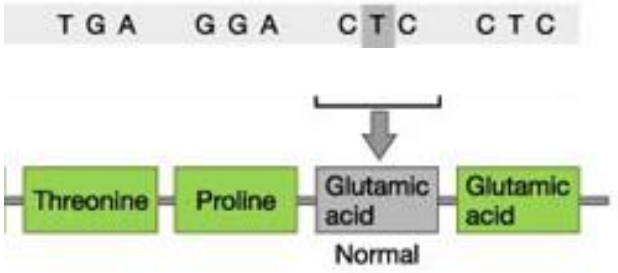
Tsumkwe - Bushmanland

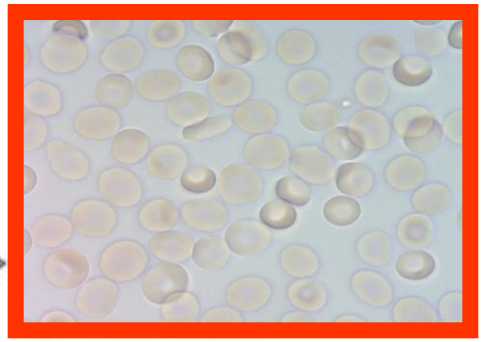




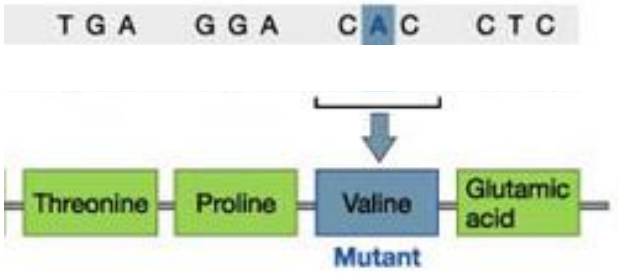


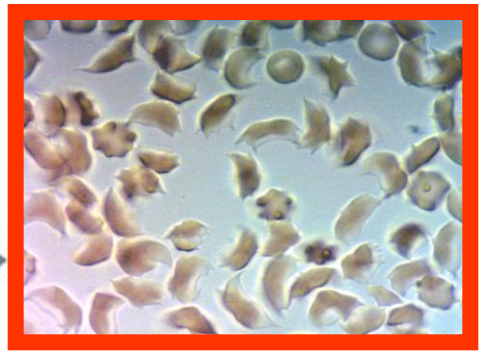
Diagnostic tests: Sickle cell anaemia





Normal red blood cells





Sickle red blood cells

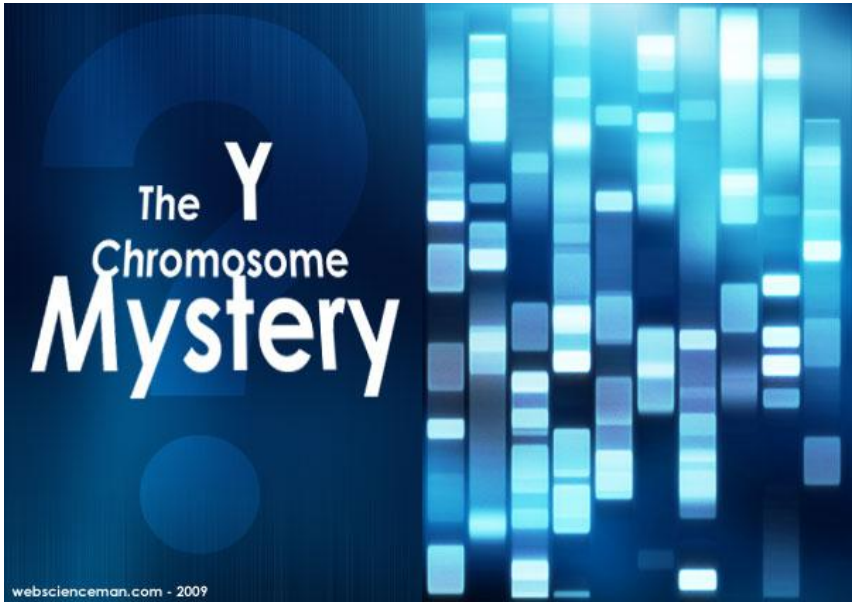
Antenatal diagnosis of sickle-cell anaemia by means of DNA restriction analysis

MICHÈLE RAMSAY, JENNIFER A. THOMSON, T. JENKINS

South African Medical Journal, July 1984

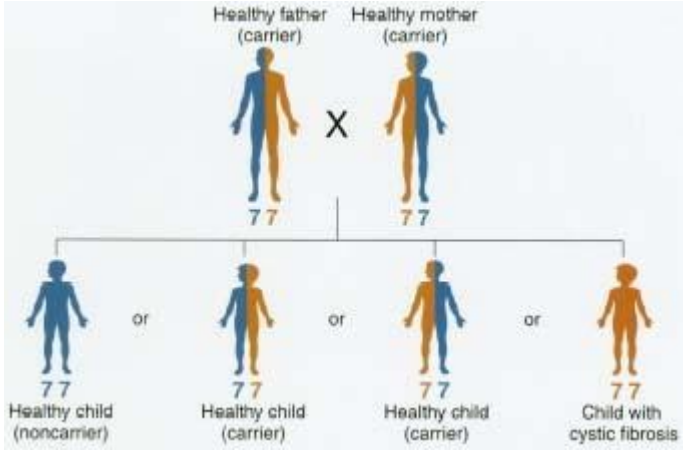
Renèe Bernstein

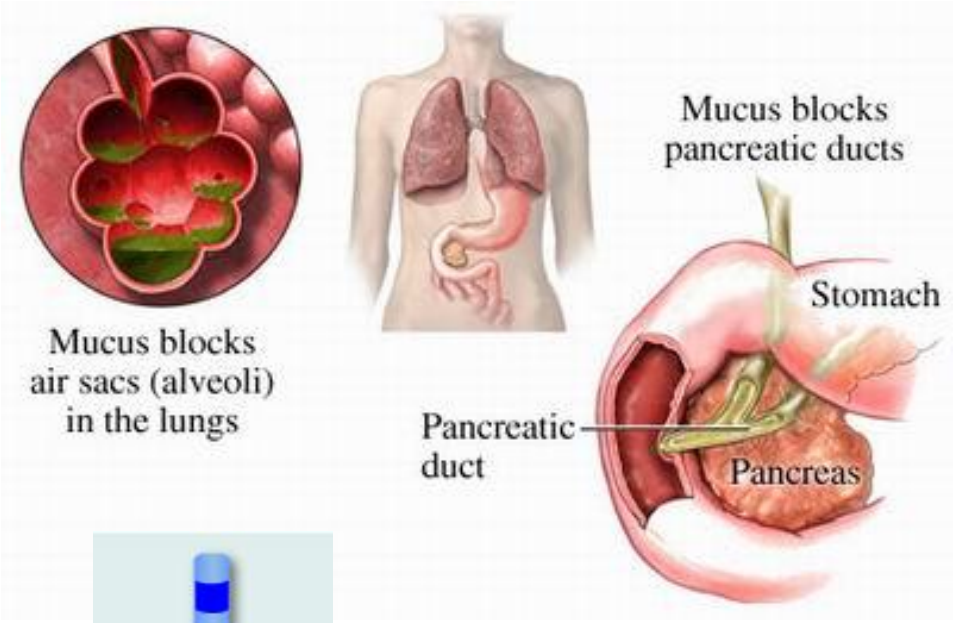




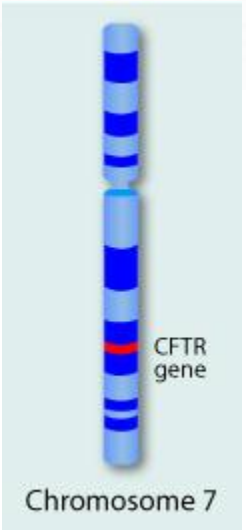
The Era Gene Hunting

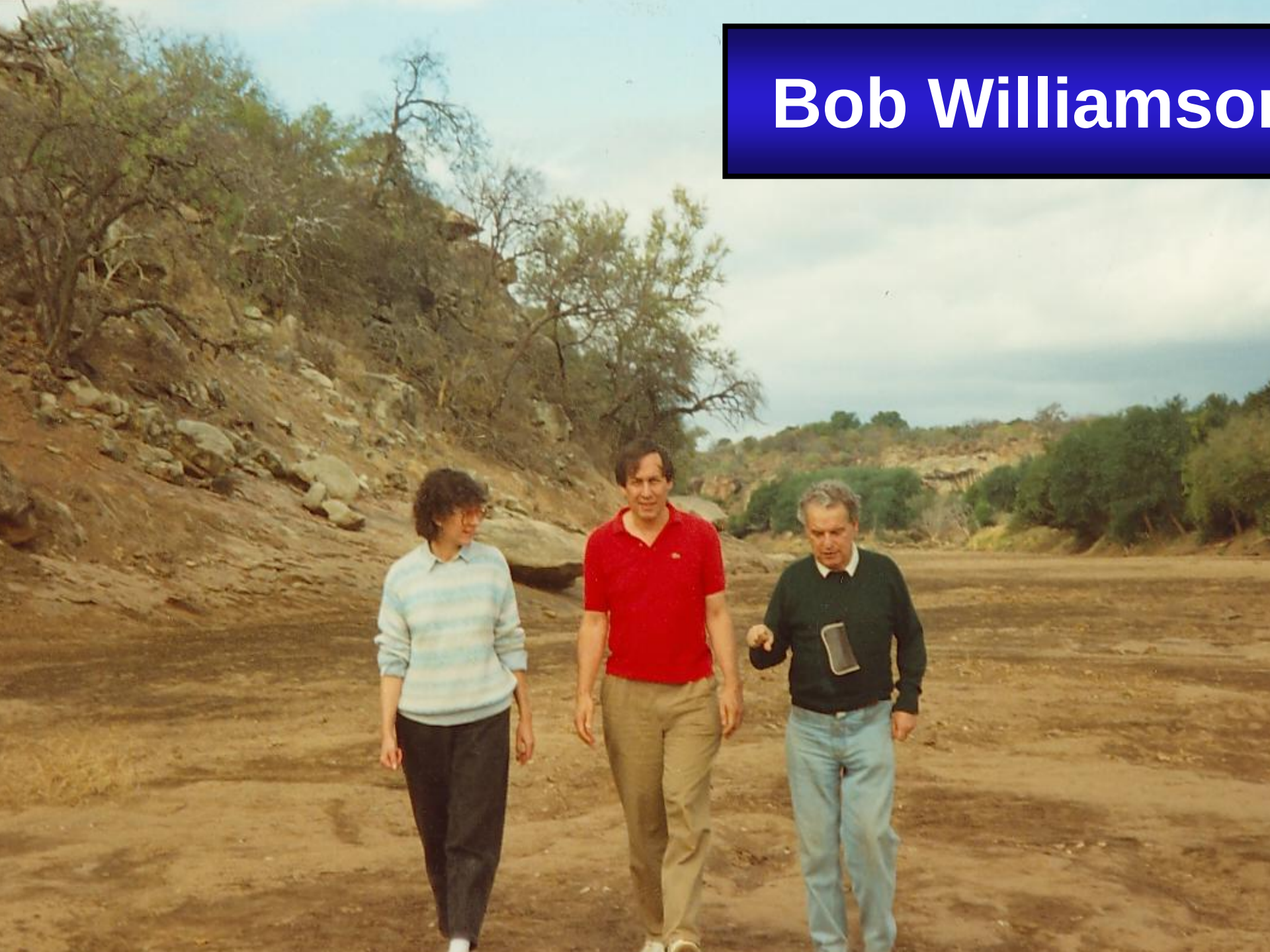
Cystic Fibrosis

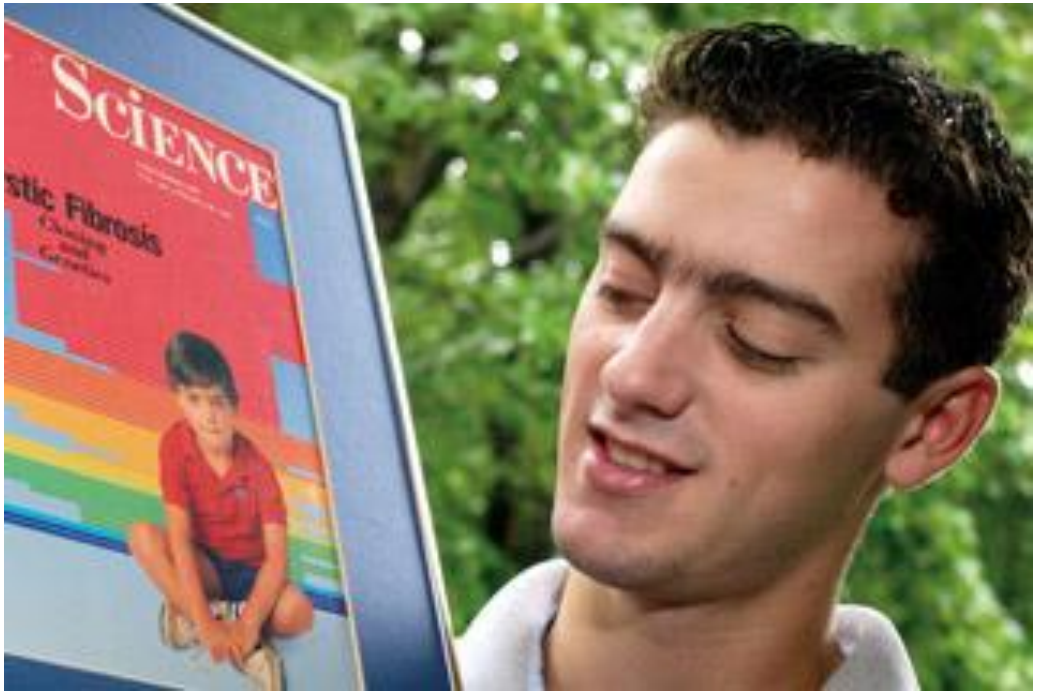


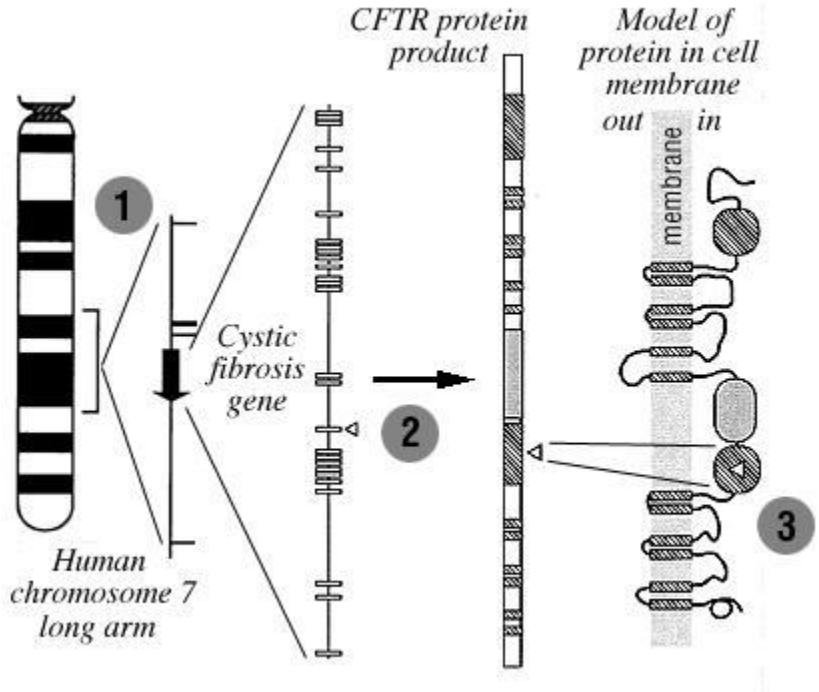


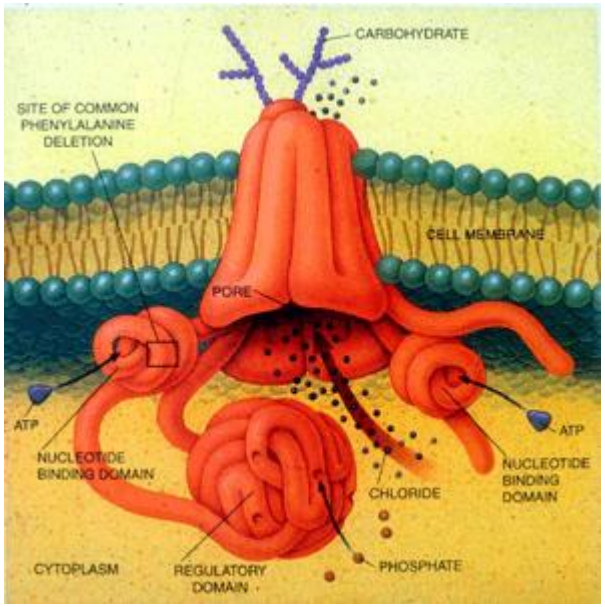




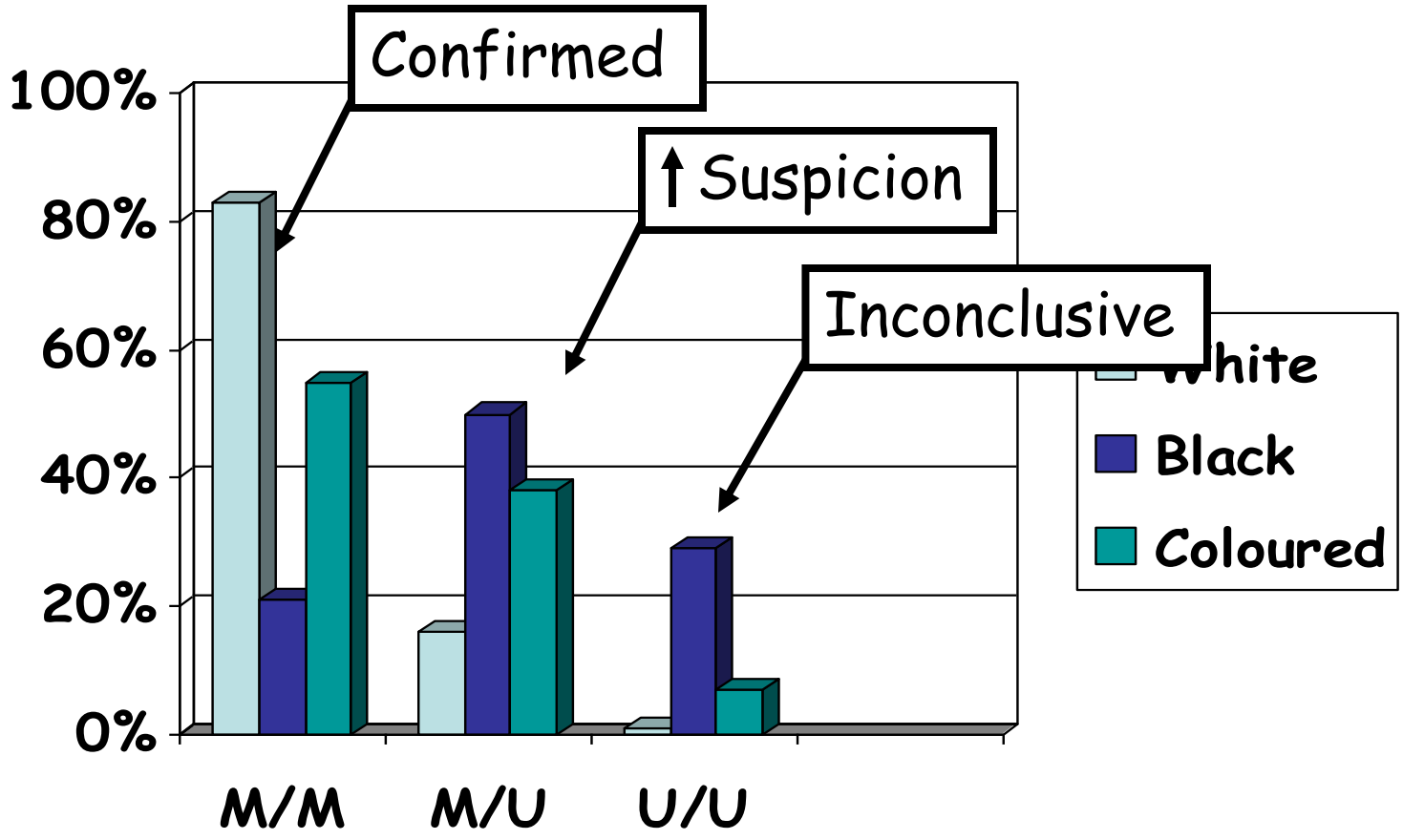

Bob Williamson


SCIENCE


CFTR protein product
Model of protein in cell membrane
out
in
membrane
1
Cystic fibrosis gene
2
3
Human chromosome 7 long arm


CARBOHYDRATE
SITE OF COMMON PHENYLALANINE DELETION
CELL MEMBRANE
PORE
ATP
NUCLEOTIDE BINDING DOMAIN
CHLORIDE
ATP
NUCLEOTIDE BINDING DOMAIN
CYTOPLASM
REGULATORY DOMAIN
PHOSPHATE

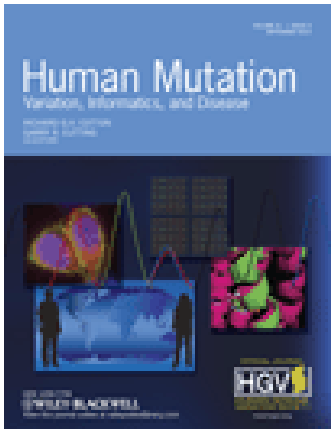
Confirmation of CF diagnosis



Detection rates: White-91% Black-46% Coloured-74.4%

Mireille Claustres

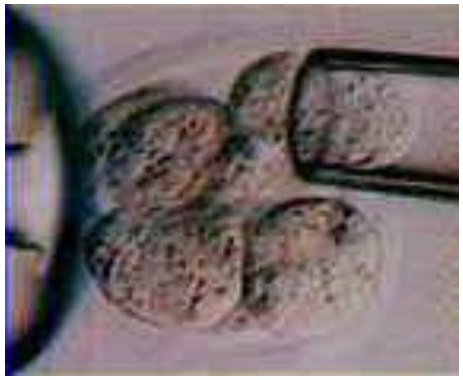




UMD-*CFTR*: A database dedicated to CF and *CFTR*-related disorders

C Bareil et al. and Mireille Claustres

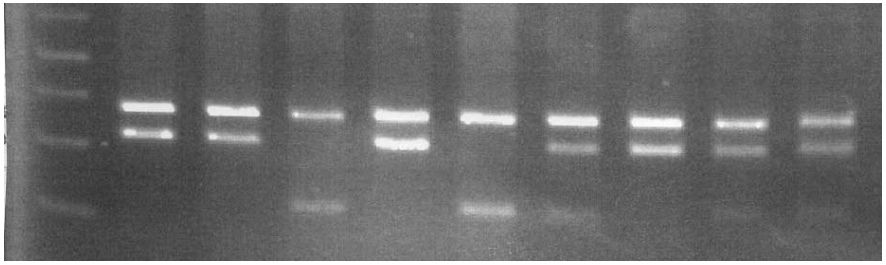
Human Mutation 6 JUL 2010

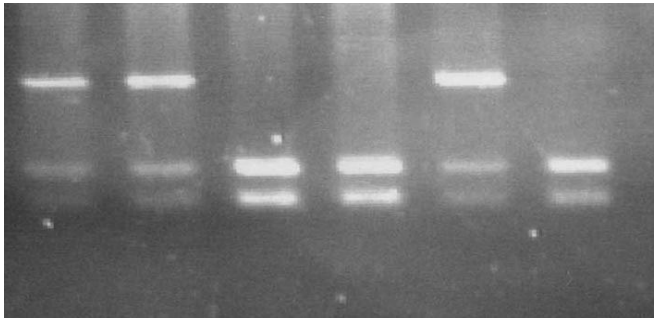


PCR



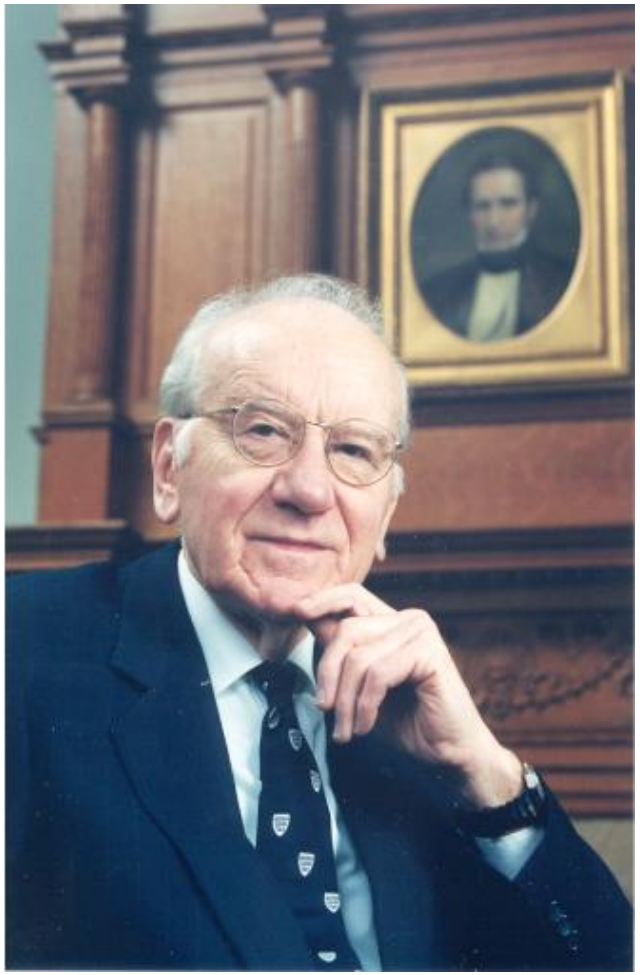






OMIM

http://www.ncbi.nlm.nih.gov



Compendium of human genes and genetic phenotypes

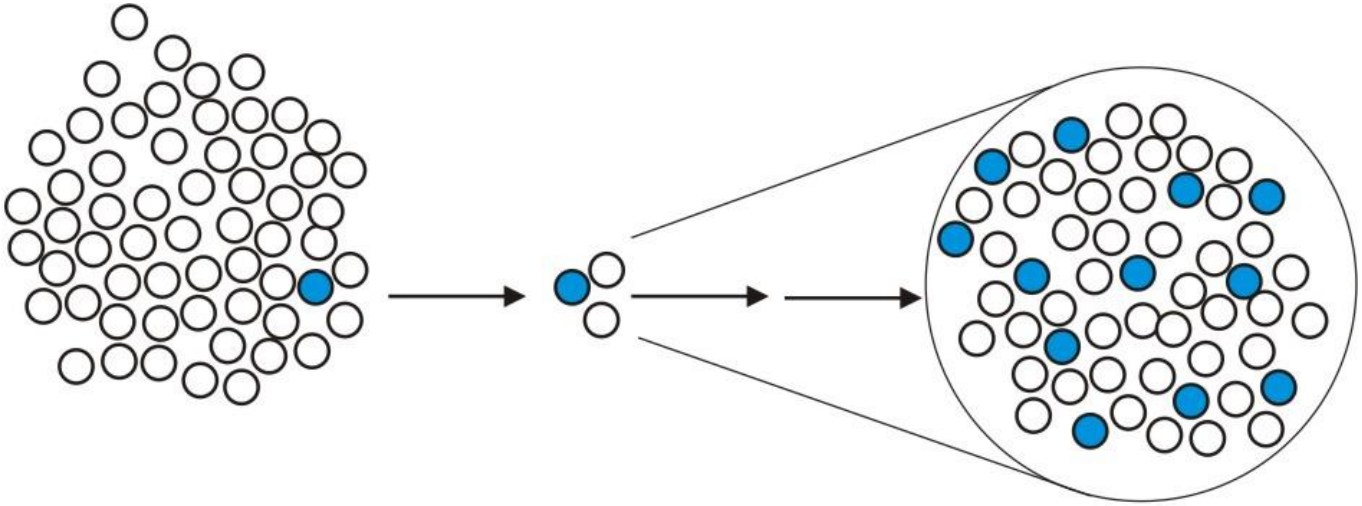
OMIM focuses primarily on inherited, or heritable, genetic diseases

