Practical Challenges for Clinical Genetic Services

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Practical Challenges for Clinical Genetic Services

• Genetics in the clinic
  – What we do in Genetic Medicine that others don’t
  – Incorporating research
  – Issues we have faced

• How Genetic Medicine is changing
  – Array technologies
  – Pharmacogenetics
  – Treatment of genetic disease
  – Next generation sequencing
  – Concerns about DTC testing
Medical Genetics as a clinical specialty

*What we do in genetics that others don’t*

- Services for affected patients and families
- All age groups
- All body systems
- Over generations
- Knowledge of rare disorders
- Screening, monitoring and anticipating complications
- Genetic counselling to affected and apparently healthy people
- Major source of information
- Education role
Practical Challenges for Clinical Genetic Services

- Recognition of clinical/medical genetics as a medical specialty
- Recruiting the right people with the right background
- Ensuring the curriculum reflects the changing nature of the specialty
Genetics Medicine has always incorporated research

- Genes mutated in almost all ‘common’ monogenetic disorders found
  - Translated into services for patients
    - Diagnostics, risk assessment, anticipatory care

- Genetic clinics were never limited to families with chromosomal and single gene disorders

- Complex cohorts collected
  - cancer, clefting, obesity, diabetes, learning disability, dementia etc
  - pedigrees and phenotypes well documented
Genetics involves whole families and information changes over time.
Genetic tests can make a difference

*DMD*

DNA tests - effect on numbers at risk

1987 214 families, 929 females at risk

2009 320 families, 308 females carriers

*NWR Genetic Family Register*
Practical challenges for clinical genetic services

the rise of cancer genetics – now 50% of referrals

Monogenic cancer prone syndromes

Subsets of common cancers

5% monogenic (bowel, ovary and breast cancers)
Medical Genetics a changing specialty

Heart disease

Rare forms due to single gene mutations
- Genes causing long QT
- Cardiomyopathy

Defibrillators, drugs etc

Challenge is getting doctors to recognise and refer
In Genetic Medicine we have faced many of the issues being considered today

- Predictive testing
- Consent
- Privacy
- Communication
- Unexpected results

**Predictive testing for Huntington’s disease: the calm after the storm**

Predictive testing for Huntington’s disease has now been offered for longer than for any other genetic disease. A DNA marker linked to the disease was discovered in 1983, and prenatal and predictive testing programmes for Huntington’s disease began in 1988. Predictive testing became technically simpler after the identification of the Huntington’s disease gene and the demonstration that the disease was always due to trinucleotide-repeat expansion, whereas prior to this, enrolling a large number of family relatives for linkage analysis was difficult. Peter Harper and colleagues have recently described the information collected by the UK Huntington’s disease family planning, but to relieve the uncertainty of whether or not they carry the gene and to under life and career decisions.

What is remarkable is how this predictive test has become primary and overtaking responsibility of the geneticist is to the patient assuming for testing led to change to the international guidelines to include those at 23% prior risk. Another reason for the successful integration of this test into national health services has been universal access to the test irrespective of the ability to pay. By contrast, in the USA, despite the development of programmes in many states, patients may choose to be tested outside of established programmes for reasons of convenience, cost, or privacy. As a result, there are numerous stories of disheartening results that are not given by telephone or without counselling. A recent standard of care—which includes pre-test counselling, disclosure of results to persons, and the availability of post-test counselling and support—has also.

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**Revealing false paternity: some ethical considerations**

Arunet Luconnon, Michael Farley

**Introduction**

Advances in genetic research are allowing increasing numbers of conditions to be diagnosed at the molecular level. Confirmation of a genetic condition in one person almost inevitably has implications for others. To reveal information not only about the person tested but also where the information has reproductive implications for both partners. But what is current practice?

**Current perspectives in clinical practice**

The consensus emerging from the literature is not to tell the husband directly of the result. Only one report on the consultation, Mary reveals that Peter is not the father of her child. In this case, it would normally be considered inappropriate for the GP to inform Peter without Mary’s permission. The same duty of respect for confidentiality ought to apply in the case of Sarah and John unless there is a morally significant difference between the cases. There are in fact several key differences that make this approach equally difficult. Firstly, the information about paternity in...
Challenges of new technologies and applications

• How Genetic medicine is changing
  – Array technologies used to investigate MR/multiple malformations
  – Pharmacogenetics
  – Treatment of genetic disease
  – Next generation sequencing
Better diagnosis and disease characterisation

For causes of developmental disorders
Case study

1982 Referral from Paediatric neurologist - Please see this patient who has severe developmental delay and seizures. He has had the following investigations; TORCH screen, metabolic workup, chromosome analysis

