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Oral Presentations

Plenary 1
PREDICTIVE TESTING FOR HUNTINGTON'S DISEASE AND END-OF-LIFE ISSUES: THE DUTCH EXPERIENCE

Aad Tibben

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One of the main reasons why individuals at risk for Huntington's disease and other hereditary neurodegenerative disorders apply for predictive testing is to exert control over their life and to prevent the humiliating deterioration they have witnessed in close relatives. For some individuals identification of the disease-related mutation means the articulation of an advance directive regarding end-of-life when the disease has entered a stage that is considered as incompatible with quality of life. Such a directive, the ultimate expression of control, ought to be the reflection of a process of many years in which family and professional caregivers are also involved. According to the Dutch law, which reflects a year-long social and political process, euthanasia and physician-assisted suicide are considered to be legitimate provided strict conditions are met. Discussing end-of-life wishes require in-depth exploration of the moral convictions and belief systems of both the patient and the professional caregivers involved. In addition, given the impact of self-chosen death on the family and friends, such a decision asks also for a family-system approach.

Plenary 2
THE UCSC GENOME BROWSER

Robert Kuhn

UCSC Genome Browser Center for Biomolecular Science & Engineering, Baskin School of Engineering, Santa Cruz, CA, USA

For 13 years the UCSC Genome Browser has been providing a visual display for genomic data from human and other organisms (now numbering more than 80). Serving nearly 200,000 different users monthly, the Browser has grown to be a collection of useful bioinformatic tools. This presentation will demonstrate the Browser and a selected set of the most useful features. The Table Browser provides a convenient interface on the massive underlying data; Blat and isPcr allow users to align sequences and predict the products of PCR, respectively. User data, including the results from sequencing experiments, may be uploaded as Custom Tracks for juxtaposition with Browser-resident data, which include gene predictions, genomic variants ranging from the 50 million SNPs of dbSNP to large CNVs, disease associations, curated data from OMIM and RefSeq, and cross-species alignments.

Plenary 3
THE GENETICS OF EYE DISORDERS: AN OVERVIEW

Graeme Black

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Over half of the conditions causing childhood blind and partial-sighted registration are genetic. For both monogenic and complex disease, the study of the inherited ocular disease represents a success of modern molecular genetics, from the huge genetic heterogeneity now uncovered for inherited retinal disease to the delineation of genetic variants in the complement pathway as key genetic contributors to AMD.

This overview will examine the multidisciplinary clinical approaches required for diagnosing genetic ophthalmic disease. Given the high genetic heterogeneity that exists among many genetic ophthalmic disorders (optic atrophy; congenital cataract; retinal dystrophy), next-generation sequencing approaches are proving valuable not only for ongoing gene discovery, which will be discussed, but also in a diagnostic context. The latter will be explored to show how individualized management of patients with complex phenotypes is being delineated by high throughput genomic technologies. Finally, the talk will explore how functional understanding of the pathways underlying inherited ocular disease is making the development of novel treatment modalities a reality.

Plenary 4
THE GENETICS OF MICROPHTHALMIA/ANOPHTHALMIA

Robyn Jamieson

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Anophthalmia and microphthalmia, where there is absent or very poor development of the eye, are among the most devastating disorders causing blindness due to their congenital nature and paucity of treatment options. Examination of the child and family must include consideration of associated systemic and dysmorphic features which may lead to a syndrome diagnosis. There is marked ocular phenotypic heterogeneity with associated disorders of the anterior segment (sclerocornea), lens (cataract) or optic fissure (coloboma) often identified. Variable expression and penetrance of the ocular features in

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family members is very common, so detailed ophthalmic examination must be undertaken in at least all first-degree relatives to provide accurate recurrence risk information. Mutations in SOX2 account for approximately 10 to 20% of cases with anophthalmia, while mutations in other genes including OTX2, RAX, BMP4, and FOXE3 each account for a smaller proportion of cases, with the underlying disease gene unknown in many patients. Our next-generation sequencing studies of patients with balanced chromosomal translocations, and exome sequencing using a trio approach and families with informative pedigree structure, is leading to novel candidate disease gene identification. The cell-based assays we have developed, as well as our use of the zebrafish as a model system in eye development, are used to facilitate validation of our novel candidate disease genes.