History:
- **Initiated in 1960's by Victor McKusick**
- **12 Book editions (1966 to 1998)**
- **online since mid 1980s**
- **All known Mendelian Disorders**
- **Information on over 12 000 genes**
- **Updated daily**

Victor McKusick

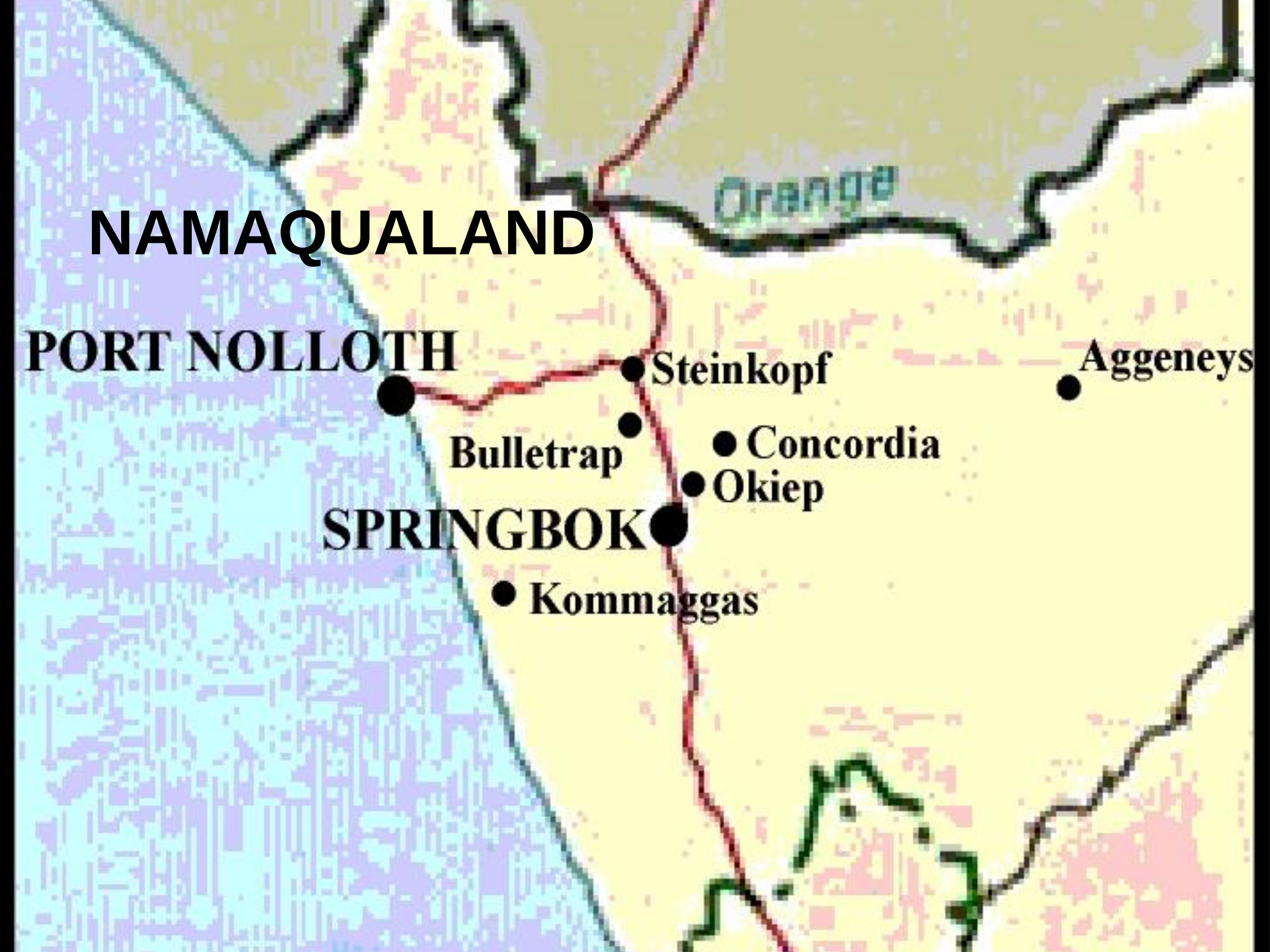
Lipoid proteinosis (LP)





Original population	Founding population	A later population
eg. Holland in the 17th Century	Collonists to South Africa	in South Africa in the 21st Century
Low	High	High

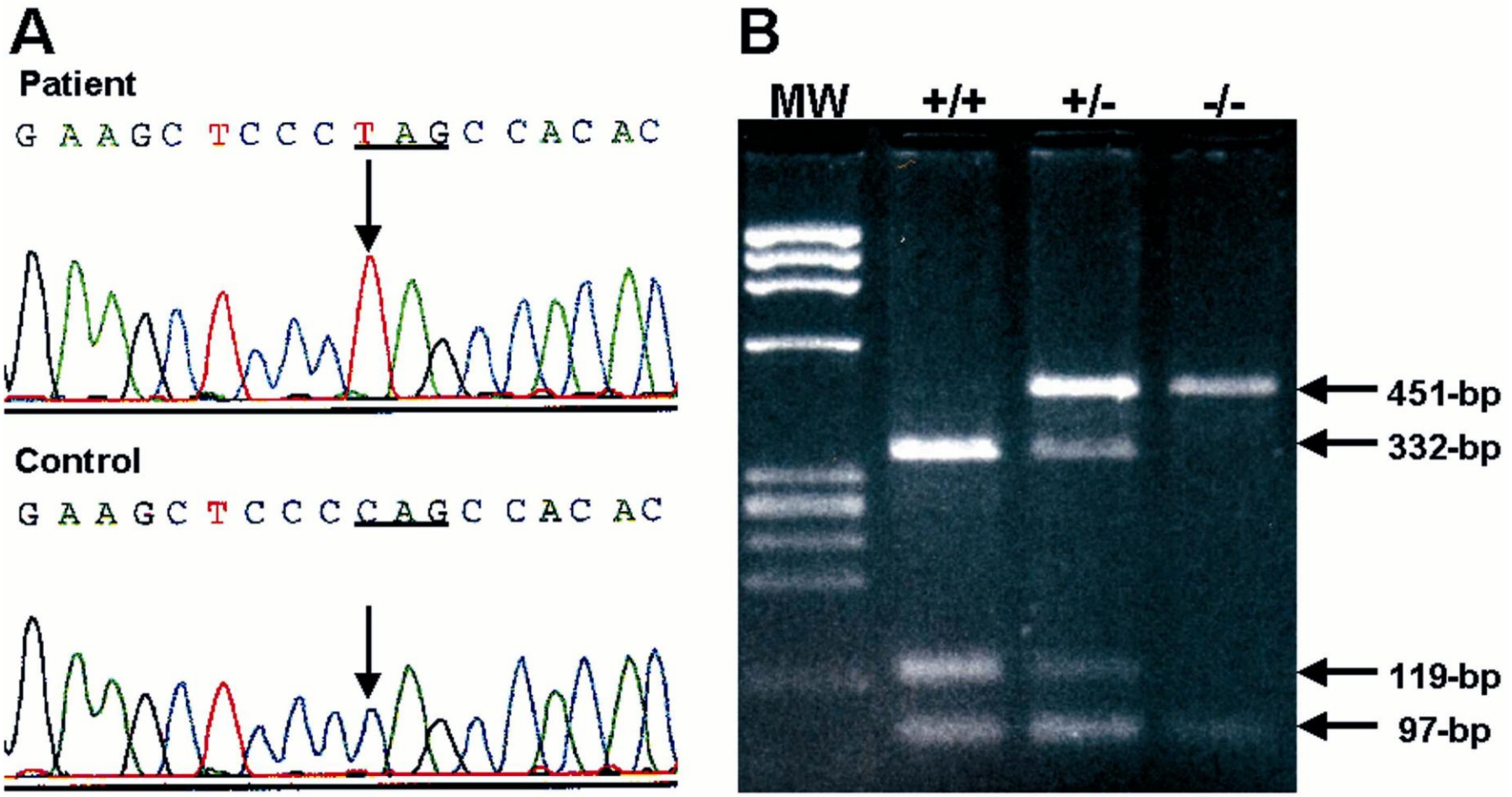

Cape Town International Airport
Streamline
nac
737
320


NAMAQUALAND
Orange
PORT NOLLOTH
Steinkopf
Aggeneys
Bulletrap
Concordia
Okiep
SPRINGBOK
Kommaggas





Extracellular matrix protein 1 (*ECM1*)



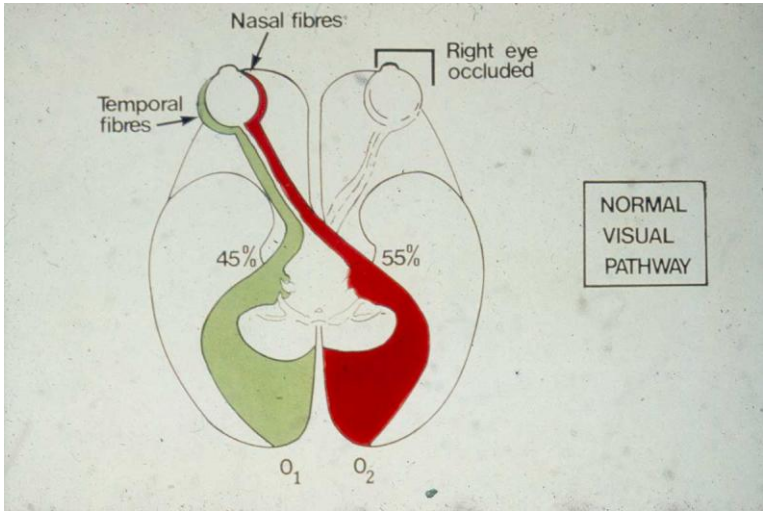


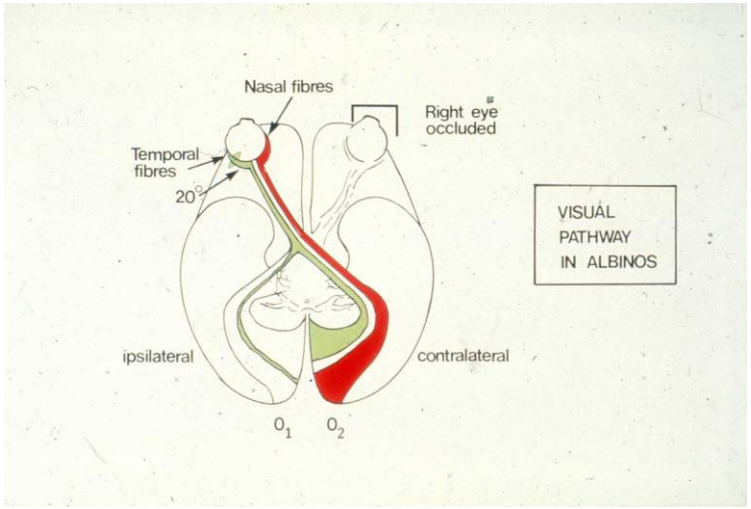
1875


Michael Friederich Dongez.
Geb. d. 2 Augustus 1867.
Gest. d. 3 Mei 1878.
"Ja Ik heb u liefgehad met eene eeuwige liefde!"
Jer. 31. 3.

ALBINISM




Nasal fibres
Right eye occluded
Temporal fibres
45%
55%
O_1
O_2
NORMAL VISUAL PATHWAY


Nasal fibres
Right eye occluded
Temporal fibres
20%
VISUAL PATHWAY IN ALBINOS
ipsilateral
contralateral
O_1
O_2

Jennifer Kromberg







Esther Zwane







Myths

More questions

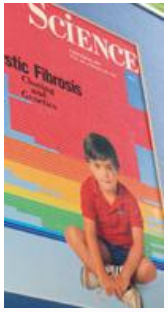
Annotated genome databases

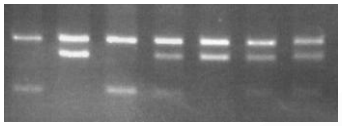
HGP started

Disease related information from over 12 000 genes

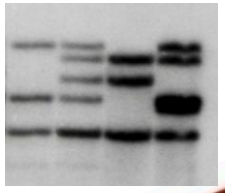
CF

PCR





SB



OMIM

1990

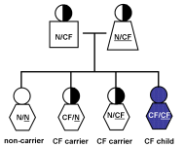
2000





LP gene

CF in black Africans

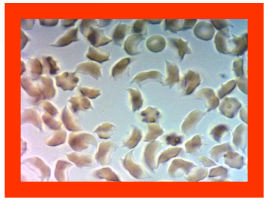


Y chromosome

1980

Molecular genetics diagnostic laboratory





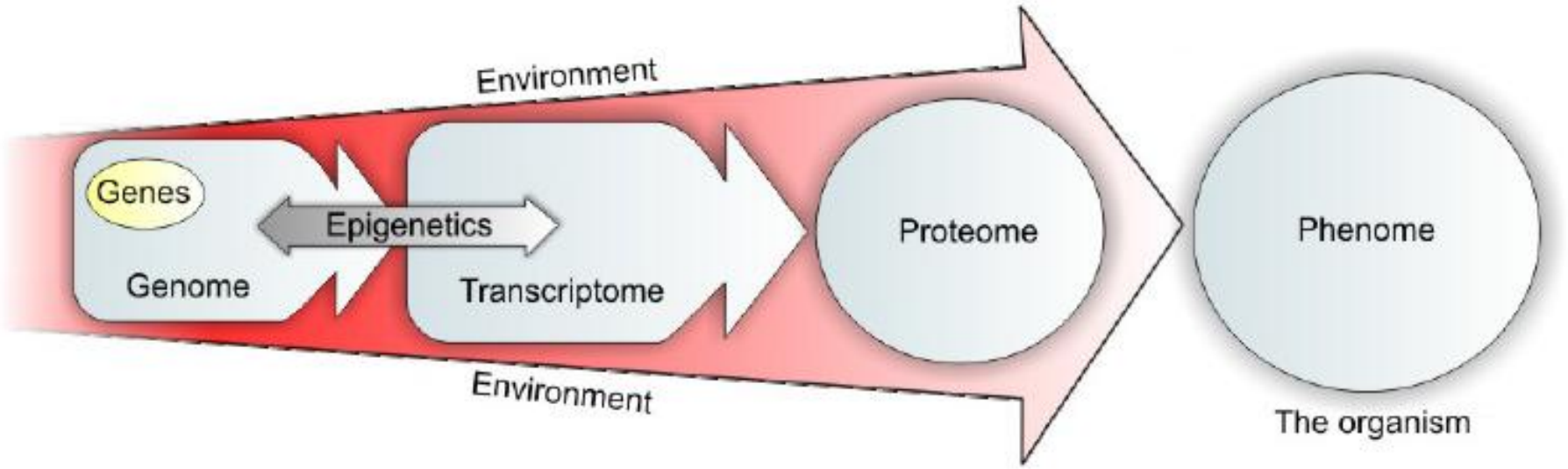
Prenatal diagnosis by DNA analysis

Stage 2
The challenge of complex questions

Twenty First Century Science



From genome to phenotype



Gene-gene and gene-environment interactions



Nature, 15 Feb 2001



Science, 16 Feb 2001

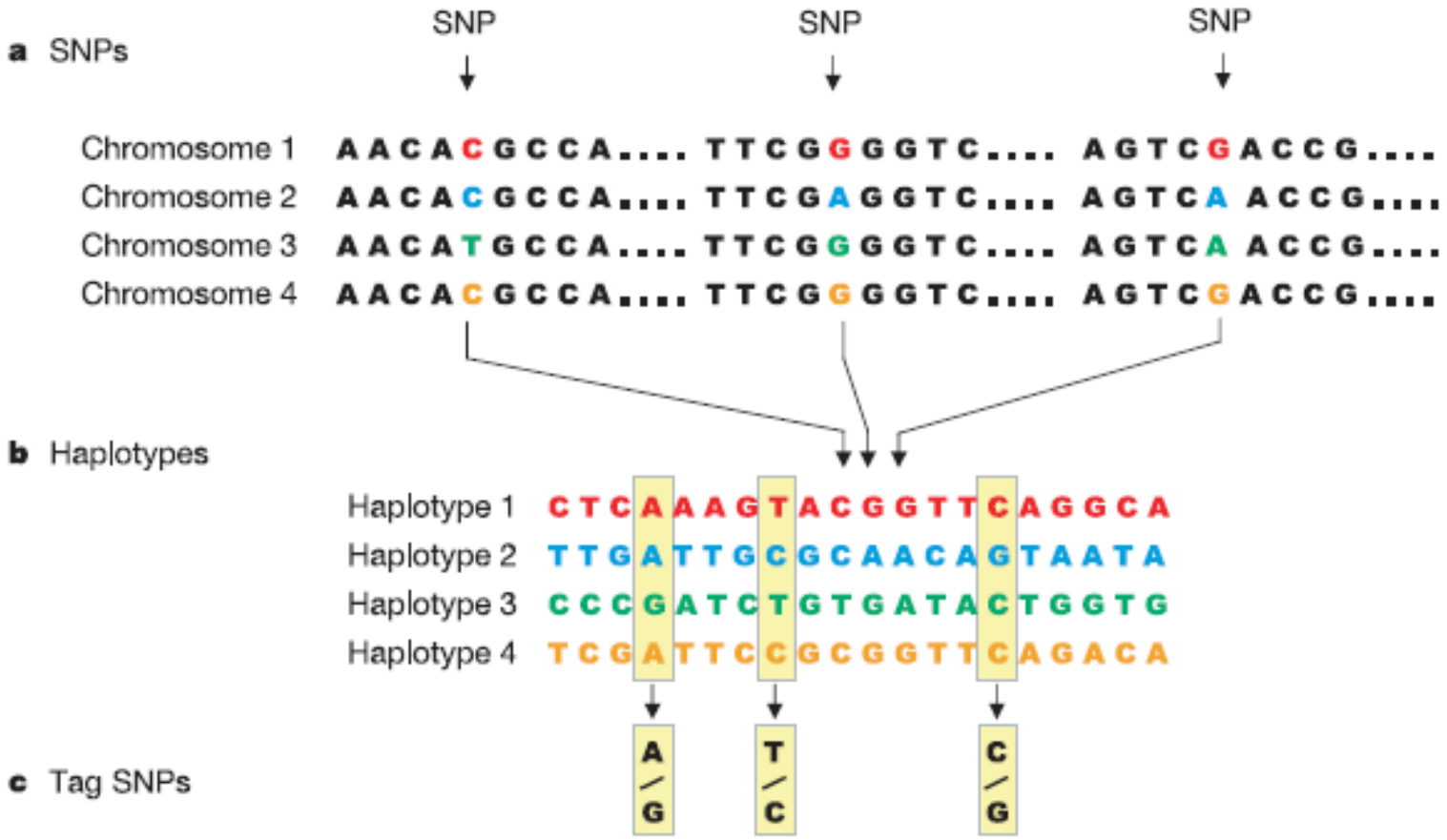
? ? ?