Severe retardation
Seizures
‘mannersitic’ behaviour
Unusual hair whorls
Prominent lips
Case study

Similar appearance to brother
Hand wringing
Lip smacking
Severe LD
At 19 yrs 20 words

Investigations over the years
ATRX, ARX, MECP2, UBE3A, telomere screen, 1Mb array.
Entered in GOLD study

Sister counselled likely XLR inheritance
1 in 2 risk of being a carrier
Decision to have prenatal sexing and TOP of males
Pregnant Dec 2007
245kb deletion eliminates exons 2-15 of MAOA and all 15 exons of MAOB, NDP remains intact – confirmed with Affymetrix V6 array.

Deletion of MAOA and MAOB in a male patient causes severe developmental delay, intermittent hypotonia and stereotypical hand movements

Annabel Whibley1, Jill Urquhart2, Jonathan Dore2, Lionel Willatt3, Georgina Parkin3, Lorraine Gaunt2, Graeme Black2, Dian Donnai2 and F Lucy Raymond*1

Monoamine oxidases (MAO-A and MAO-B) have a key role in the degradation of amine neurotransmitters, such as dopamine, norepinephrine and serotonin. We identified an inherited 240 kb deletion on Xp11.3-p11.4, which encompasses both monoamine oxidase genes but, unlike other published reports, does not affect the adjacent Norrie disease gene (NDP). The brothers who inherited the deletion, and thus have no monoamine oxidase function, presented with severe developmental delay, intermittent hypotonia and stereotypical hand movements. The clinical features accord with published reports of larger microdeletions and selective MAO-A and MAO-B deficiencies in humans and mouse models and suggest considerable functional compensation between MAO-A and MAO-B under normal conditions.

European Journal of Human Genetics advance online publication, 19 May 2010; doi:10.1038/ejhg.2010.41

Keywords: monoamine oxidase; MAOA and MAOB; array CGH; X chromosome; abnormal hand movement
Clinical implications of diagnosis

April 2010. Admitted to hospital with chest infection. Started on antibiotics. Sudden collapse – transferred to ICU. Febrile, hypertensive and restless therefore sedated but no improvement? Small cerebral bleed’

Because he has no MAOA/MAOB he responds abnormally to certain foods and drugs – life threatening
Incidental findings with serious consequences

Predictive diagnosis of the cancer prone Li–Fraumeni syndrome by accident: new challenges through whole genome array testing

T Schwarzbraun, A C Obenauf, A Langmann, U Gruber-Sedlmayr, K Wagner, M R Speicher, P M Kroisel


Patient with 5q23.1 deletion includes APC gene
Challenges of new technologies and applications

_Pharmacogenetics_

*Predict whether a specific drug (dose) will be effective or cause complications*

Used in RA, IBD, psoriasis, transplantation, leukaemia
65,000 patients put on this drug every year in UK

TPMT (Thiopurine methyltransferase) testing detects;
1 in 200 people who have the deficient genotype and develop severe bone marrow problems
Tamoxifen use in BRCA1/2 positive patients

The effect of CYP2D6 genotype (*4 allele) and of CYP2D6 inhibitors

Will patients see the use of pharmacogenetic testing as drug rationing?
Treatment of Genetic Disease

Many options

Management of complications
Dietary management
Vitamin responsive metabolic diseases
Enzyme therapies
Organ transplantations
Protein/drug engineering
Gene therapy
Conventional pharmacology
Treatment Trials with already licensed drugs

- Marfan Syndrome
  - Losartan
- Tuberous sclerosis
  - Rapamycin
- Huntingtons disease
  - Dopamine stabilisers
  - Dimebon
- NF1 and NF2
  - Rapamycin and sorafenib
- FRAX
  - fenobam
Practical Challenges for Clinical Genetic Services

Next generation sequencing


Miller syndrome

Schinzel-Gideon syndrome

Hoischen et al Nature Genetics
aol pub May 2010
Personal genomes

Whole-Genome Sequencing in a Patient with Charcot–Marie–Tooth Neuropathy

Background
Whole-genome sequencing may revolutionize medical diagnostics through rapid identification of alleles that cause disease. However, even in cases with simple patterns of inheritance and unambiguous diagnoses, the relationship between disease phenotypes and their corresponding genetic changes can be complicated. Compre-

Clinical assessment incorporating a personal genome

Summary
The cost of genomic information has fallen steeply, but the clinical translation of genetic risk estimates remains unclear. We aimed to undertake an integrated analysis of a complete human genome in a clinical context.