Plenary 5
THE GENETICS OF ANTERIOR CHAMBER DISEASE

Andrea Vincent

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The anterior segment of the eye consists of the cornea — the clear window allowing light through, the anterior chamber, the iris and the crystalline lens. Genetic disorders affecting the anterior segment consist of (1) arrested development with disruption and congenital defects of these components, (2) progressive bilateral inherited disorders — the corneal dystrophies, resulting in clouding and scarring, (3) progressive thinning and ectasias, such as keratoconus, the leading cause for corneal transplantation in New Zealand, and (4) involvement in systemic disorders, such as the lens subluxation observed in Marfan syndrome. The presentation will give an overview of the work conducted in the Genetic Eye Disease Investigation (GEDI) laboratory relating to anterior segment genetics. The three main topics will cover the process of identification of a unique corneal dystrophy causing recurrent corneal erosions and scarring, with candidate gene screening, linkage genome-wide scan and exome sequencing to identify a novel gene. Investigation of the genetic cause for keratoconus will cover candidate genes screening in VSX1 and ZNF469, and a genome-wide scan in Maori and Polynesian families. The final component will present the result of ADAMTSL4 analysis in a group of 'marfanoid' FBN1 negative patients. This work contributes to the knowledge of the genetic and phenotypic heterogeneity of this group of disorders.

Sutherland Lecture
ON THE IMPORTANCE OF THE SHOULDERS OF OTHERS

Stephen Robertson

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Plenary 6
NEWBORN SCREENING PANELS: HOW THEY ARE SELECTED AND MEASURING THEIR BENEFITS

R. Rodney Howell

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Newborn screening developed following the dramatic discovery in Norway of the biochemical basis of phenylketonuria (PKU) and the spectacular benefit when PKU was treated early using a special diet. In order to identify infants before brain damage occurs, it was necessary to develop an inexpensive, reliable test that could be applied to every baby born. Such a test was developed by Guthrie in Buffalo, New York, using dried blood spots for testing.

These discoveries led almost overnight to mandated newborn screening in every US state by the mid-1960s. Additional newborn screening tests were later developed for other conditions, which greatly expanded capabilities to both diagnose and treat serious fatal or damaging conditions. This led to a marked increase in newborn screening throughout the United States.

As this is a public health program, the decision as to what tests are performed is under individual state regulation. By 2000 there had developed enormous variation from state to state as to the tests being chosen for the newborn screening panel. Major federal efforts developed to harmonize these tests. The Health Services and Resource Administration (HRSA) funded the American College of Medical Genetics (ACMG) to bring together experts (physicians, scientists, lawyers, families, patients) to review newborn screening, and particularly to develop a 'core recommended panel'. This has become known widely as the ACMG panel. At the same time, the US Congress passed the Healthy Child Act of 2000, which directed the establishment of a Federal Advisory Panel, the Advisory Committee on Hereditary Disorders in Newborns and Children (ACHDNC), which had a broad charge to advise the Secretary of Health and Human Services about genetic testing in children, especially newborn screening. This committee's recommendations, which are required to be evidence based, have resulted in vastly more consistency in the newborn screening panel from state to state.

Today, virtually all of the more than 4,100,000 infants born in the United States are screened for at least 30 conditions. This makes newborn screening by far the most common genetic testing performed in the United States. All of the conditions currently on the newborn screening panel are treatable, and some of these treatments are dramatically effective. The current screening program in severe combined immune deficiency (SCID) will be discussed to illustrate the benefit of such programs.

Working with the ACHDNC, the National Institutes of Health has developed the newborn screening translational research network (NBSTRN), which will provide much-needed longitudinal studies of screened individuals in order that we will have evidence-based information on the long term outcomes and benefits of these individual treatments. This network will also provide structure for the evaluation of new treatments for screened conditions.

Plenary 7
SIMILARITIES AND DIFFERENCES IN MEDICAL GENETIC PRACTICE IN ASIA AND AUSTRALASIA

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Cultural competence of health professionals is becoming increasingly important in the Australasian socio-cultural milieu. While the first wave of immigrants hailed from an Anglo-Saxon background, subsequent waves have been from other European backgrounds, with Asian and African immigrants being the most recent additions to the Australian landscape. Cultural competence is not limited to being sensitive and empathetic towards the psychosocial needs of a patient from a different background, but involves enlightened examination of the counselor's own culture, the 'yardstick' against which other cultures are measured. Compassionate comprehension, by improving cultural knowledge, but not using it to generalize and stereotype the values, character and needs of individuals, should be an aim of all culturally competent counsellors. Negative counseling experiences may arise from cultural and ethnic differences between counsellor and counselee if the differences inhibit communication. We present several observational vignettes to highlight the cultural differences and similarities of patients presenting for clinical genetic counseling in Hong Kong, a Special Administrative Region of China. Our perspectives as Asian-born clinical

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geneticists with 'Western' training provide unique insights as well as challenges.