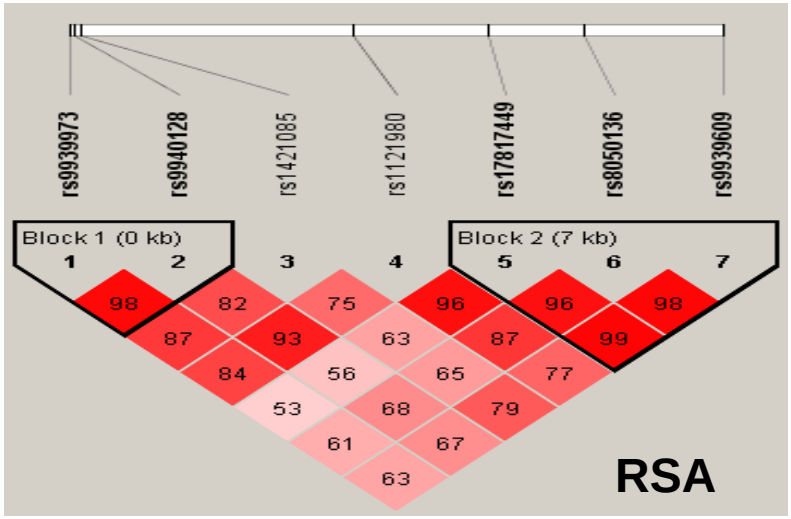


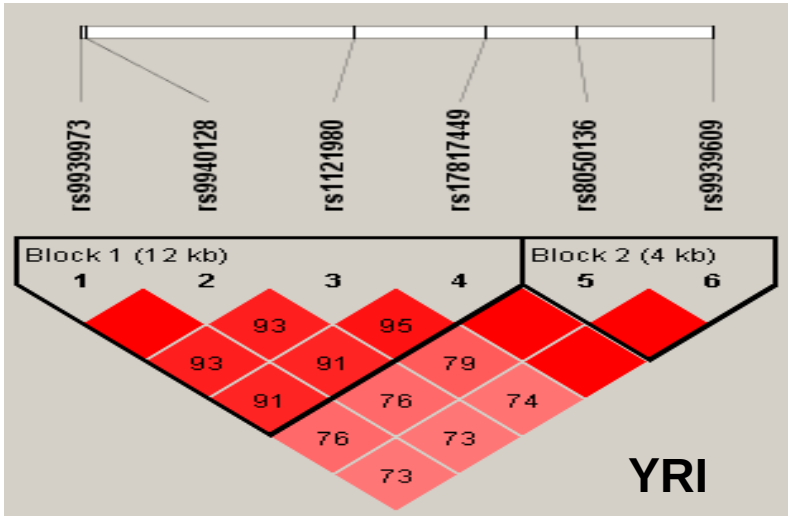
HapMap Project 2002

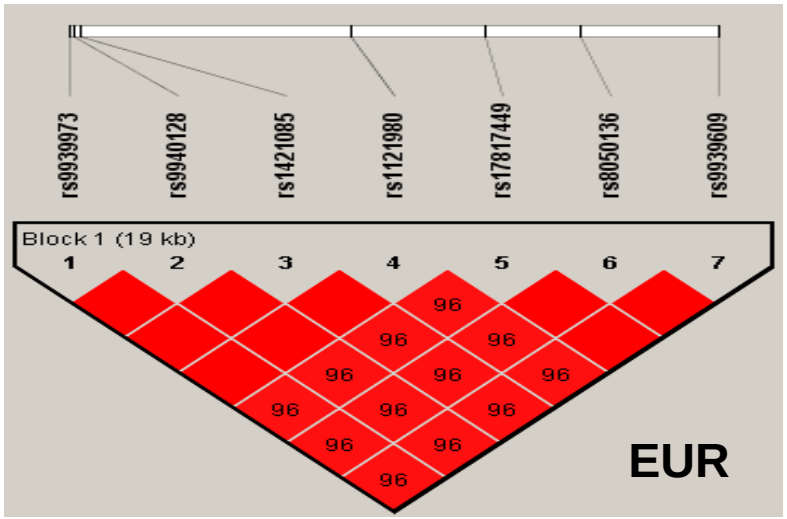
Common patterns of human genetic variation and the structure of the genome

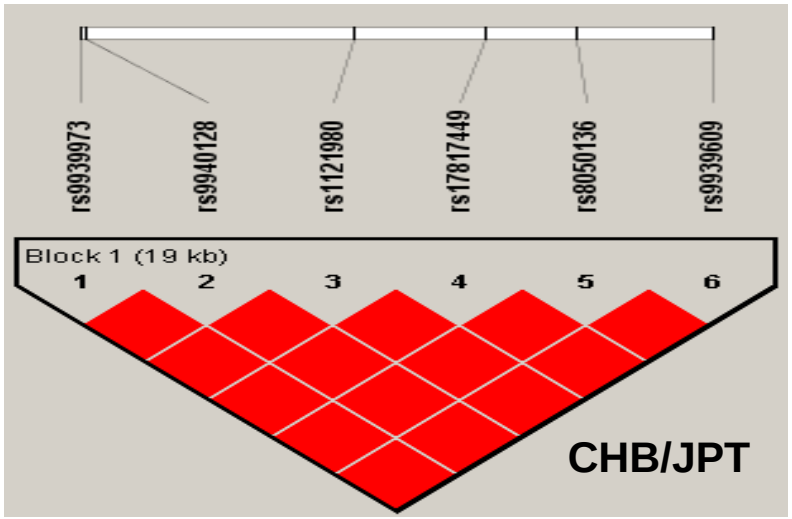


The International HapMap Consortium: Nature (Dec 2003)


rs9939973
rs9940128
rs1421085
rs1121980
rs17817449
rs8050136
rs9939609
Block 1 (0 kb)
Block 2 (7 kb)
1 2 3 4 5 6 7
98
82 75 96 96 98
87 93 63 87 99
84 56 65 77
53 68 79
61 67
63
RSA


rs9939973
rs9940128
rs1121980
rs17817449
rs8050136
rs9939609
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Block 2 (4 kb)
1 2 3 4 5 6
93 95
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96
96 96
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96 96
96
EUR


rs9939973
rs9940128
rs1121980
rs17817449
rs8050136
rs9939609
Block 1 (19 kb)
1 2 3 4 5 6
CHB/JPT

SNP discovery (2000-2005)

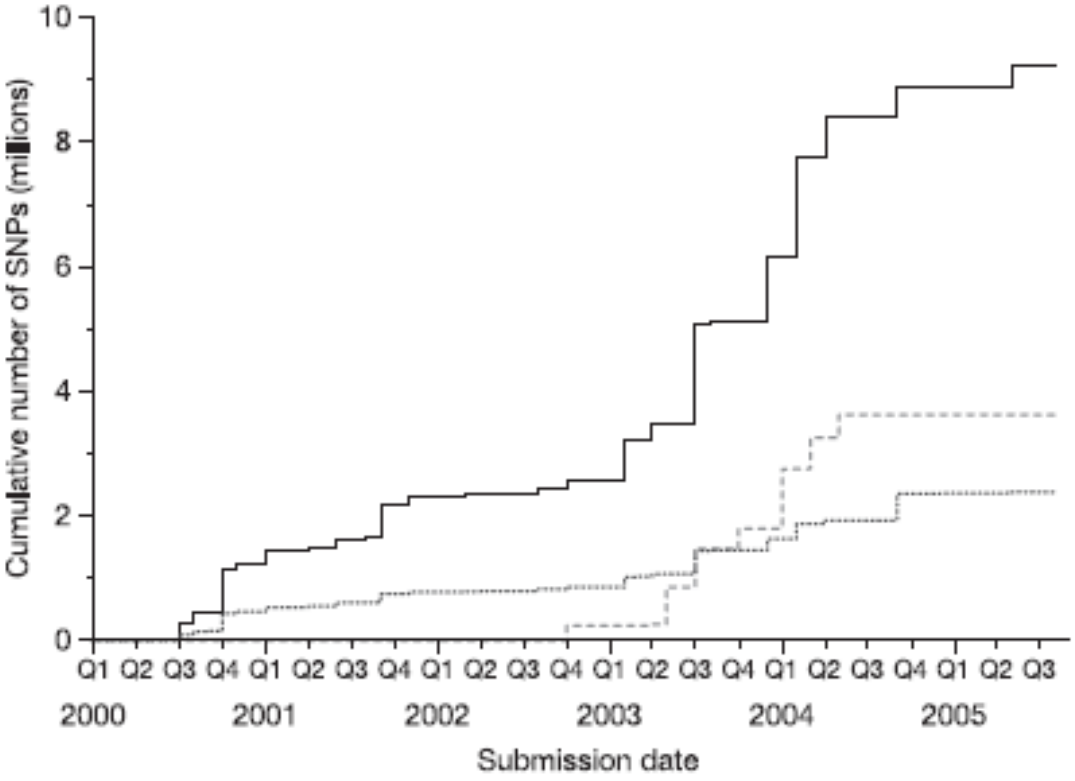


Figure 1 | Number of SNPs in dbSNP over time. The cumulative number of non-redundant SNPs (each mapped to a single location in the genome) is shown as a solid line, as well as the number of SNPs validated by genotyping (dotted line) and double-hit status (dashed line). Years are divided into quarters (Q1–Q4).

<u>February 2010:</u>

dbSNP Build 131

Genome build: 37.1

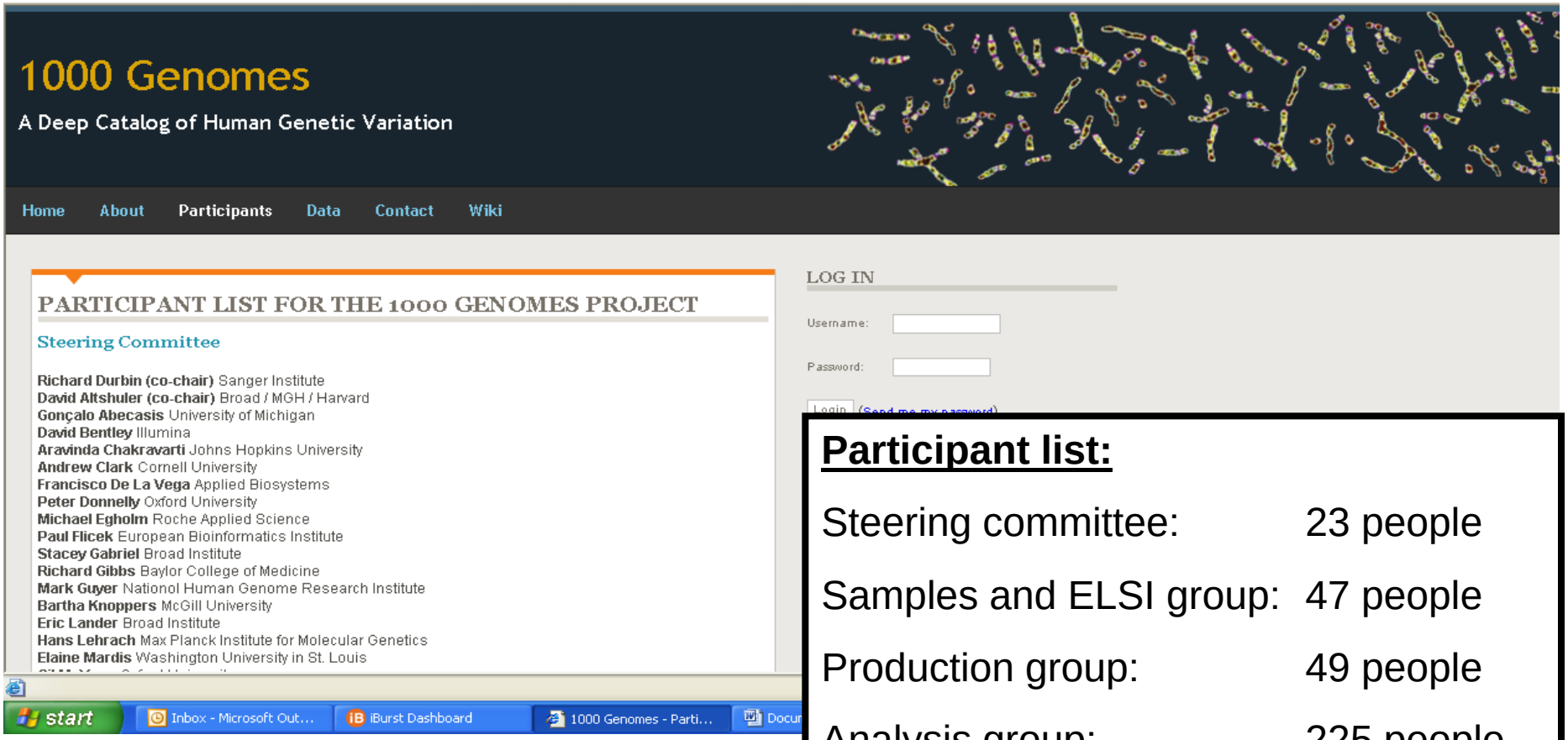
Submissions: 92 364 155

Reference SNPs: 17 804 036

Validated: 9 468 384

Frequency info: 803 969

The International HapMap Consortium: Nature (Oct 2005)



Participant list:

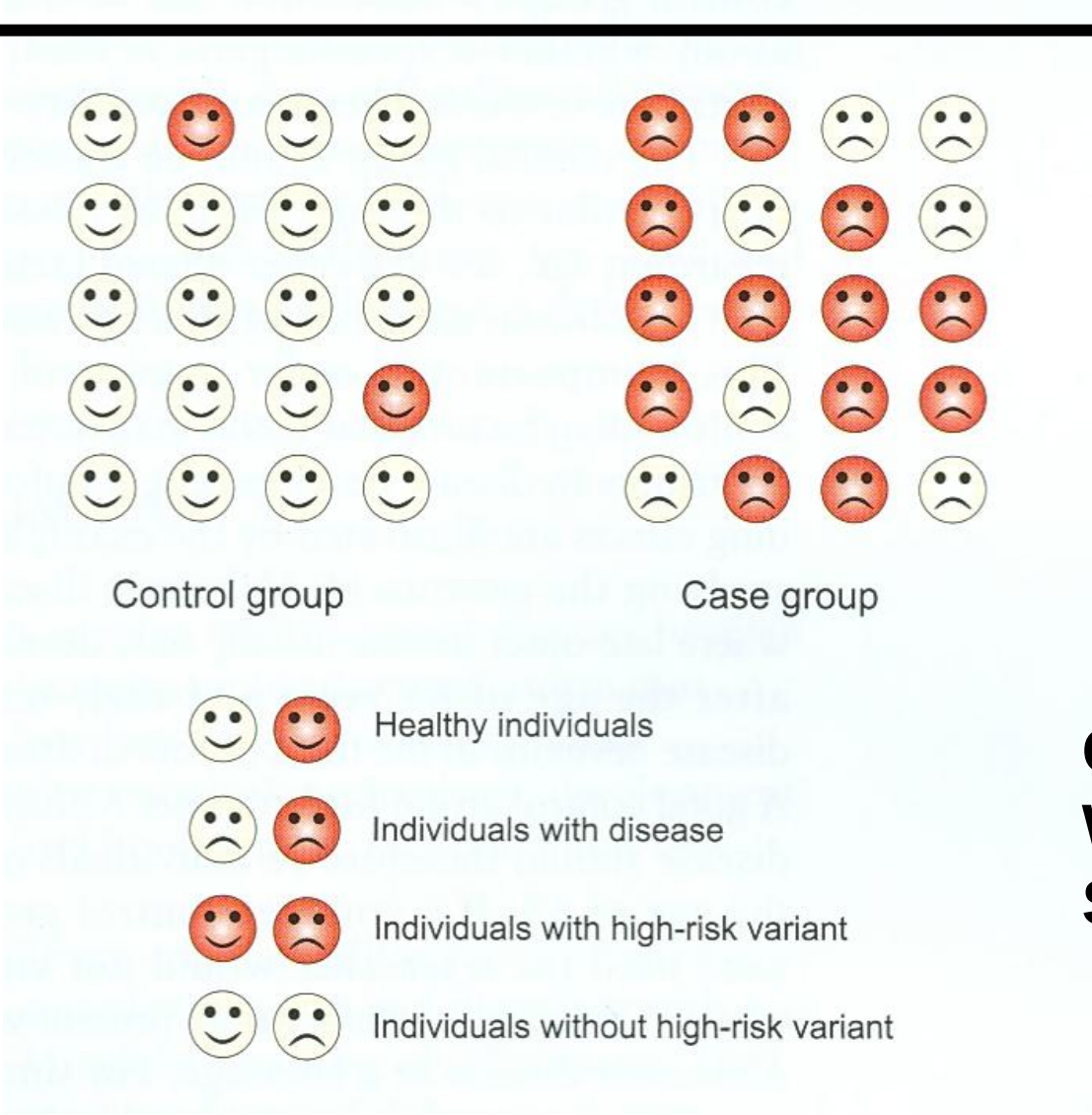
Steering committee:	23 people
Samples and ELSI group:	47 people
Production group:	49 people
Analysis group:	225 people
Data flow group:	44 people

January 2008

http://www.1000genomes.org/

Discover over 95% of genetic variants with frequencies as low as 1%

Case control association studies

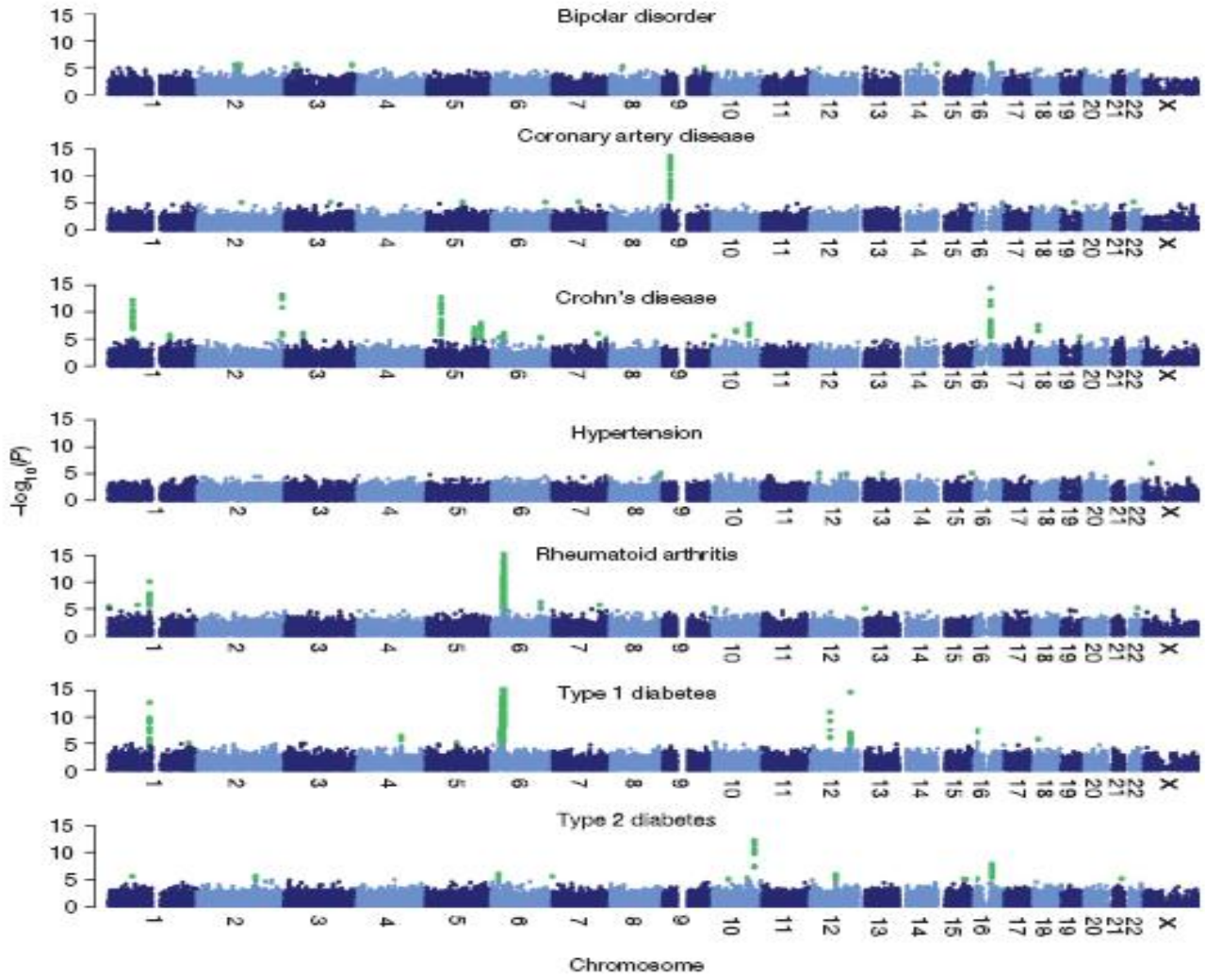


GWAS – Genome Wide Association Studies

Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls

The Wellcome Trust Case Control Consortium*

Nature (2007) Vol. 447



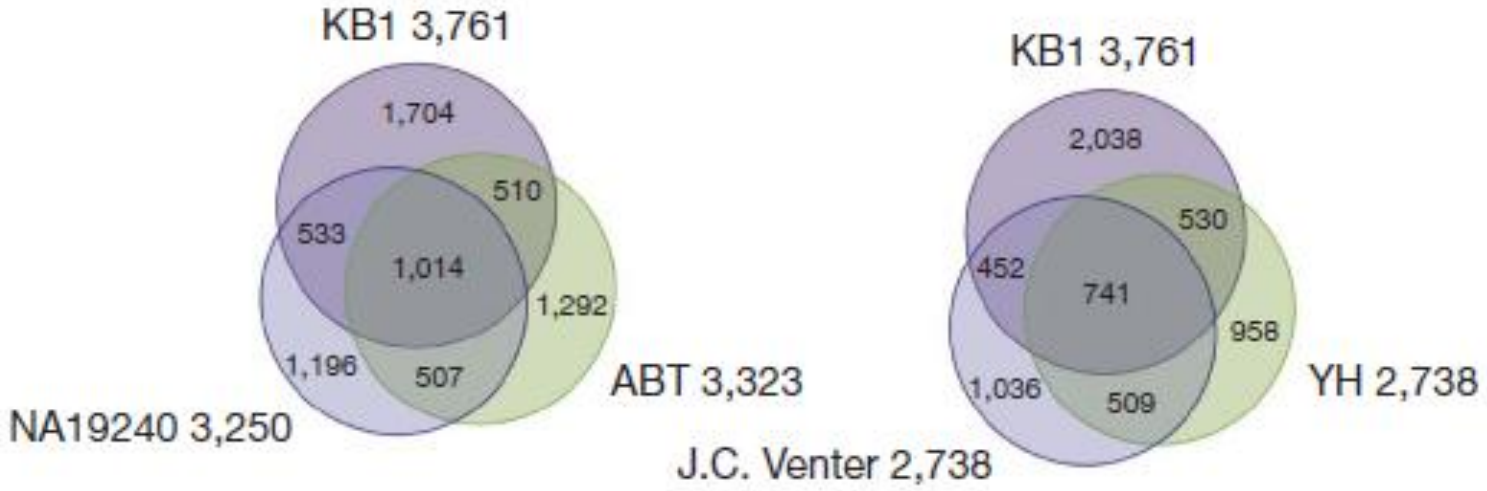
Obesity

Personalised medicine

Complete Khoisan and Bantu genomes from southern Africa

Nature, 18 February 2010





Genotyping Facility



Zané Lombard & Punita Pitamber

Collaborations

Judith Hall





Non-Mendelian inheritance

Cytoplasmic inheritance

Mosaicism

Uniparental disomy

Genomic imprinting

EPIGENETICS

Fetal Alcohol Syndrome
FAS

- **Stunted growth**
- **Behavioural & Cognitive disability**
- **Unusual facial features**







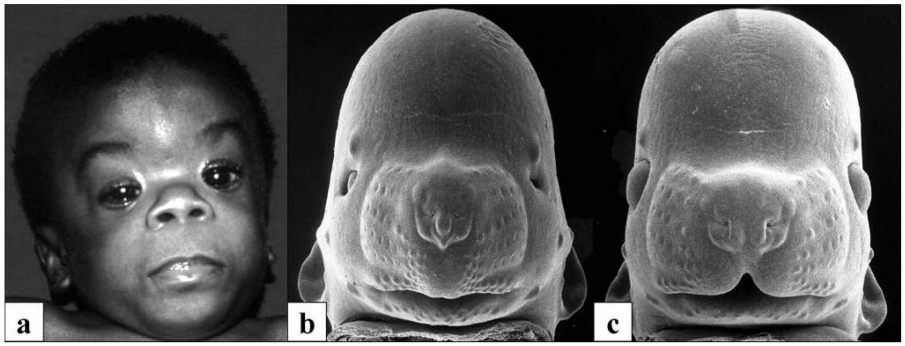
1. **65.2-74.2 / 1000 children (5-9 years)**
Viljoen *et al.* 2005 Stud Alcohol: 66 p593-604

2.



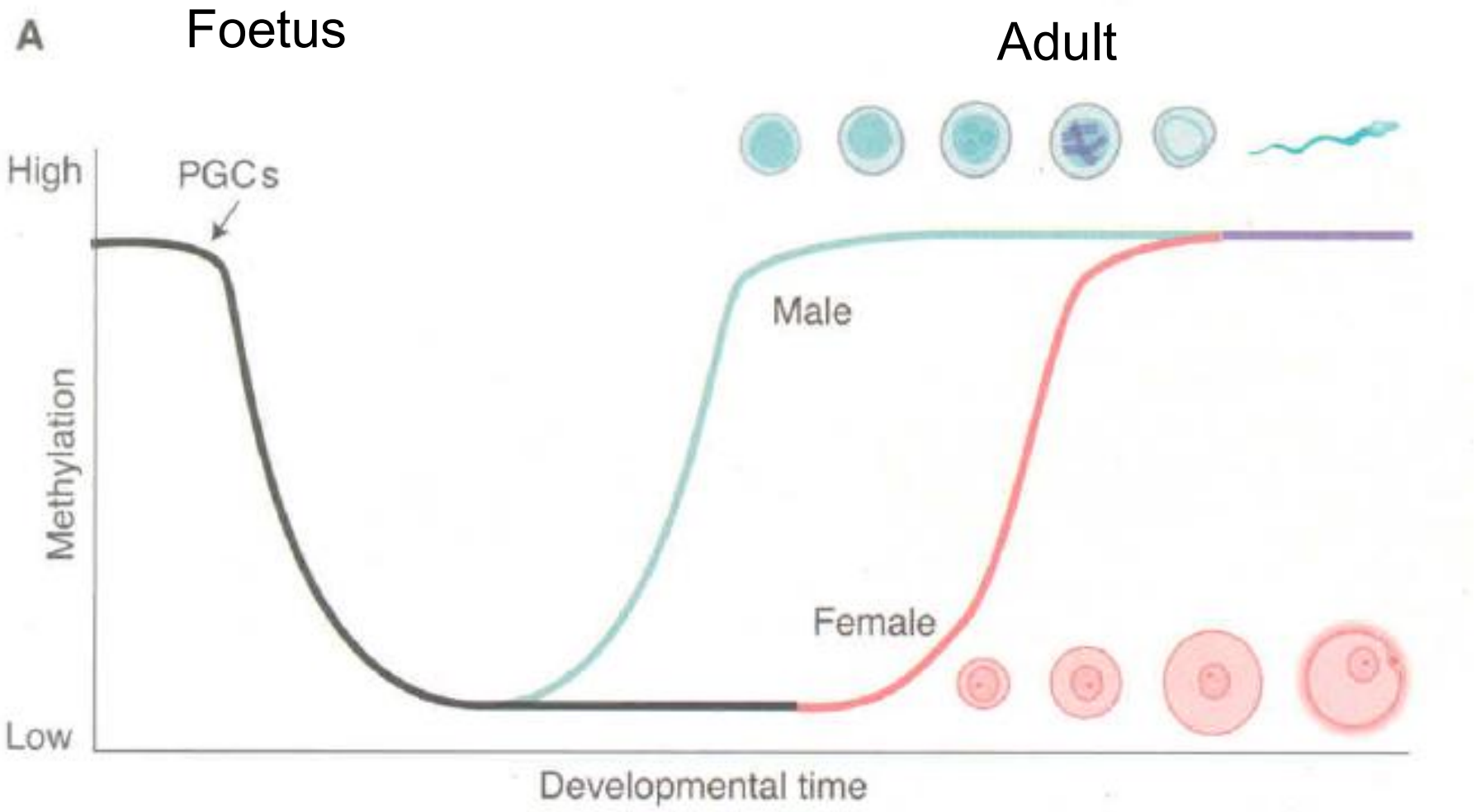


3.