Methods
We assessed a patient with a family history of vascular disease and early sudden death. Clinical assessment included analysis of this patient’s full genome sequence, risk prediction for coronary artery disease, screening for causes of sudden cardiac death, and genetic counseling. Genetic analysis included the development of novel methods for the integration of whole-genome and clinical risk. Disease and risk analysis focused on prediction of genetic risk of variants associated with mendelian disease, recognized drug responses, and pathogenicity for novel variants.

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Results
Analysis of 2.6 million single-nucleotide polymorphisms and 752 copy number variations showed increased genetic risk for myocardial infarction, type 2 diabetes, and some cancers. We discovered rare variants in three genes that are clinically associated with sudden cardiac death—EMEM43, DSBP, and MYR1. A variant in LIPA was consistent with a family history of coronary artery disease. The patient had a homozygous null mutation in CYP2C9 suggesting probable clopidogrel resistance, several variants associated with a positive response to lipid-lowering therapy, and variants in CYP2F2 and VKORC1 that suggest he might have a low initial dosing requirement for warfarin. Many variants of uncertain importance were reported.
Issues to be considered in Clinical Practice in whole genome sequencing

• Initial consent
  – Service
  – Research – consent to feedback?

• Finding linked to reason for testing or research

• Finding incidental to reason for testing/research
Issues to be considered in Clinical Practice in whole genome sequencing

• Which variants to be reported
• Verification of finding from research lab in QA assured lab

• Who feeds back
• Implications for health/screening etc
• Implications for family members
• Testing children
Practical challenges

The rise of Direct to Consumer testing

Potential impact on clinical genetic services

The ‘Worried well’ using limited services
Practical challenges

The rise of Direct to Consumer testing

• ‘Health screening’ with SNPs etc

• Whole genome screening

What about the impact of the $1000 genome?
Concerns about DTC testing

Autism genome-wide copy number variation reveals ubiquitin and neuronal genes


Autism spectrum disorders (ASDs) are childhood-onset neuropsychiatric disorders with complex genetic etiology. 1% - 2% of children born each year have identifiable genetic etiology. Ongoing studies focusing on candidate genes or genomewide have identified several copy number variations (CNVs) that are associated with various neurodevelopmental disorders. In this work, we report the identification of a total of 69 CNVs across 20 autism spectrum disorders (ASDs) in a cohort of 1,259 ASD cases and 1,039 healthy controls of European ancestry. In one study of twins discordant for ASD, in the same study, we found that CNVs that are associated with autism spectrum disorders (ASDs) are much more common in individuals with ASD than in controls. The identification of these CNVs has implications for the understanding of the genetic basis of ASDs and for the development of new therapeutic approaches.

Common genetic variants on 5p14.1 associate with autism spectrum disorders


Autism spectrum disorders (ASDs) are a group of childhood-onset neuropsychiatric disorders with complex genetic etiology. Owing to the genetic complexity of ASD, the search for genetic factors associated with ASD has been challenging. The identification of genetic variants associated with ASD is crucial for understanding the biology of ASD and developing targeted treatments. In this study, we searched for genetic variants associated with ASD, specifically focusing on 5p14.1, which is known to be associated with autism spectrum traits. Our analysis revealed several common genetic variants in the 5p14.1 region that are associated with autism spectrum traits. These variants may contribute to the risk of ASD and provide insights into the genetic mechanisms underlying ASD.

Nature online 28.4.2009
Autism and genetics: A breakthrough that sheds light on a medical mystery

By Steve Connor, Science Editor
Thursday, 10 June 2010

Scientists have discovered the first significant link between autism and DNA, in a study that could revolutionise understanding of this disturbing behavioural disorder which affects more than half-a-million Britons.

The researchers believe the changes they have found to the genetic make-up of autistic children play a significant role in causing the developmental illness. Their findings could eventually lead to early diagnostic tests for autism and new forms of treatment, based on the genetics.

Functional impact of global rare copy number variation in autism spectrum disorders

A list of authors and their affiliations appears at the end of the paper.
Practical Challenges for Clinical Genetic Services

Medical Geneticists must get back in the ‘mainstream’ of medicine

Patients with rare diseases need continuing care and treatment, their relatives need our services

We must embrace the new technologies and ensure they are used appropriately for our patients

We should engage with patient groups, the public and media
Public engagement

Public engagement ‘onion’
For a sustainable model of public engagement and meaningful dialogue, need to support all layers.

Target Groups

– Schools and young people
– Public
  • Broad approach (exhibitions, TV, electronic media)
  • In more depth (polls and debates)
  • Healthcare professionals and allied groups
– Patient groups and cohorts