Plenary 8
MEETING THE CHALLENGE OF PREPARING FOR THE 21ST CENTURY PATIENT — AUSTRALIAN AND INTERNATIONAL PERSPECTIVES IN UNDERGRADUATE AND POSTGRADUATE EDUCATION IN THE NEW MEDICAL GENOMICS

Emma Palmer

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Medical genomics includes the health-care application of new genomic technologies; for example, chromosomal microarray testing, direct-to-consumer genomic profiling and next-generation genome sequencing. Such technological developments promise improvement in diagnosis, therapy and preventative medicine. Limitations are recognised — for example, genomic diagnostic techniques evolve faster than our ability to interpret their results. Increasingly, internet-competent, proactive patients, interested in preventative health care, are seeking access to, and interpretation of, their genetic information. Their time-constrained physicians report a lack of confidence in discussing genomic medicine and question the clinical utility and relevance to their practice. There is public concern about the level of physicians' knowledge and ability to discuss genomics-based medicine. Patients may bypass their physicians; in the face of slick advertising from commercial genomic enterprises. This could result in missed opportunities to maximize potential benefits and minimize potential harms of genomic medicine. Effective engagement of the physician in learning about the new genomic medicine is key. Major challenges include how to increase the perceived clinical relevance of these diagnostic tools and how to foster dialogue between genetic and non-genetic physicians. A shift to a more collaborative patient–physician relationship may be required, as well as radical changes to traditional 'symptom-led' medical consultations. Australasian and international approaches to medical genomics education will be presented, as well as medical student and physician perceptions of their genomics education and knowledge. Lessons learnt from the adoption of chromosomal microarray testing by non-geneticists and innovative approaches to preparing the physician to meet the challenge of new genomic medicine will be discussed.

Plenary 9
LEARNING HAPPENS

Maggie Meeks

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'Doctor' is a term that comes from the Latin word 'to teach', but many of us feel ill prepared for the role of teacher. A 'teacher' to us conjures up a different image that may not agree with our self-image of research scientist, clinician or geneticist. Some teachers, or those that educate (including parents!), may be heard to use the phrase 'do as I say and not as I do', but the reality is that much of our learning follows what we see being done. In the area of communication we are more likely to believe the non-verbal than the verbal when there is conflict between these two messages, and as teaching can be considered a form of communication, our non-verbal role-modeling can be critical. I want to explore this thought a little more in the context of the conference with reference to what it is to be human with our particular patterns of behavior and behavioral influences.

The second part of my talk will discuss the evidence-based teaching. We do now have access to an abundance of information in this area, particularly in regard to children and adolescents. Although there is an argument that 'adult education is different', I do not think that this is the whole story and I will summarize some key points in these areas.

Plenary 10
THE UCSC BROWSER AS AN EDUCATIONAL TOOL

Robert Kuhn

UCSC Genome Browser Center for Biomolecular Science & Engineering, Baskin School of Engineering, Santa Cruz, CA, USA

The Educational Workshop will demonstrate how the Genome Browser graphical display can be used to present concepts in molecular biology and medicine, including gene structure and expression, transposons and repeats, and variation within the human population. The Conservation and Chain/Net data tracks are used to illustrate evolutionary relationships between organisms, including the accumulation of mutants in introns that accrue through time, conservation in functionally important regions such as exons, and the power of conservation to drive research into genomic elements of unknown function. The UCSC Genes track will be presented as a gateway to a vast array of external datasets.

Plenary 11
DYNAMIC DUPLICATIONS, NEUROCOGNITIVE DISEASE, AND HUMAN EVOLUTION

Evan Eichler

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Duplicated sequences are important sources for the evolution of new gene function within species. By dint of their homology, duplicated sequences are also hotspots of genomic rearrangement and one of the primary sources of structural variation. Humans and great apes have a preponderance of intrachromosomal duplications organized in an interspersed fashion as opposed to tandem, which is the archetype in most other mammalian genomes. We have reconstructed the evolutionary history of these regions within the primate lineage. All of these data point to a burst of segmental duplications in the common ancestor of humans and apes in contrast to other mutational processes that have slowed. I will show that much of the interspersed human duplication architecture is focused around core duplicons corresponding to the expansion of gene families, which show strong signatures of positive selection and lack orthologs in other mammalian species. I will provide examples of novel genes that have evolved within the human lineage and may be important in terms of brain function, including unique adaptations on the ancestral human lineage. Paradoxically, the duplication architecture has led to a high background rate of copy number variation mutations associated with neuropsychiatric and neurodevelopmental disease in the human species, suggesting that novel adaptations and increased disease burden are linked.

HGSA Oration
GENETICS IN CLINICAL PRACTICE: INTEGRATING NEW DISCOVERIES INTO PATIENT CARE OVER THREE DECADES

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