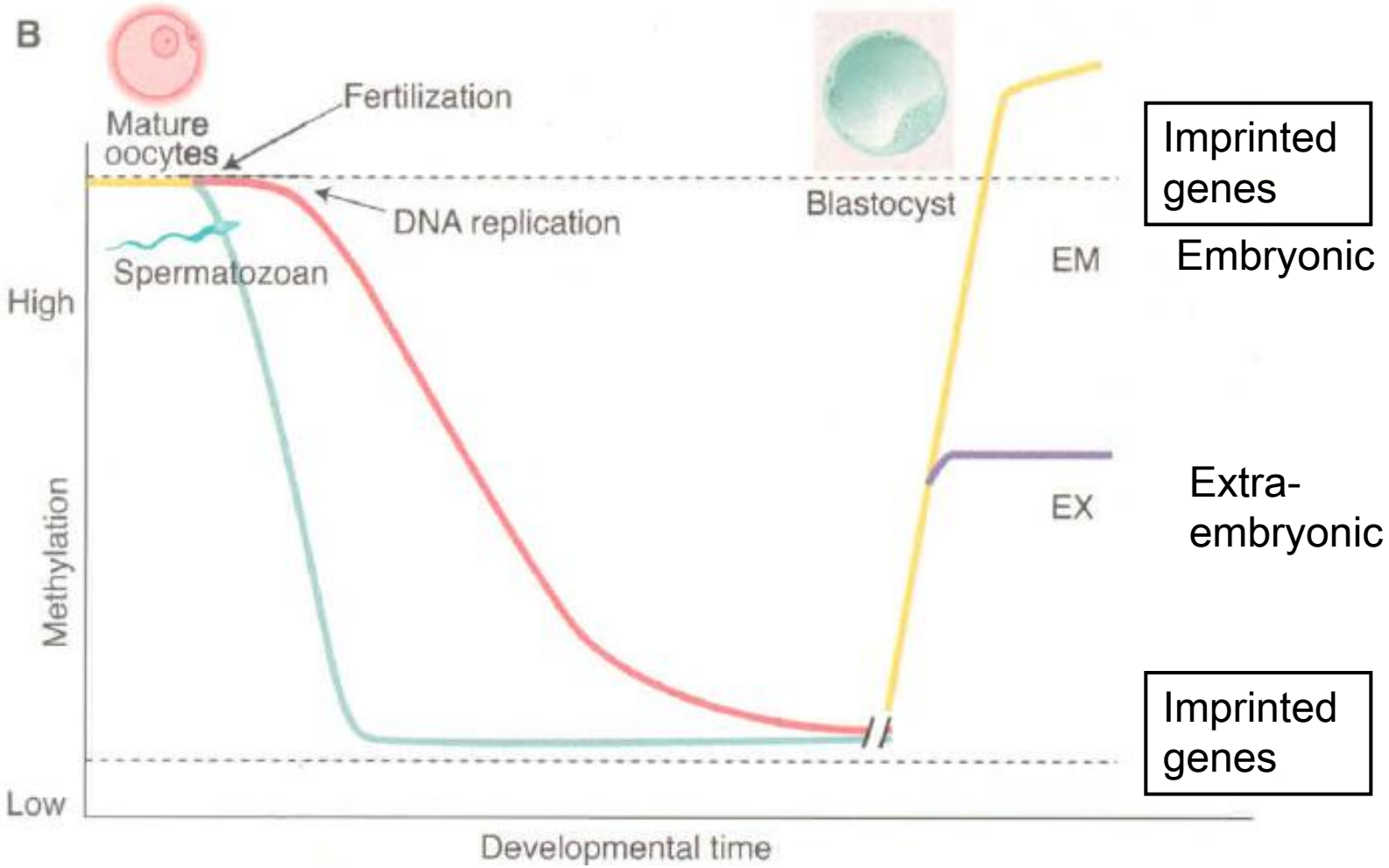


Germ line methylation reprogramming



Reik et al. 2001 Science 293:1089

Preimplantation embryos – methylation reprogramming



Reik et al. 2001 Science 293:1089

Preimplantation effect of alcohol in a mouse model

Igf2/H19 gene cluster – fetal growth and placental differentiation





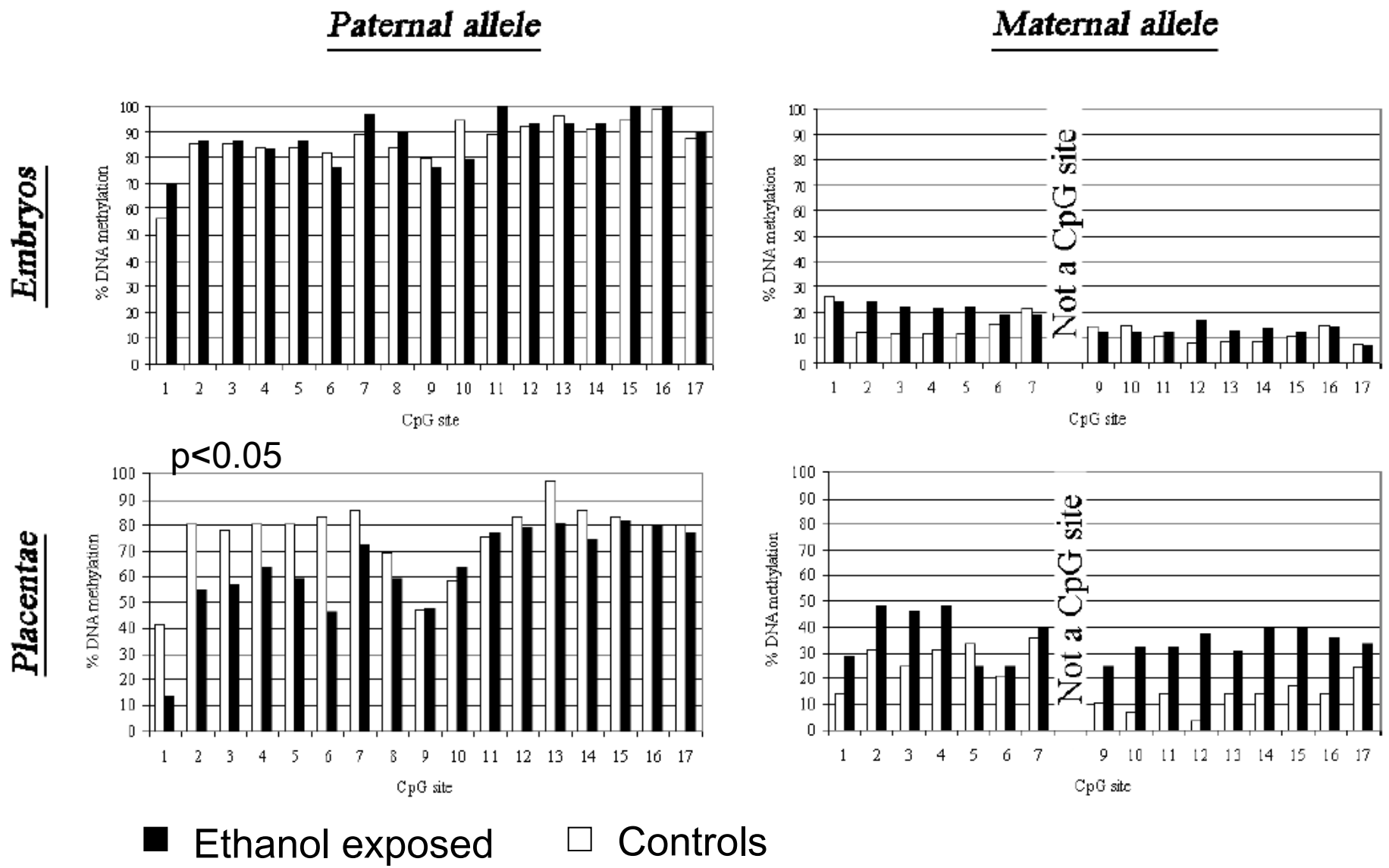
Ethanol exposure: acute dose at 1.5 and 2.5 dpc (2.9g/kg)

Harvest: 10.5 dpc

Effect on weight:

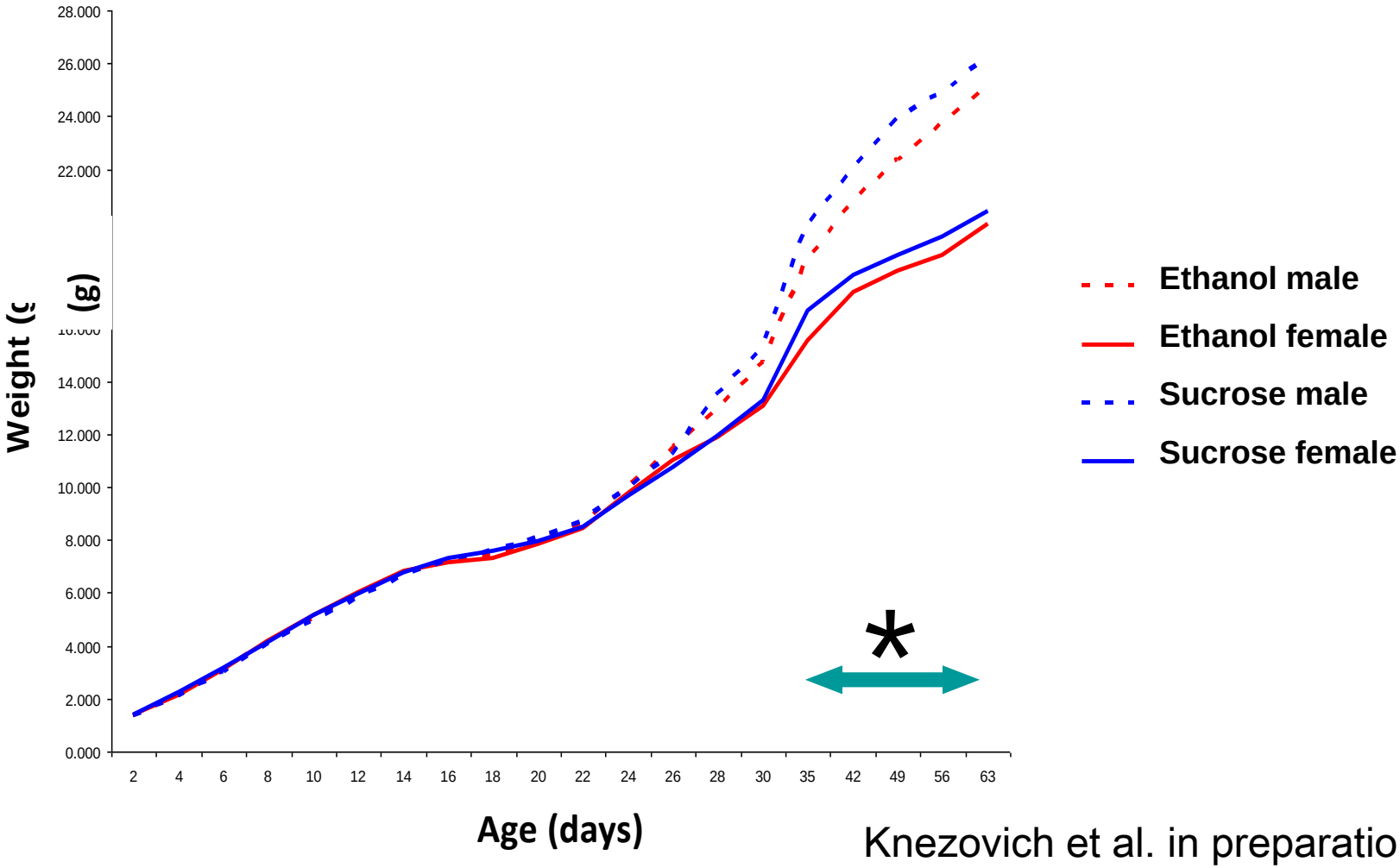
	Embryo	Placenta
Control	48.4+17.2	50.5 +16.5
Ethanol	19.8+6,5	33.4 + 12.2
p	<0.001	<0.01

Haycock and Ramsay (2009) Biology of Reproduction 81:618-627



Haycock and Ramsay (2009) Biology of Reproduction 81:618-627

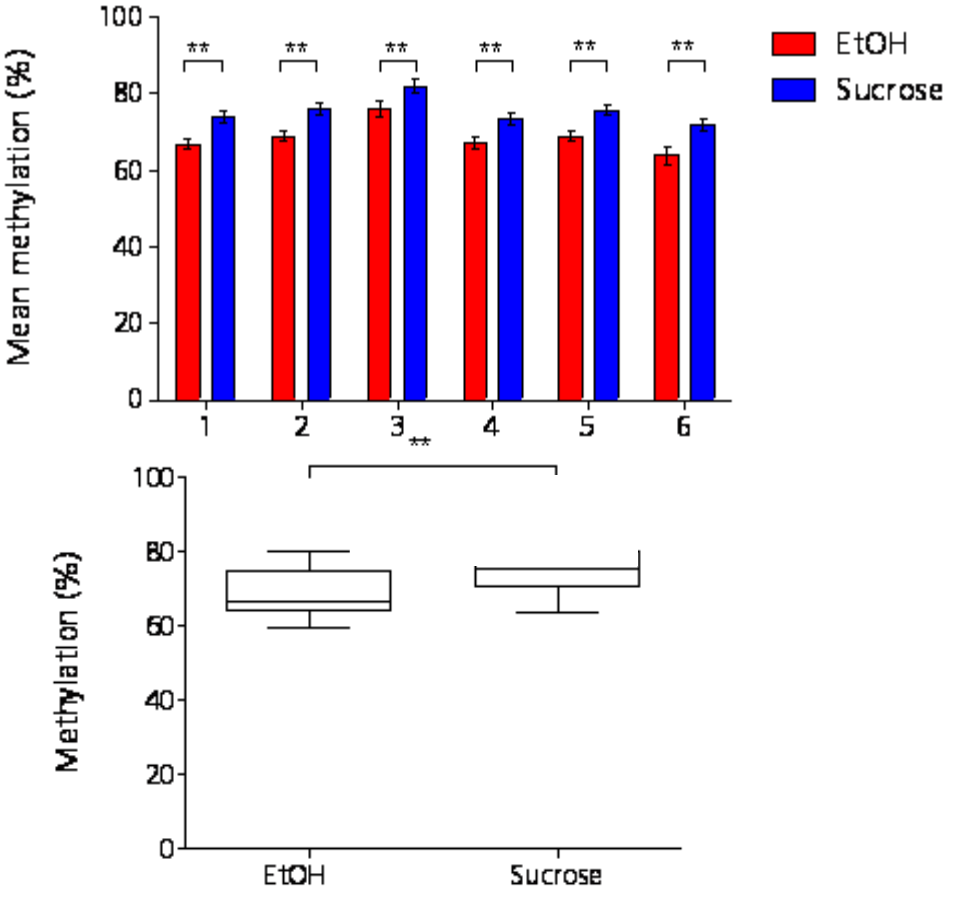
Mouse study: Effect of paternal alcohol exposure on mouse offspring growth



Knezovich et al. in preparation 2010

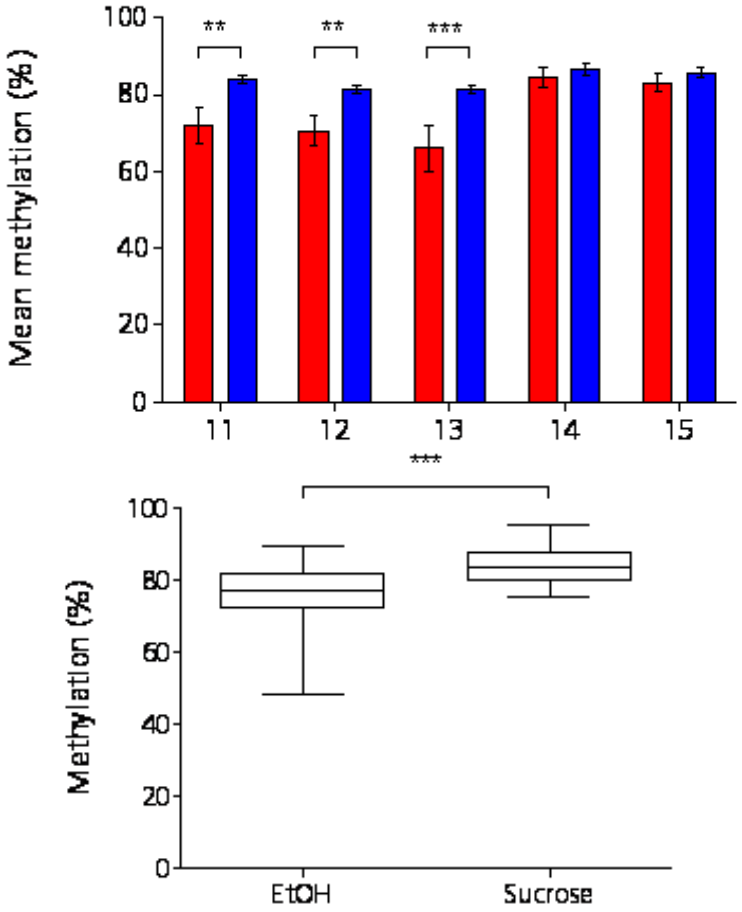
Effect of paternal alcohol exposure on offspring DNA methylation

H19 DMR CTCF 1

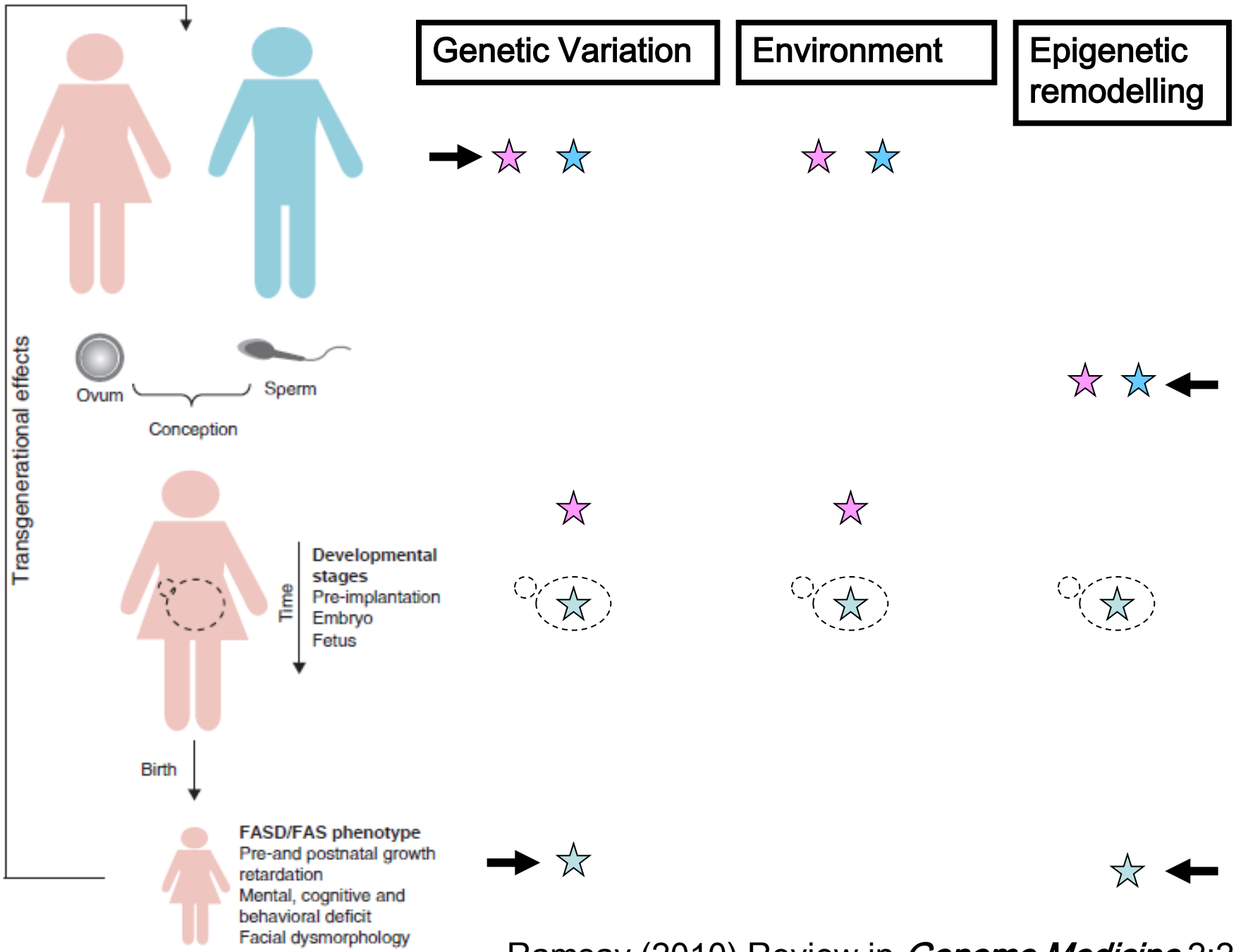


** p<0.01 *** p<0.001

H19 DMR CTCF 2



Knezovich et al. submitted 2010



Ramsay (2010) Review in *Genome Medicine* 2:24





GWAS

WTCCC





HapMap Project

SNPs

AACACGCC
AACACGCC
AACATGCC
AACACGCC

2000

2005

2010



Obesity study



Genotyping facility

Rheumatoid arthritis

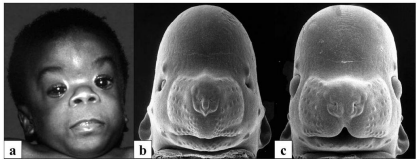
Bone mineral density

Glaucoma



epigenetics

Wits Bioinformatics



FAS

Stage 3
Building projects for the future

Sydney Brenner Institute
for Molecular Bioscience
SBIMB



A WORLDCLASS RESEARCH
ENVIRONMENT FOR THE STUDY OF
NON-COMMUNICABLE DISEASES
IN AFRICANS



Ralph Ramsay



Development and construction of databases and analysis tools to store, organise, select, retrieve, compare, analyse, integrate and share vast amounts of biological data

Wits Research Thrusts



Sydney Brenner Institute for Molecular Bioscience

SBIMB



A WORLDCLASS RESEARCH ENVIRONMENT FOR THE STUDY OF NON-COMMUNICABLE DISEASES IN AFRICANS

SBIMB

Genomics

Epigenetics & Developmental Biology

Molecular & Cell Biology

Computational & Structural Biology

Applied Clinical Research & Epidemiology

Extensive collaboration



Emphasis on studying populations of African origin

AFRICAN DIASPORA



Acknowledgements

Mentors and role models:
Trefor Jenkins
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Jennifer Kromberg
Judith Hall
Denis Viljoen
Peter Hull

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Lillian Ouko
Zané Lombard
Philip Haycock
Desmond Schnugh
Katpaham Shantikumar
Tony Pomario
Jason van Beukering
Sarah Shankman
Michelle Starfield
Premila John
Carolyn Padoa

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Amanda Krause
Debbie Morris
Andy Goldman
Robyn Kerr
Fahmida Essop

Genotyping facility:
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Punita Pitamber

Emma Ogilvie
Mshengu Tshabalala
Wesley van H-Tulleken
Steven Lubbe
Dahmari Naidoo
Shelley McCauley
Candice de Carvalho
Tarryn Greenberg

Wits collaborators:
Nigel Crowther
Shane Norris
John Pettifor
Gavin Norton
Angela Woodiwiss
Karen Sliwa
Kerstin Klipstein-Grobush
Steve Tollman

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Jackie Frost
Angela Hobbs
Lee-Ann Wood
Punita Pitamber
Sanam Patel
Michelle Ungerer
Andrew May
Thandiswa Ngcungcu
Silke Arndt
Matshane Masemola
Jaysen Knezovich
Ovokeraye Achinike
Susan Williams



NATIONAL HEALTH
LABORATORY SERVICE







National
Research
Foundation

L. Patrick Mellon
MENTORSHIP PROGRAM



NATIONAL
BIOINFORMATICS
NETWORK



March
of Dimes®
Saving babies, together®



science
& technology
Department:
Science and Technology
REPUBLIC OF SOUTH AFRICA





FOGARTY


TALIA

PARALLEL JOURNEYS

The birth and growth of molecular genetics and its influence on a career spanning three decades



NATIONAL HEALTH
LABORATORY SERVICE



Michèle Ramsay

Division of Human Genetics

NHLS & University of the Witwatersrand

30 August 2010

Stage 1
The beginnings of molecular genetics and translational science



Stage 2
The challenge of complex questions



Stage 3
Building projects for the future

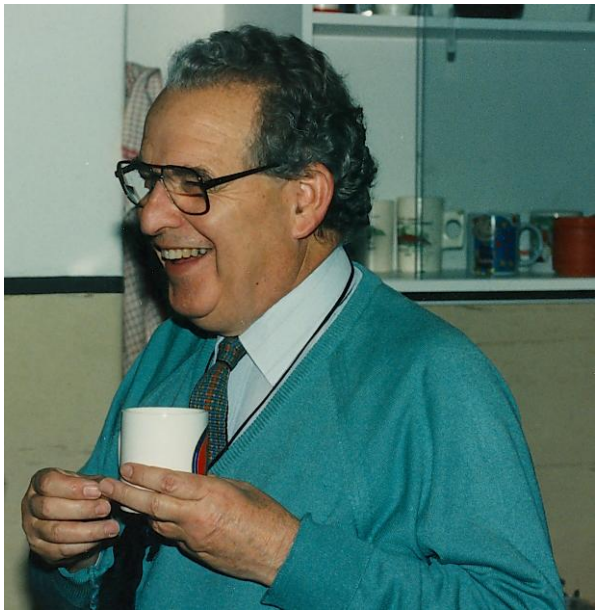


Stage 1
The beginnings of molecular genetics and translational science

Eigthties and Nineties

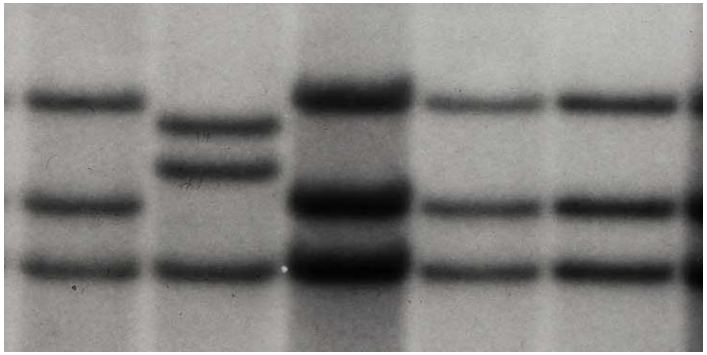


Trefor Jenkins









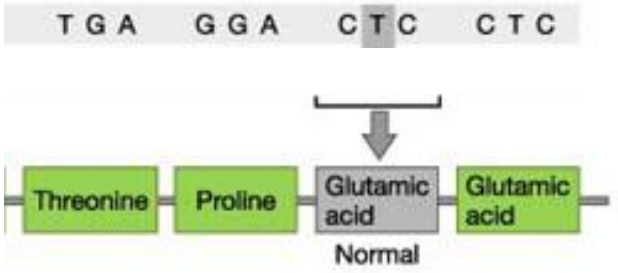
Tsumkwe - Bushmanland

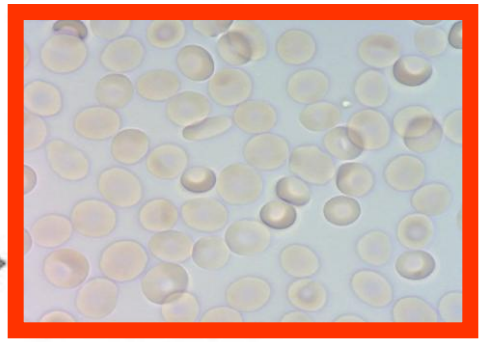




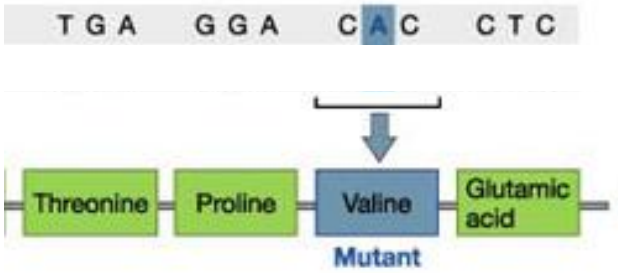


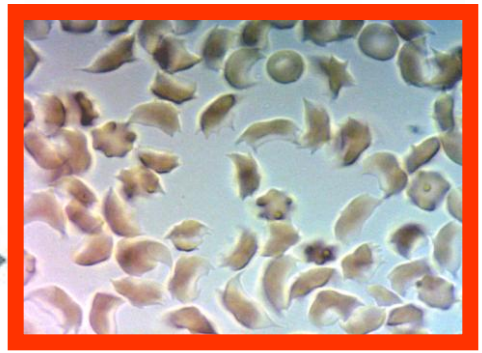
Diagnostic tests: Sickle cell anaemia





Normal red blood cells





Sickle red blood cells

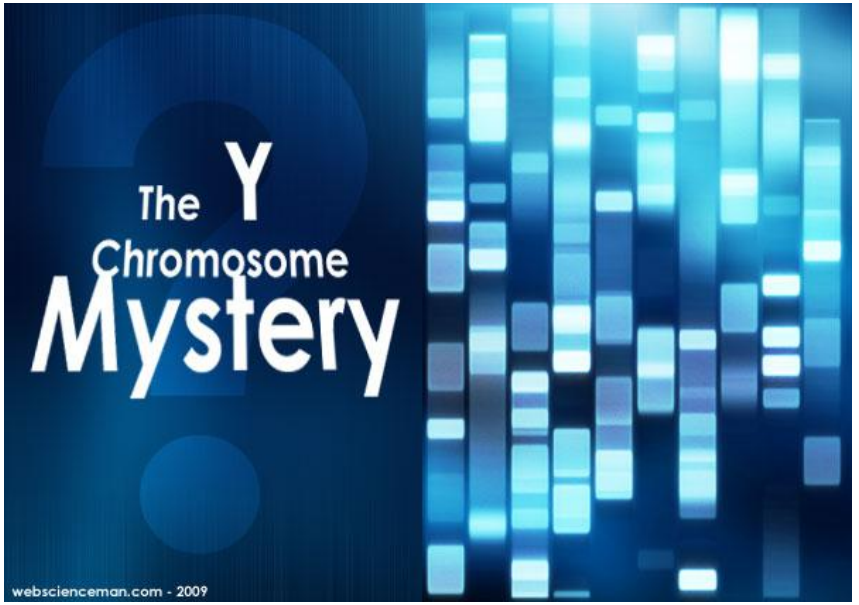
Antenatal diagnosis of sickle-cell anaemia by means of DNA restriction analysis

MICHÈLE RAMSAY, JENNIFER A. THOMSON, T. JENKINS

South African Medical Journal, July 1984

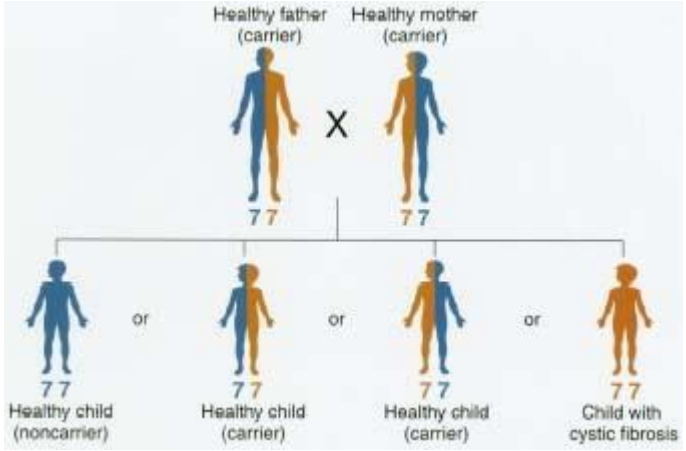
Renèe Bernstein

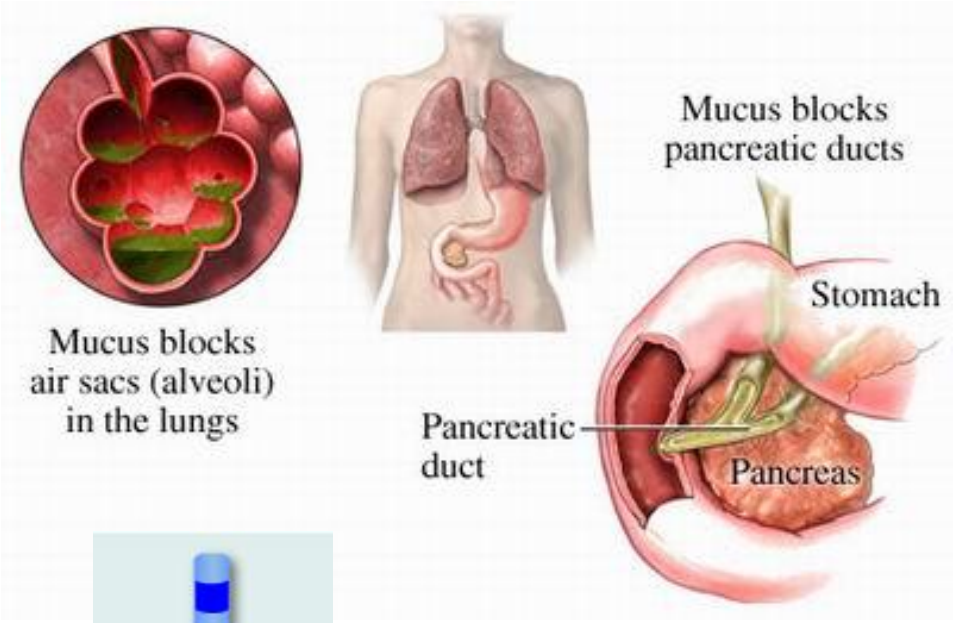




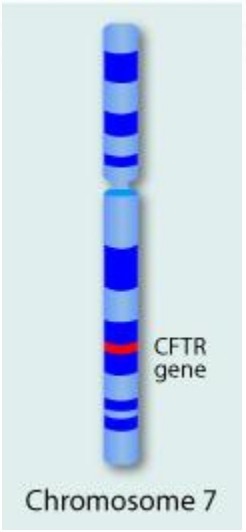
The Era Gene Hunting

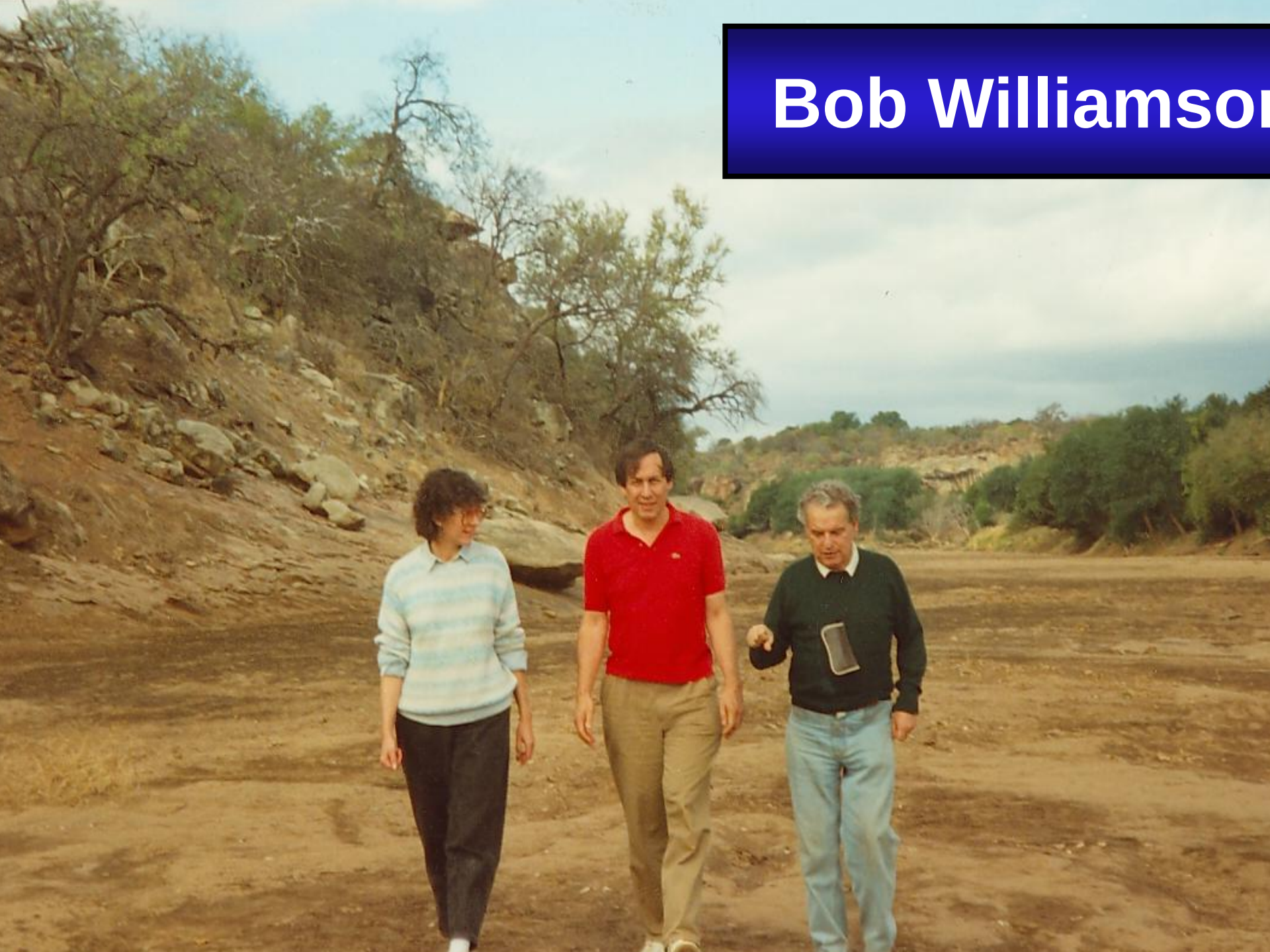
Cystic Fibrosis

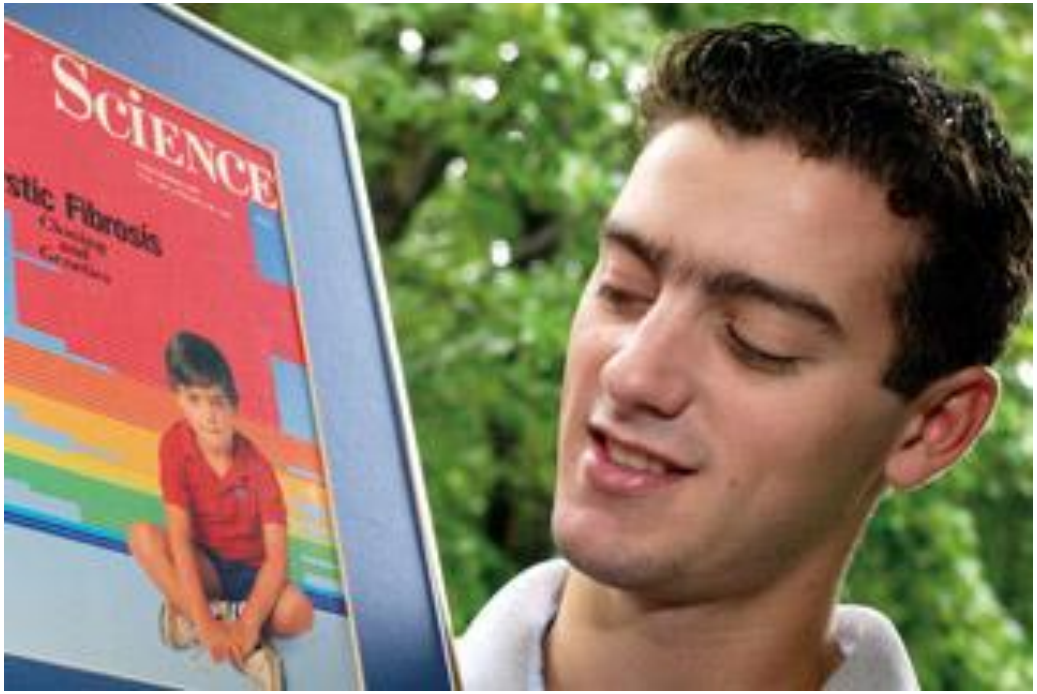


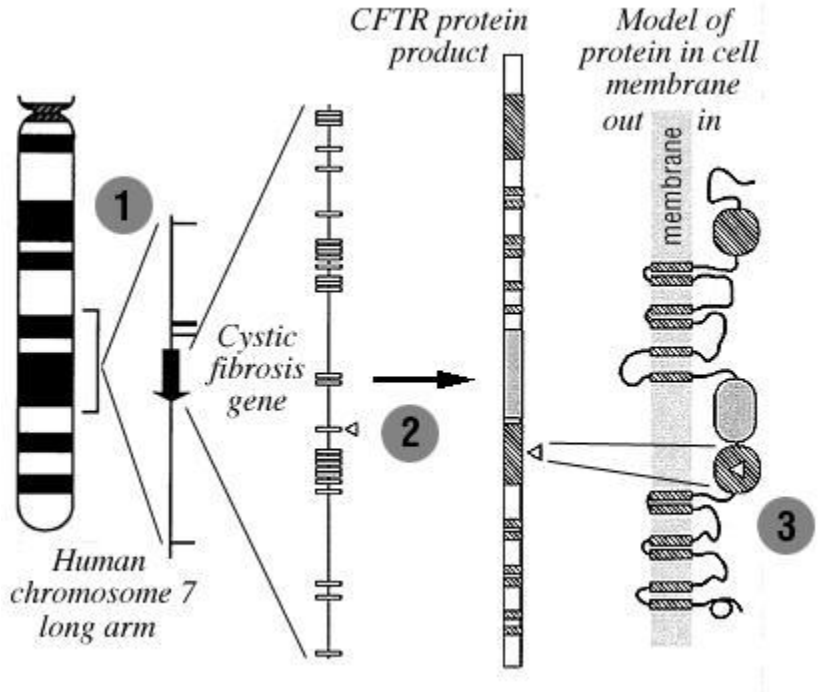


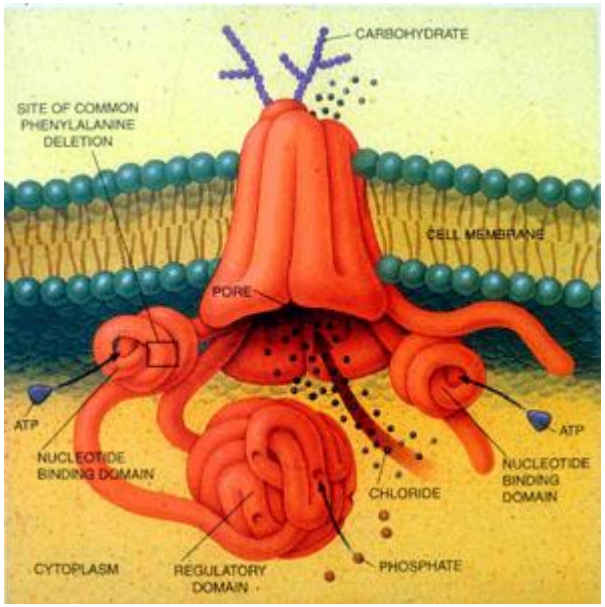




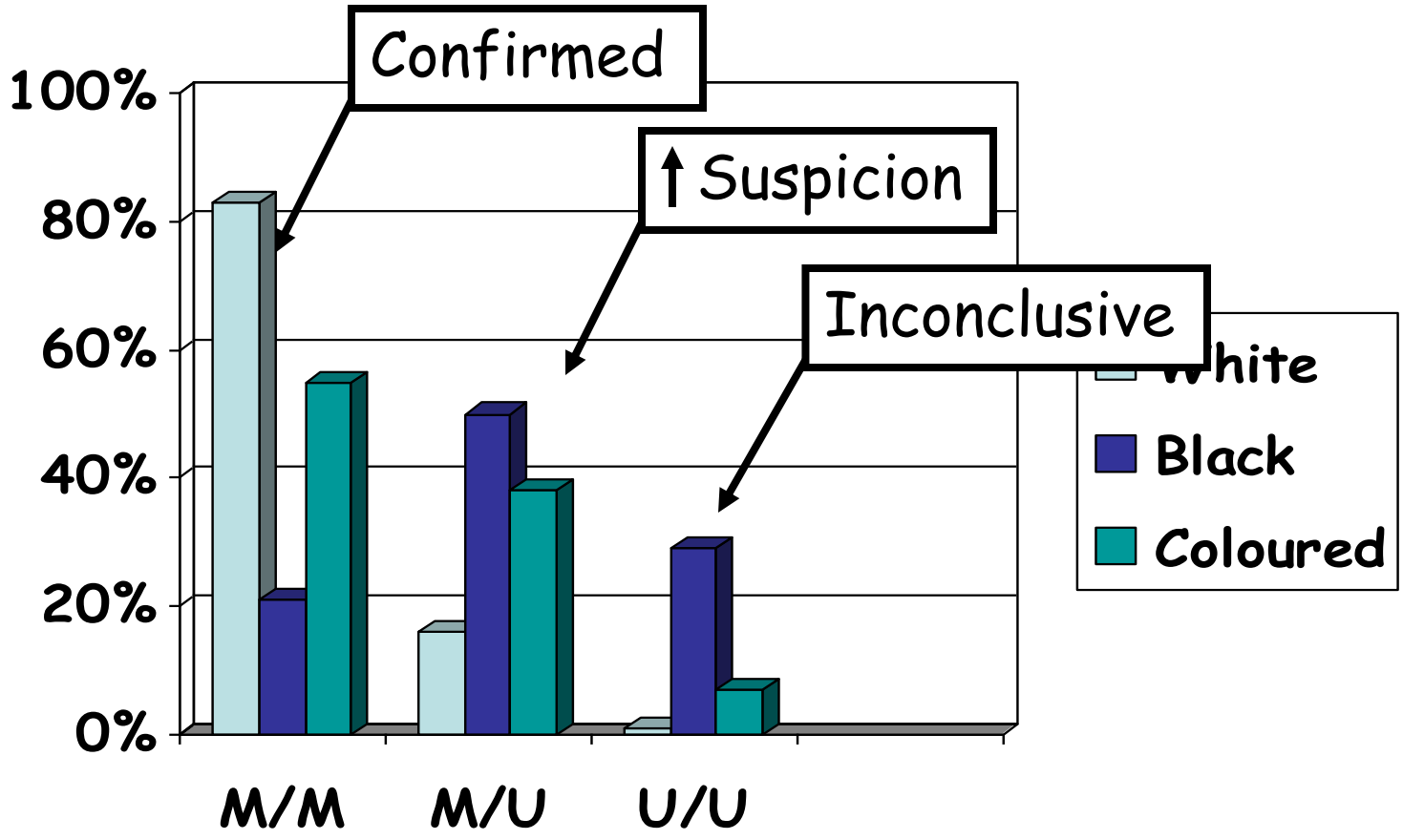

Bob Williamson


SCIENCE


CFTR protein product
Model of protein in cell membrane
out
in
membrane
1
Cystic fibrosis gene
2
3
Human chromosome 7 long arm


CARBOHYDRATE
SITE OF COMMON PHENYLALANINE DELETION
CELL MEMBRANE
PORE
ATP
NUCLEOTIDE BINDING DOMAIN
CHLORIDE
ATP
NUCLEOTIDE BINDING DOMAIN
CYTOPLASM
REGULATORY DOMAIN
PHOSPHATE

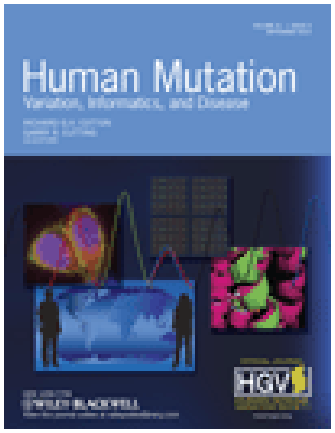
Confirmation of CF diagnosis



Detection rates: White-91% Black-46% Coloured-74.4%

Mireille Claustres

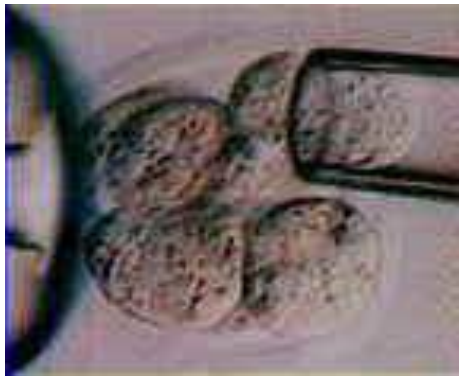




UMD-*CFTR*: A database dedicated to CF and *CFTR*-related disorders

C Bareil et al. and Mireille Claustres

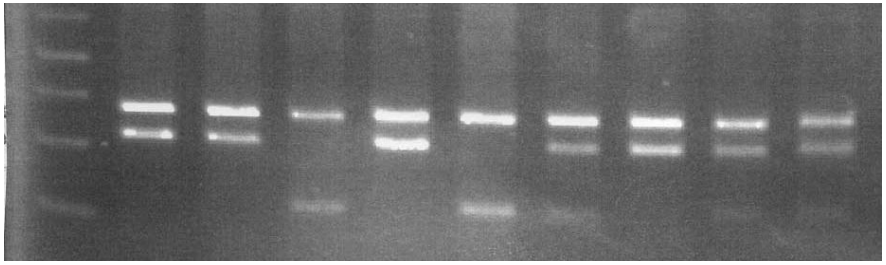
Human Mutation 6 JUL 2010

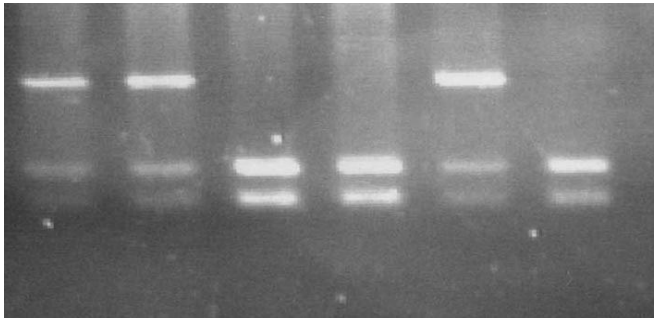


PCR



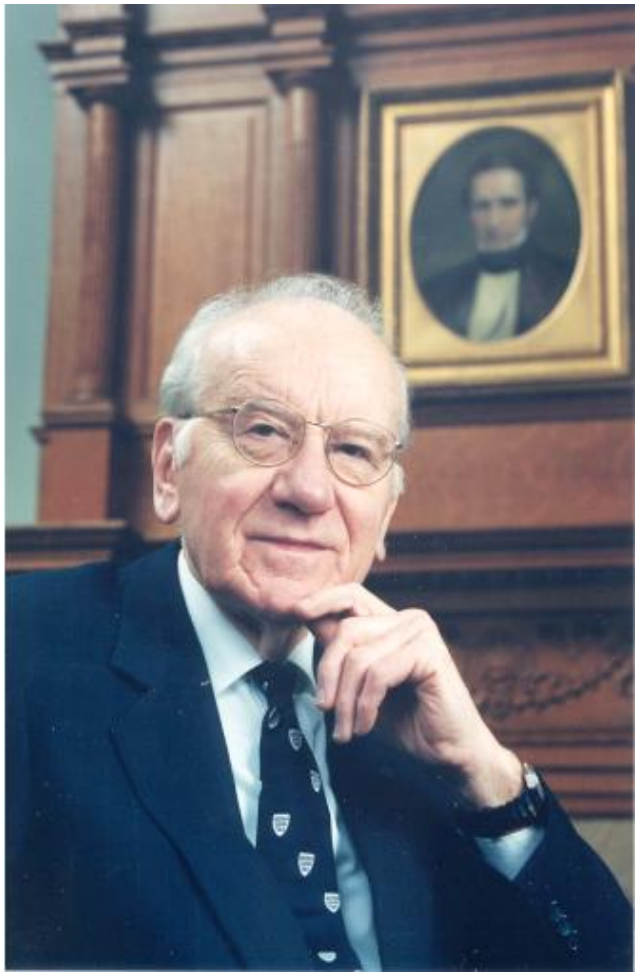






OMIM

http://www.ncbi.nlm.nih.gov



Compendium of human genes and genetic phenotypes

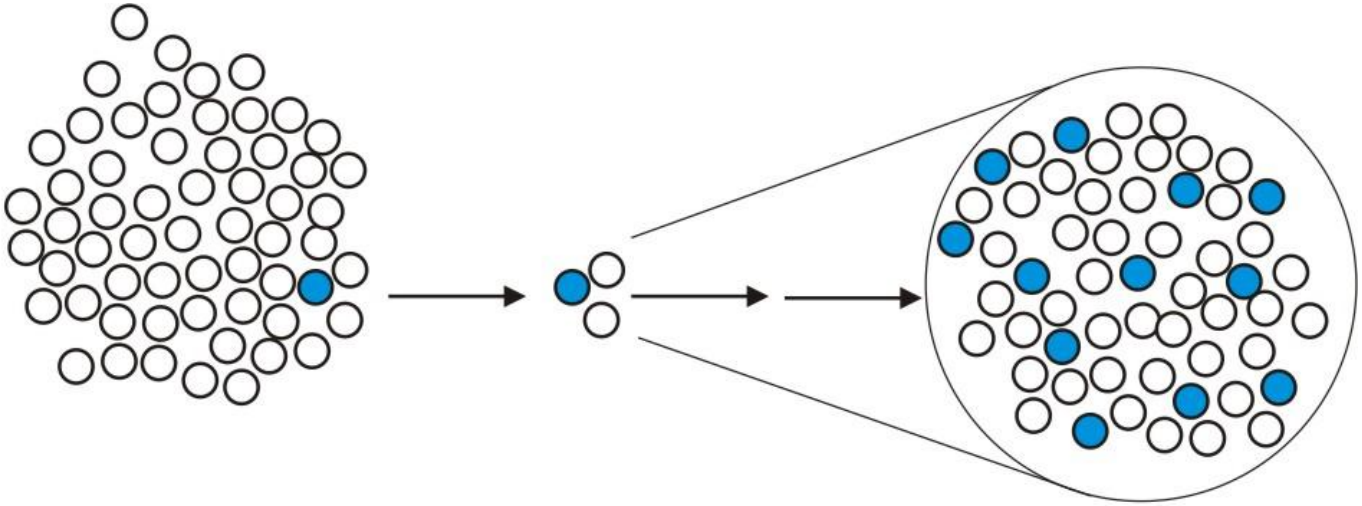
OMIM focuses primarily on inherited, or heritable, genetic diseases

History:
- **Initiated in 1960's by Victor McKusick**
- **12 Book editions (1966 to 1998)**
- **online since mid 1980s**
- **All known Mendelian Disorders**
- **Information on over 12 000 genes**
- **Updated daily**

Victor McKusick

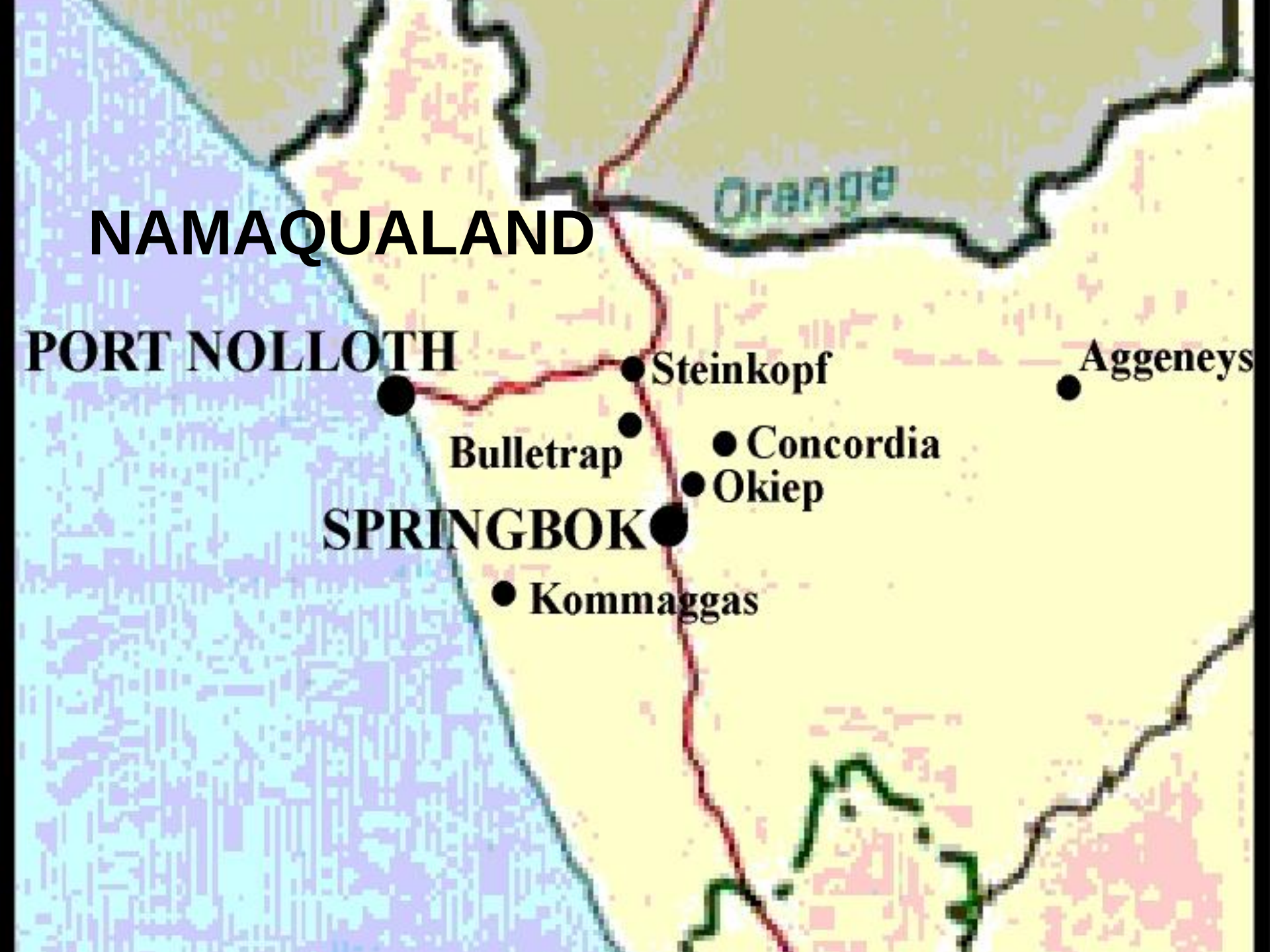
Lipoid proteinosis (LP)





Original population	Founding population	A later population
eg. Holland in the 17th Century	Collonists to South Africa	in South Africa in the 21st Century
Low	High	High

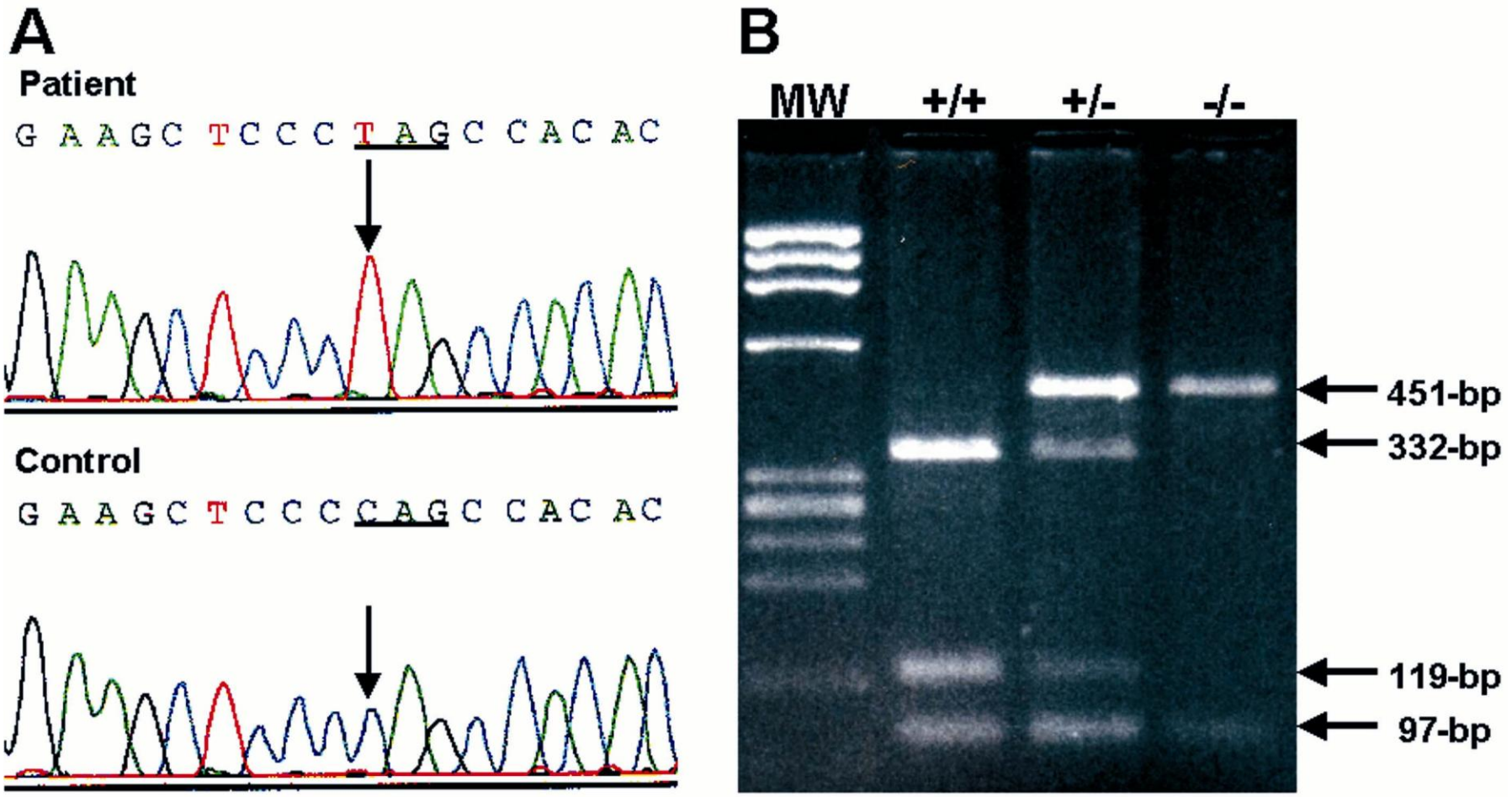

Cape Town International Airport
Streamline
nac
737
320


NAMAQUALAND
Orange
PORT NOLLOTH
Steinkopf
Aggeneys
Bulletrap
Concordia
Okiep
SPRINGBOK
Kommaggas





Extracellular matrix protein 1 (*ECM1*)



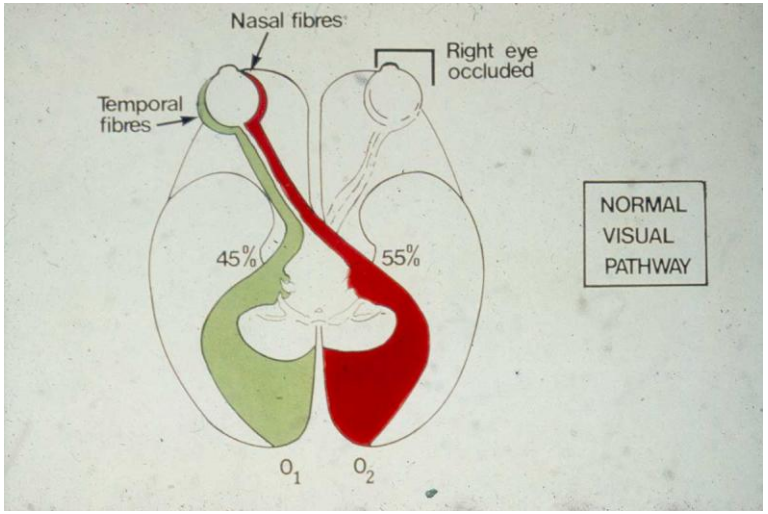


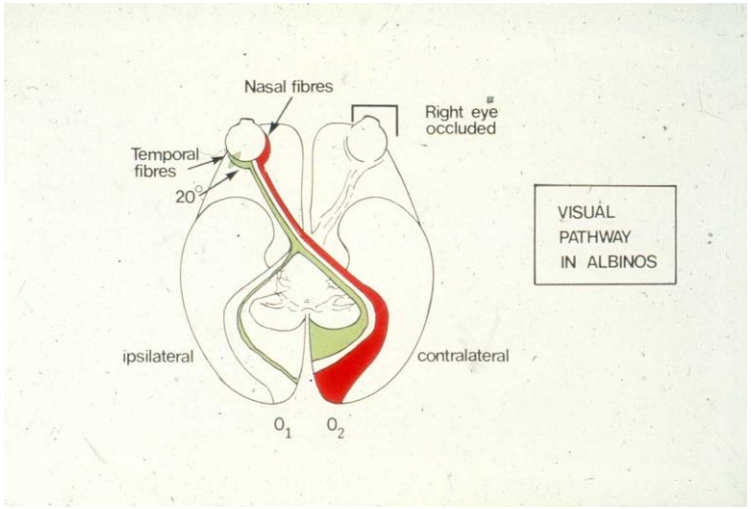
1875


Michael Friederich Dongez.
Geb. d. 2 Augustus 1867.
Gest. d. 3 Mei 1878.
"Ja Ik heb u liefgehad met eene eeuwige liefde!"
Jer. 31. 3.

ALBINISM




Nasal fibres
Right eye occluded
Temporal fibres
45%
55%
O_1
O_2
NORMAL VISUAL PATHWAY


Nasal fibres
Right eye occluded
Temporal fibres
20%
VISUAL PATHWAY IN ALBINOS
ipsilateral
contralateral
O_1
O_2

Jennifer Kromberg







Esther Zwane







Myths

More questions

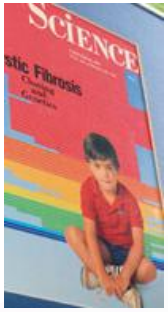
Annotated genome databases

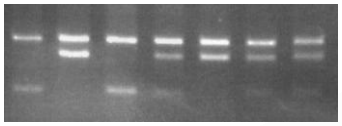
HGP started

Disease related information from over 12 000 genes

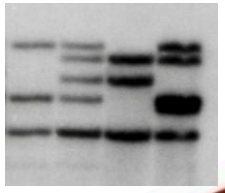
CF

PCR





SB



OMIM

1990

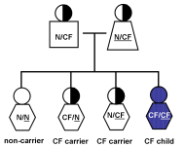
2000





LP gene

CF in black Africans

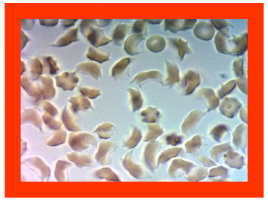


Y chromosome

1980

Molecular genetics diagnostic laboratory





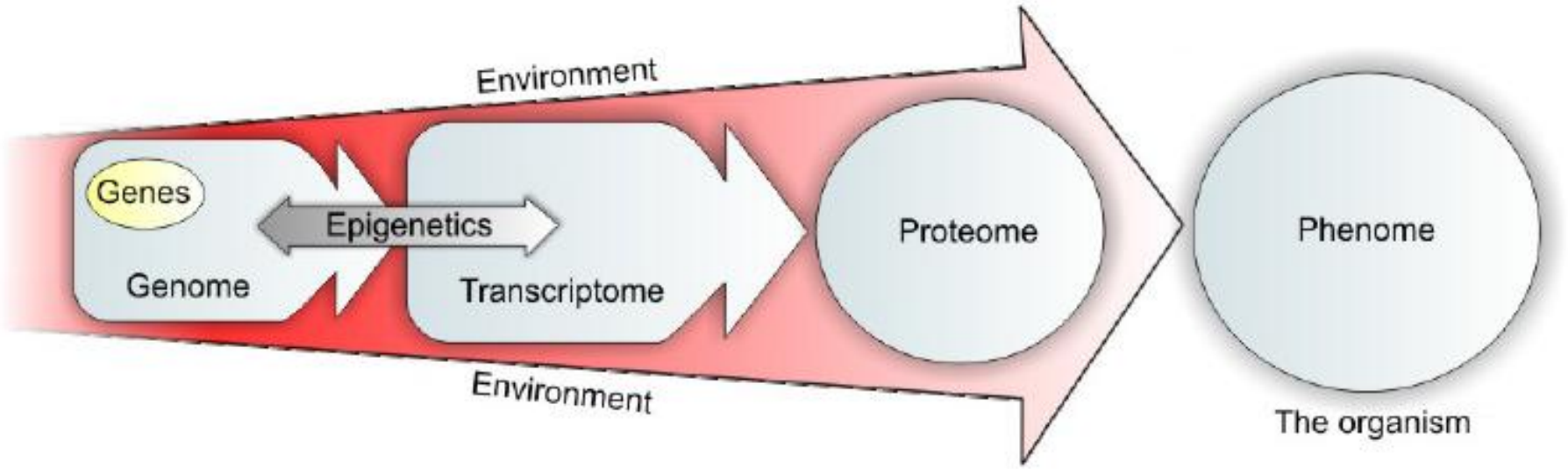
Prenatal diagnosis by DNA analysis

Stage 2
The challenge of complex questions

Twenty First Century Science



From genome to phenotype



Gene-gene and gene-environment interactions



Nature, 15 Feb 2001



Science, 16 Feb 2001

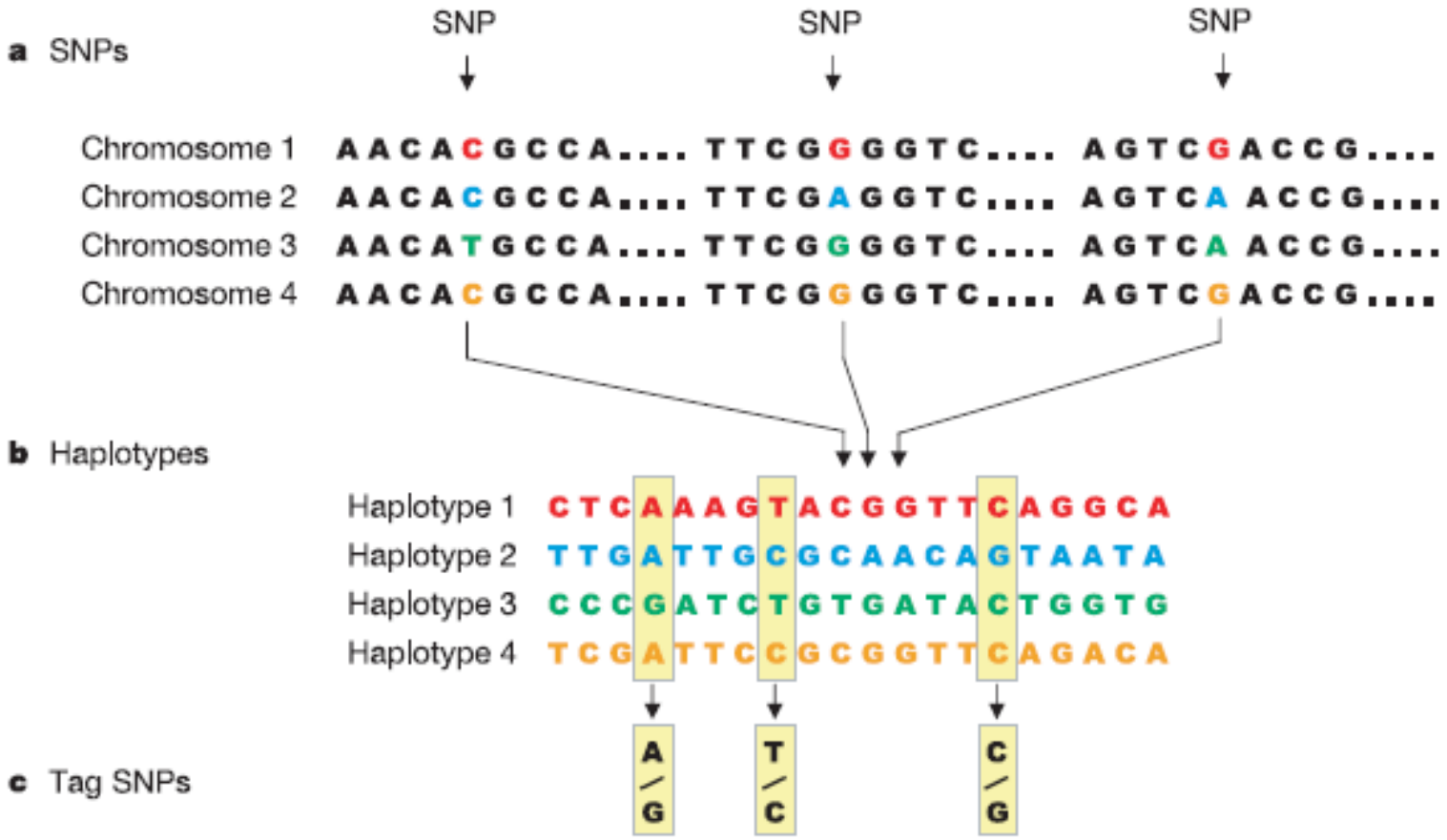
? ? ?



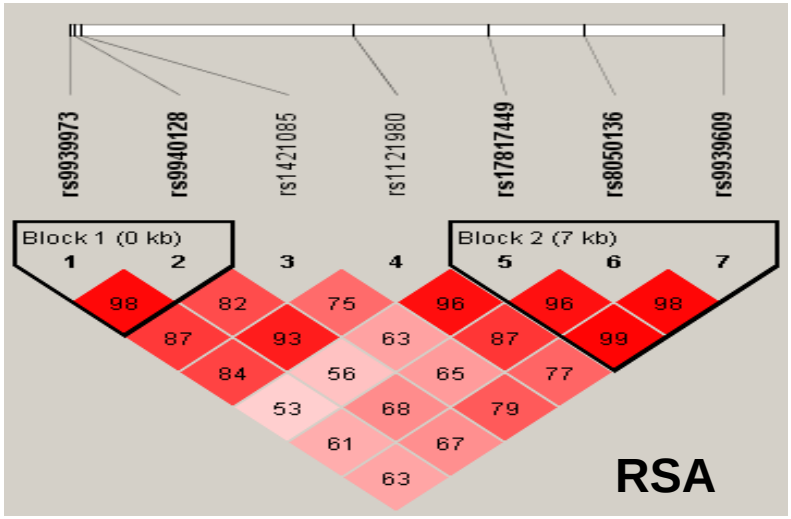


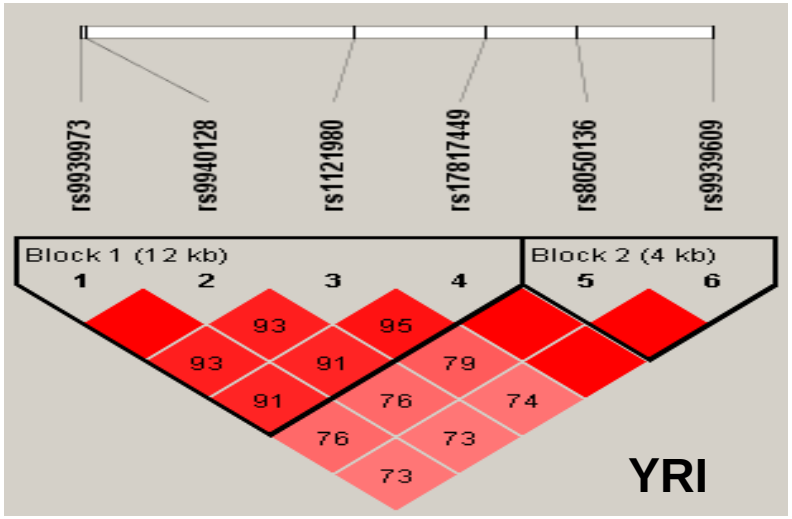
HapMap Project 2002

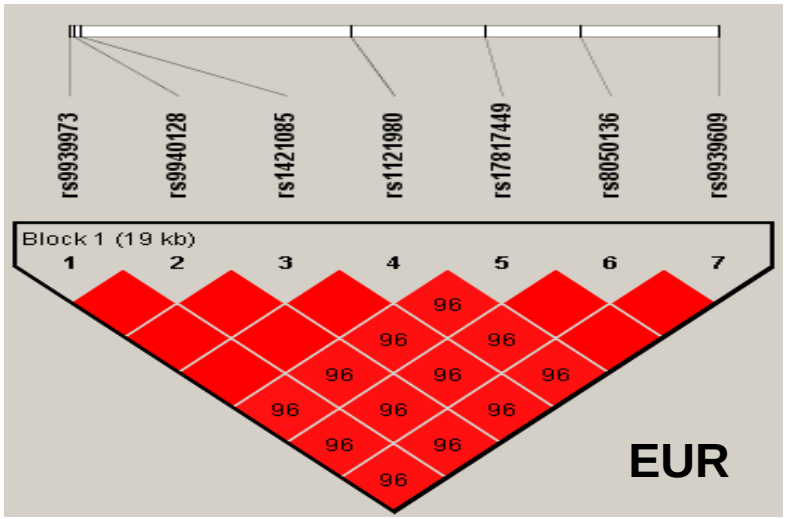
Common patterns of human genetic variation and the structure of the genome

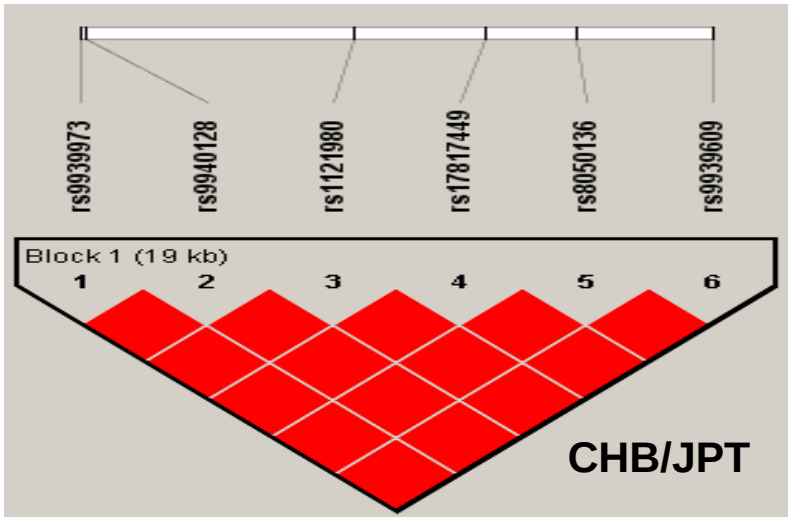


The International HapMap Consortium: Nature (Dec 2003)


rs9939973
rs9940128
rs1421085
rs1121980
rs17817449
rs8050136
rs9939609
Block 1 (0 kb)
Block 2 (7 kb)
1 2 3 4 5 6 7
98
82 75 96 96 98
87 93 63 87 99
84 56 65 77
53 68 79
61 67
63
RSA


rs9939973
rs9940128
rs1121980
rs17817449
rs8050136
rs9939609
Block 1 (12 kb)
Block 2 (4 kb)
1 2 3 4 5 6
93 95
93 91 79
91 76 74
76 73
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YRI


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Block 1 (19 kb)
1 2 3 4 5 6 7
96
96 96
96 96 96
96 96 96
96 96
96
EUR


rs9939973
rs9940128
rs1121980
rs17817449
rs8050136
rs9939609
Block 1 (19 kb)
1 2 3 4 5 6
CHB/JPT

SNP discovery (2000-2005)

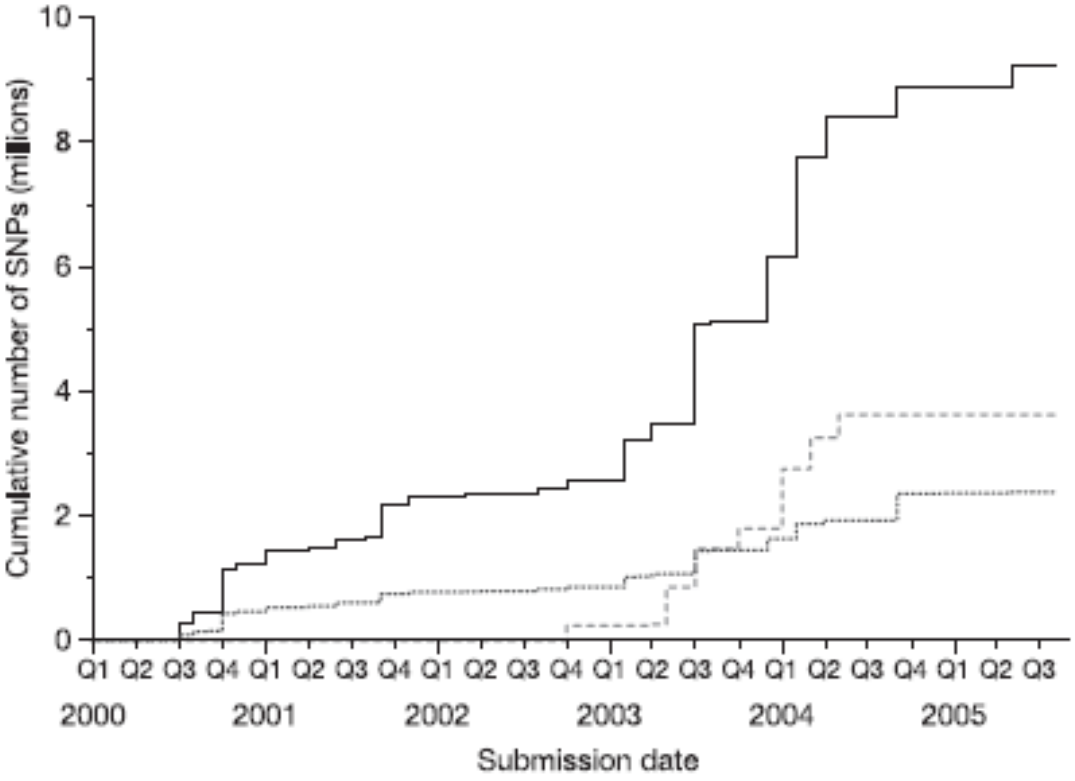


Figure 1 | Number of SNPs in dbSNP over time. The cumulative number of non-redundant SNPs (each mapped to a single location in the genome) is shown as a solid line, as well as the number of SNPs validated by genotyping (dotted line) and double-hit status (dashed line). Years are divided into quarters (Q1–Q4).

<u>February 2010:</u>

dbSNP Build 131

Genome build: 37.1

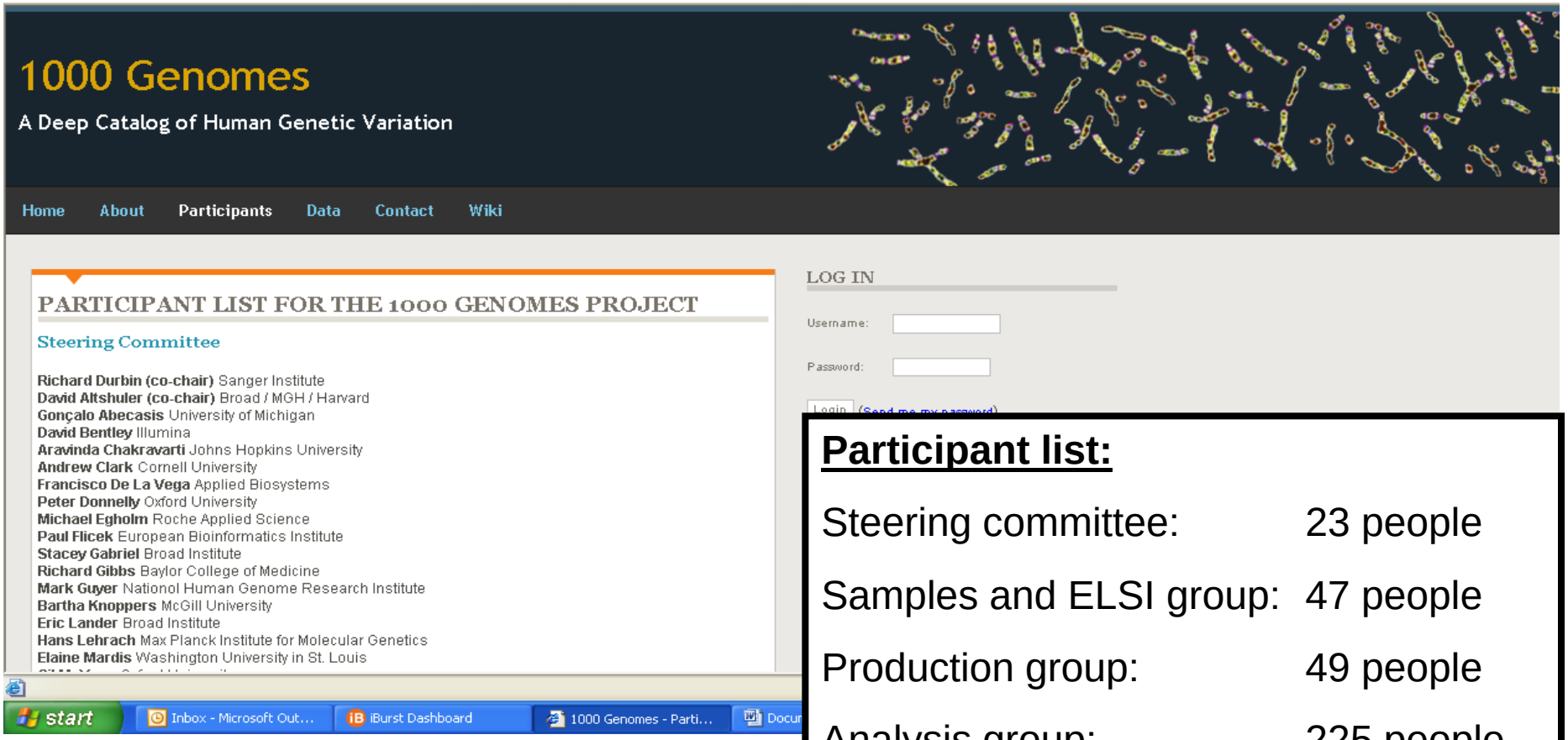
Submissions: 92 364 155

Reference SNPs: 17 804 036

Validated: 9 468 384

Frequency info: 803 969

The International HapMap Consortium: Nature (Oct 2005)



Participant list:

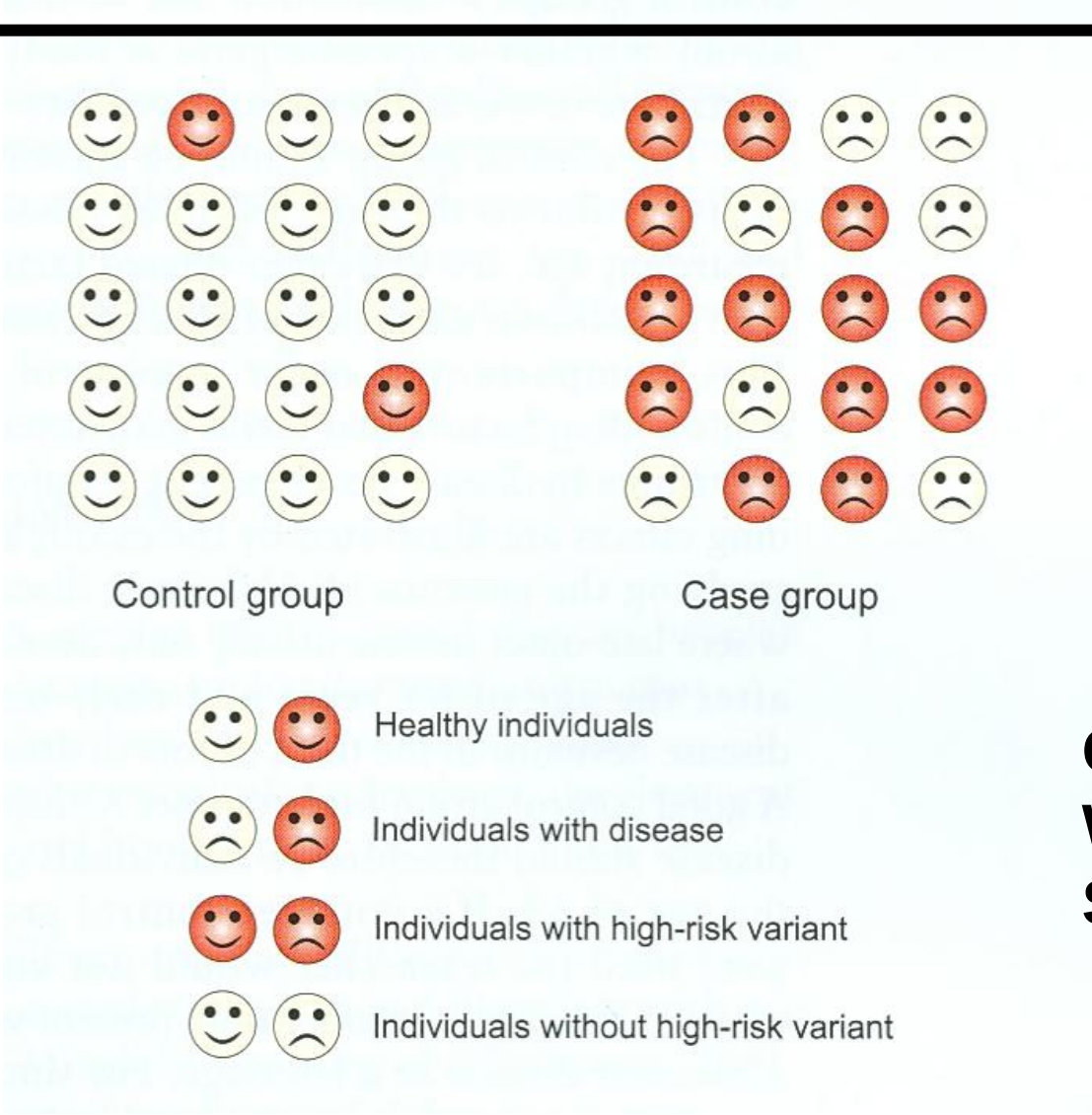
Steering committee:	23 people
Samples and ELSI group:	47 people
Production group:	49 people
Analysis group:	225 people
Data flow group:	44 people

January 2008

http://www.1000genomes.org/

Discover over 95% of genetic variants with frequencies as low as 1%

Case control association studies

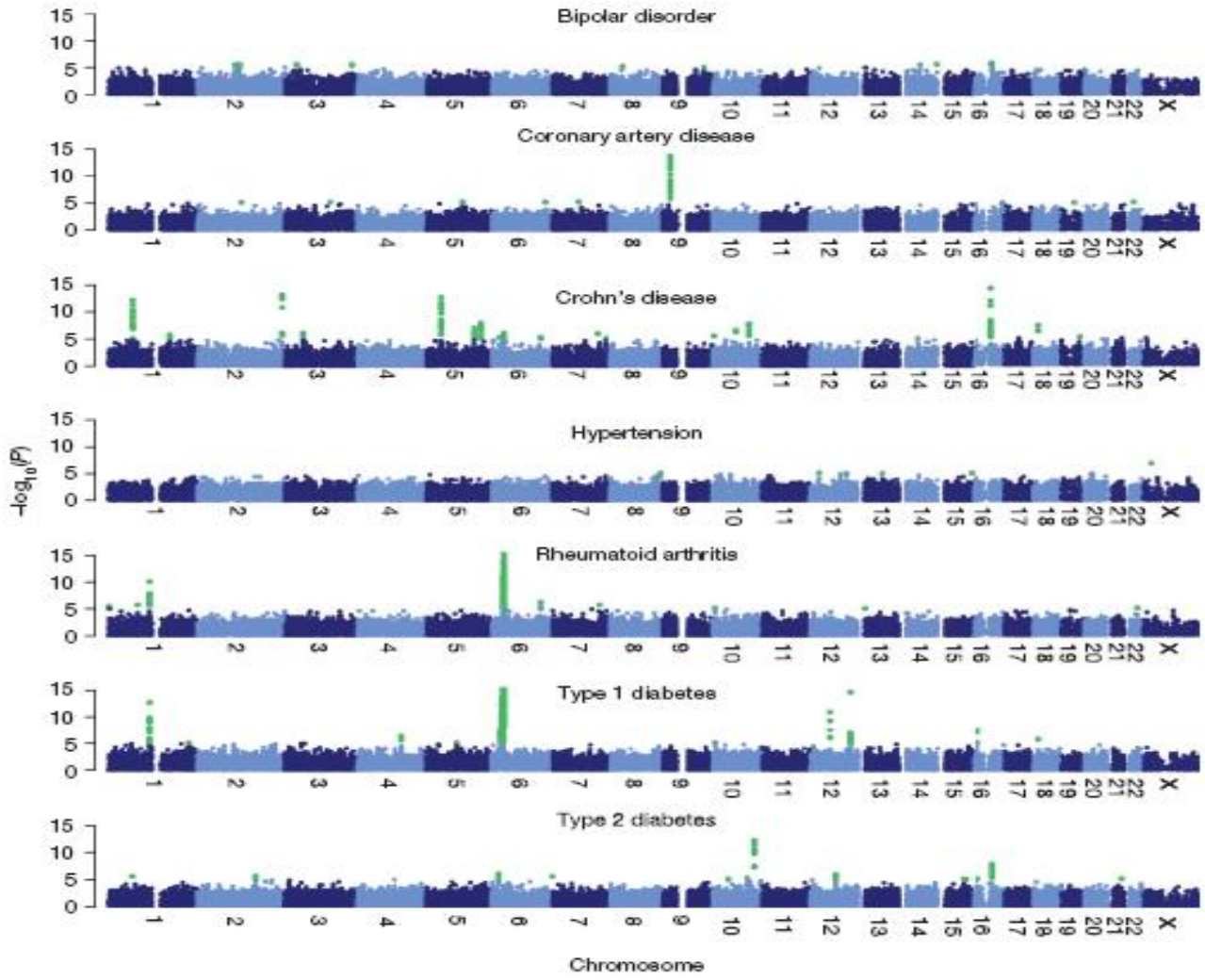


GWAS – Genome Wide Association Studies

Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls

The Wellcome Trust Case Control Consortium*

Nature (2007) Vol. 447



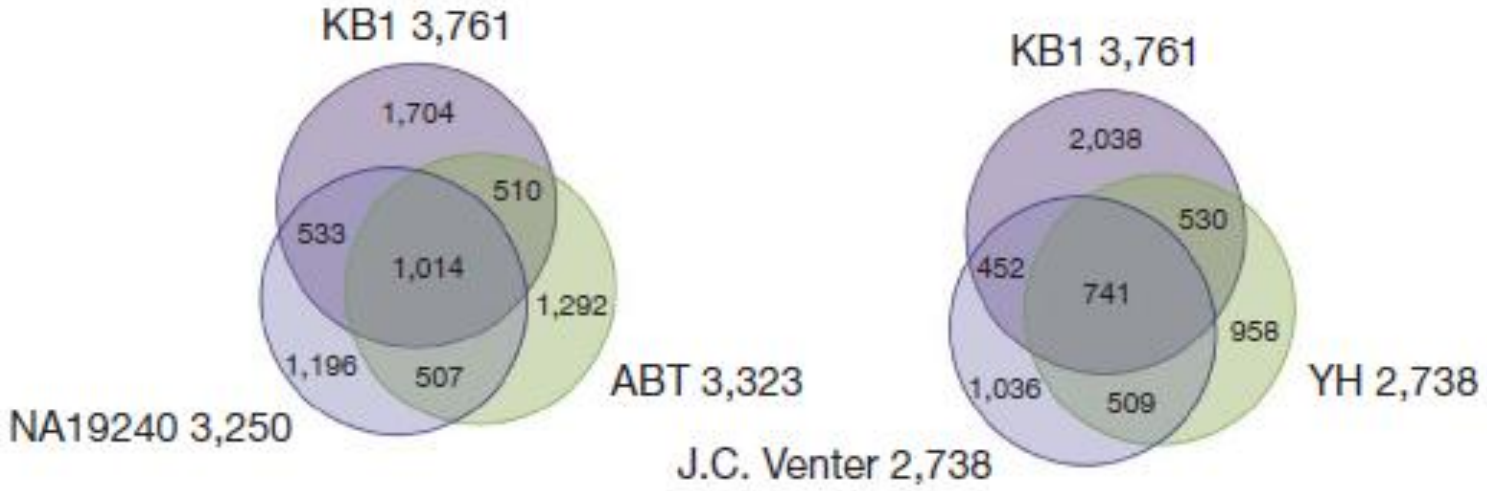
Obesity

Personalised medicine

Complete Khoisan and Bantu genomes from southern Africa

Nature, 18 February 2010





Genotyping Facility



Zané Lombard & Punita Pitamber

Collaborations

Judith Hall





Non-Mendelian inheritance

Cytoplasmic inheritance

Mosaicism

Uniparental disomy

Genomic imprinting

EPIGENETICS

Fetal Alcohol Syndrome
FAS

- **Stunted growth**
- **Behavioural & Cognitive disability**
- **Unusual facial features**







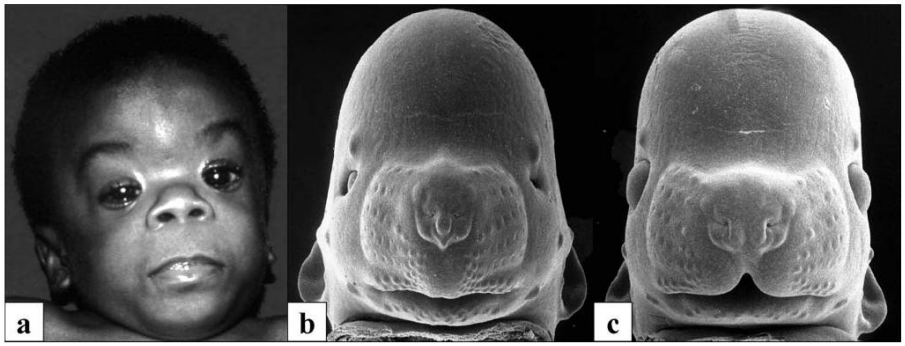
1. **65.2-74.2 / 1000 children (5-9 years)**
Viljoen *et al.* 2005 Stud Alcohol: 66 p593-604

2.



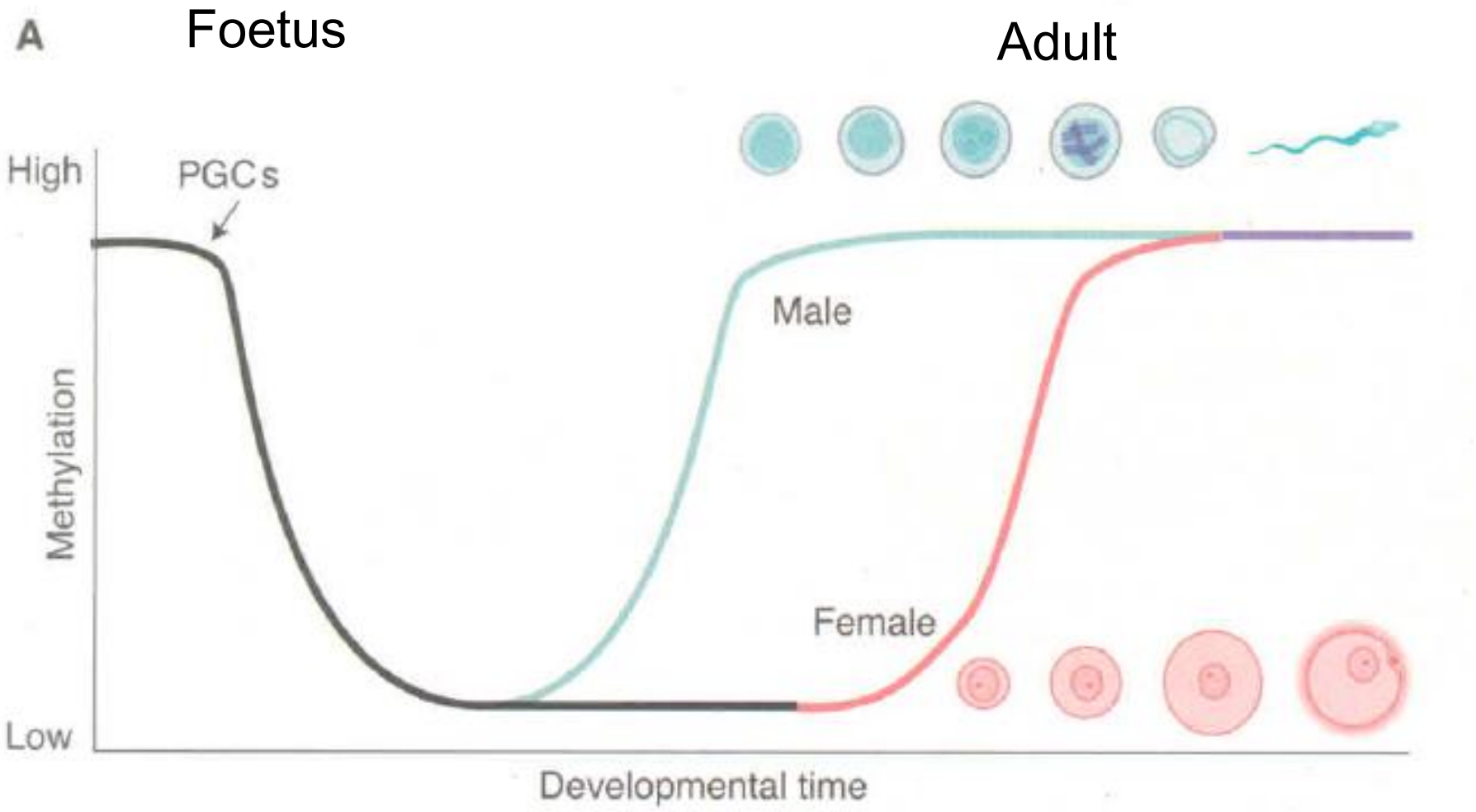


3.



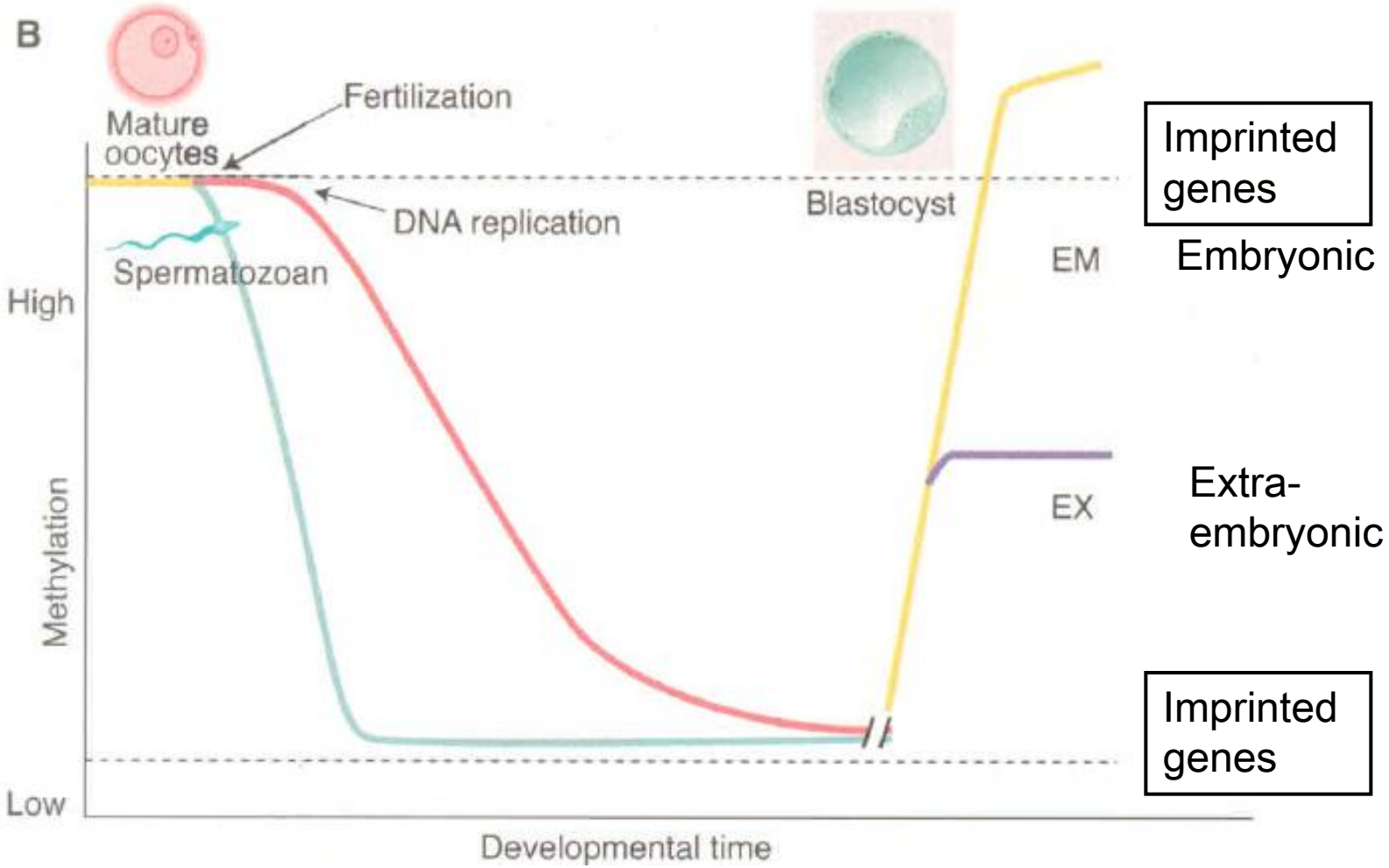


Germ line methylation reprogramming



Reik et al. 2001 Science 293:1089

Preimplantation embryos – methylation reprogramming



Reik et al. 2001 Science 293:1089

Preimplantation effect of alcohol in a mouse model

Igf2/H19 gene cluster – fetal growth and placental differentiation





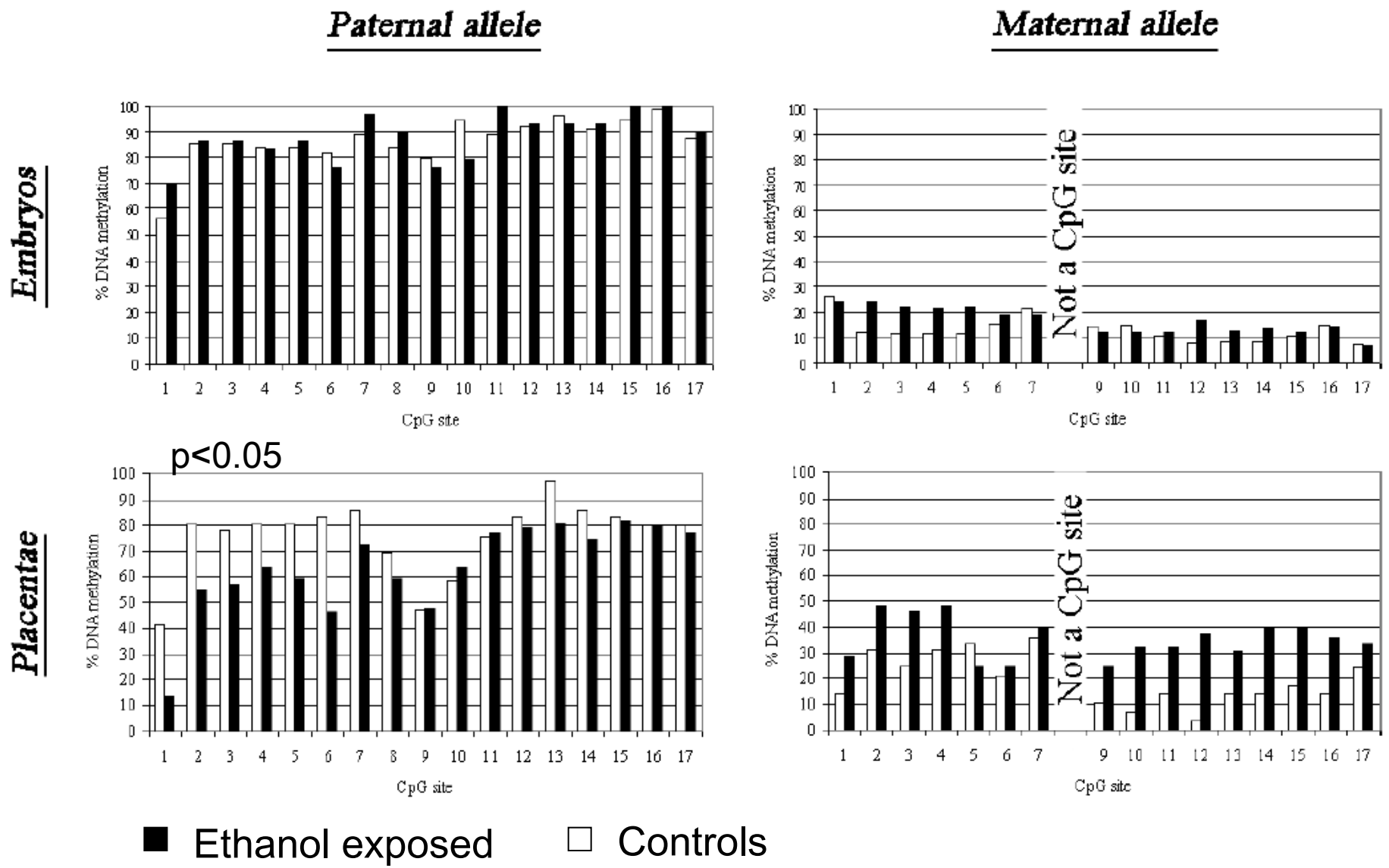
Ethanol exposure: acute dose at 1.5 and 2.5 dpc (2.9g/kg)

Harvest: 10.5 dpc

Effect on weight:

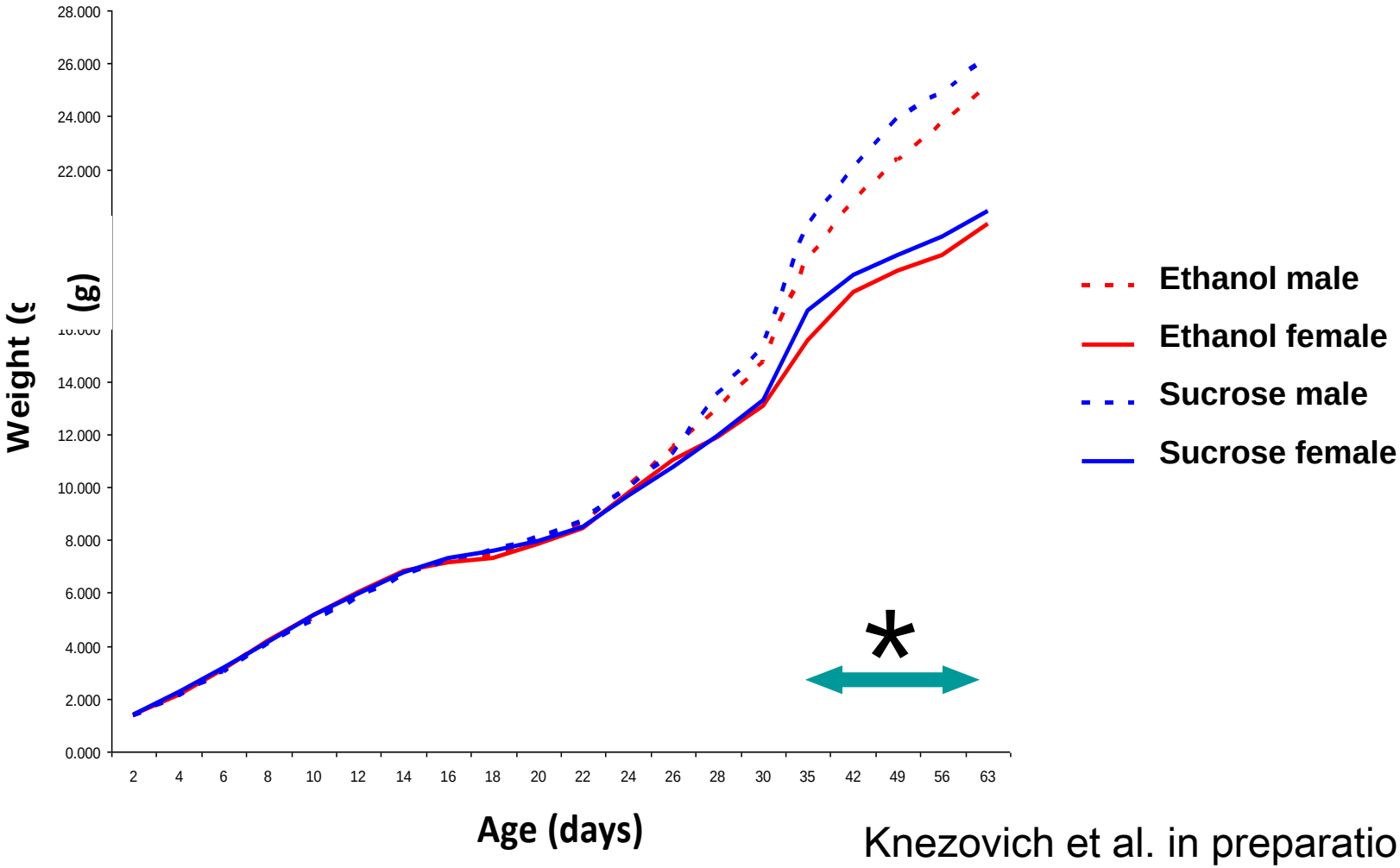
	Embryo	Placenta
Control	48.4+17.2	50.5 +16.5
Ethanol	19.8+6,5	33.4 + 12.2
p	<0.001	<0.01

Haycock and Ramsay (2009) Biology of Reproduction 81:618-627



Haycock and Ramsay (2009) Biology of Reproduction 81:618-627

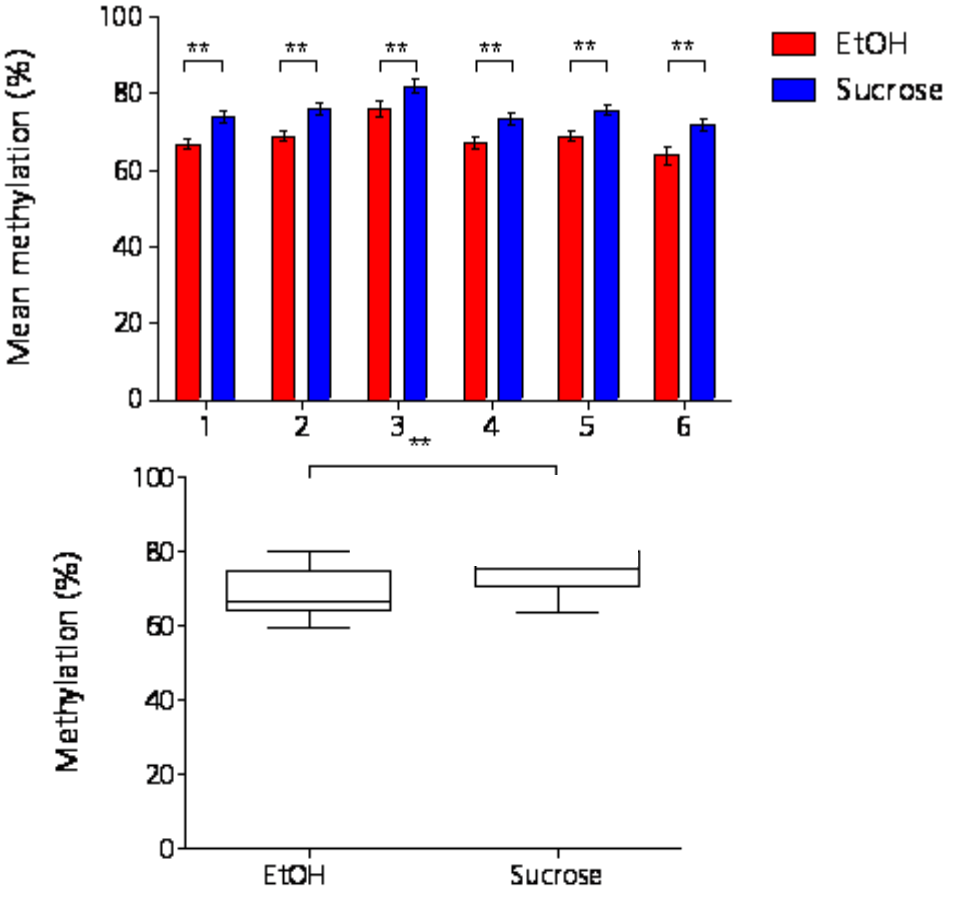
Mouse study: Effect of paternal alcohol exposure on mouse offspring growth



Knezovich et al. in preparation 2010

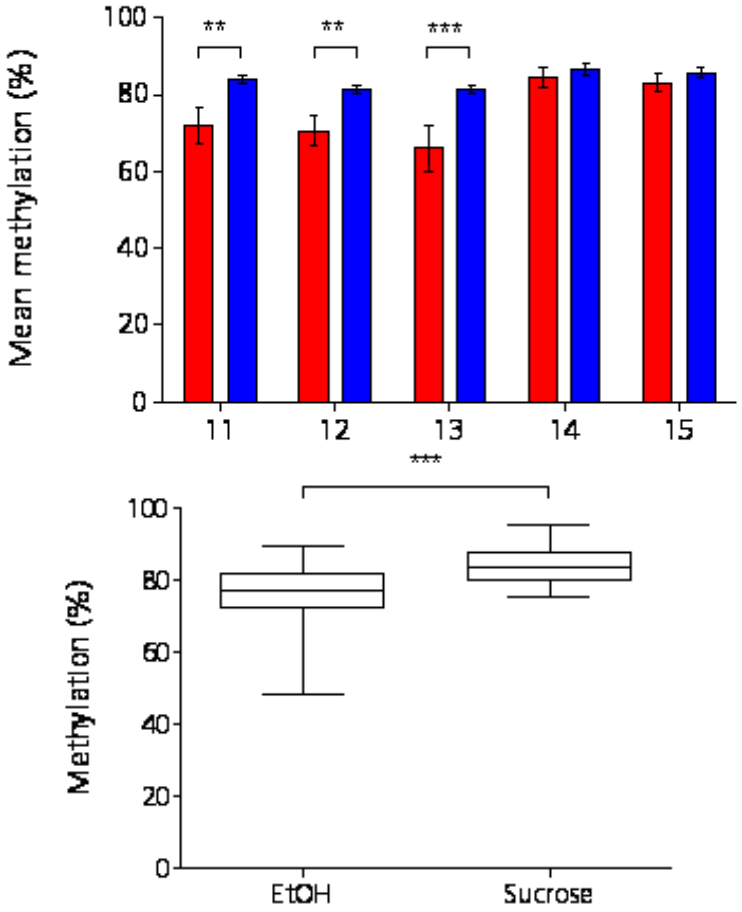
Effect of paternal alcohol exposure on offspring DNA methylation

H19 DMR CTCF 1

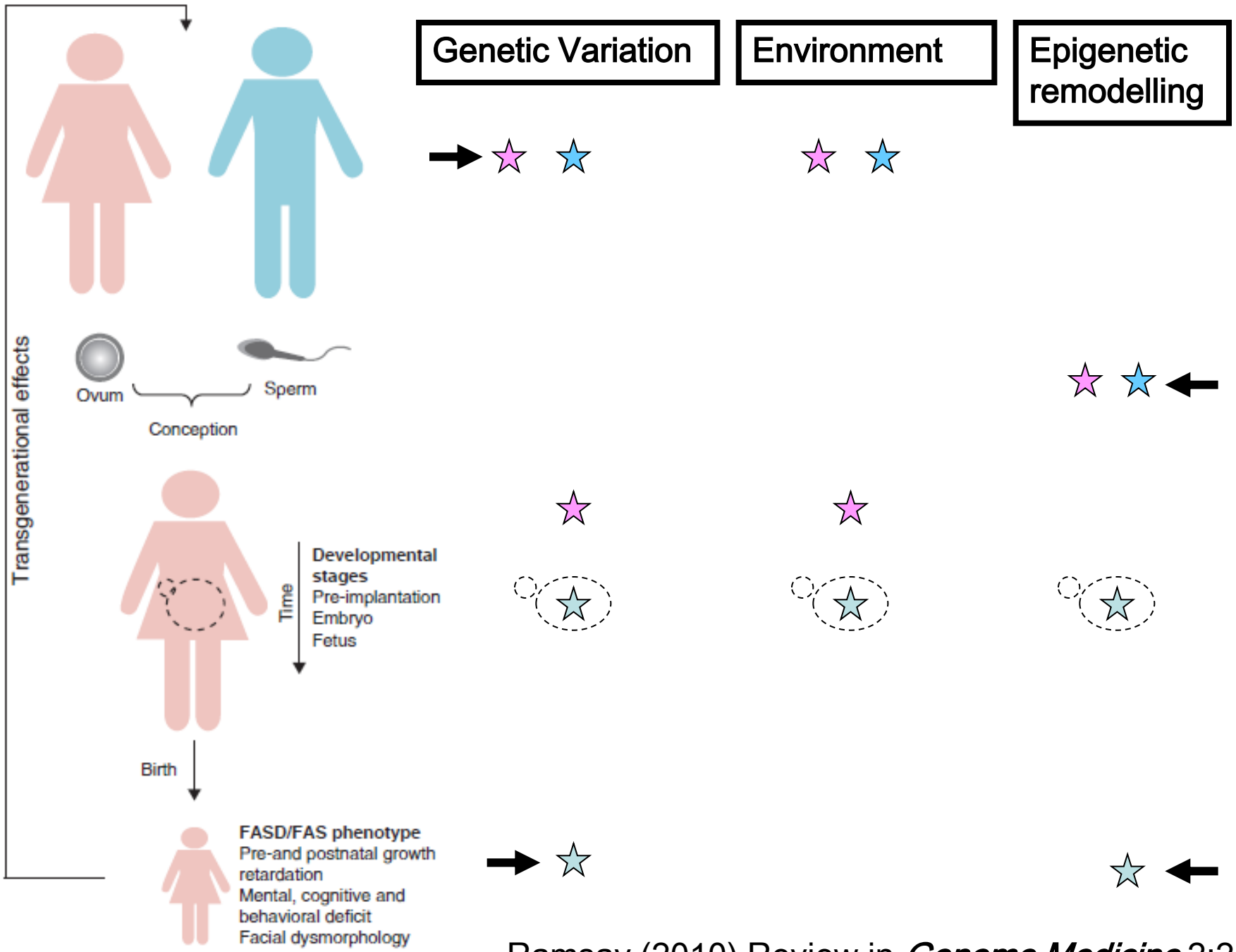


** p<0.01 *** p<0.001

H19 DMR CTCF 2



Knezovich et al. submitted 2010



Ramsay (2010) Review in *Genome Medicine* 2:24





GWAS

WTCCC





HapMap Project

SNPs

AACACGCC
AACACGCC
AACATGCC
AACACGCC

2000

2005

2010



Obesity study



Genotyping facility

Rheumatoid arthritis

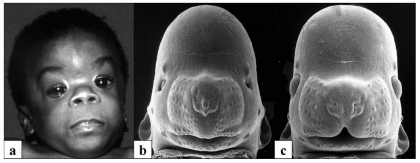
Bone mineral density

Glaucoma



epigenetics

Wits Bioinformatics



FAS

Stage 3
Building projects for the future

Sydney Brenner Institute
for Molecular Bioscience
SBIMB



A WORLDCLASS RESEARCH
ENVIRONMENT FOR THE STUDY OF
NON-COMMUNICABLE DISEASES
IN AFRICANS



Ralph Ramsay



Development and construction of databases and analysis tools to store, organise, select, retrieve, compare, analyse, integrate and share vast amounts of biological data

Wits Research Thrusts



Sydney Brenner Institute for Molecular Bioscience

SBIMB



A WORLDCLASS RESEARCH ENVIRONMENT FOR THE STUDY OF NON-COMMUNICABLE DISEASES IN AFRICANS

SBIMB

Genomics

Epigenetics & Developmental Biology

Molecular & Cell Biology

Computational & Structural Biology

Applied Clinical Research & Epidemiology

Extensive collaboration



Emphasis on studying populations of African origin

AFRICAN DIASPORA



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