Clinical Genomics: Fundamentals of Variant Interpretation in Clinical Practice

29-31 January 2020

Wellcome Genome Campus, Hinxton, Cambridge, UK

Course Programme

Wednesday 29 January 2020

10:00-11:00 **Registration with morning coffee**

11:00-11:20 **Welcome and introduction: Principles of genomic medicine**
Dr Helen Firth
Cambridge University Hospitals, UK

11:20-12:50 **Session 1: Tools for variant interpretation**
In this session, you will be introduced to the tools that are used for variant interpretation. You will learn about the fundamental principles of each of the tools, their strengths and weaknesses and how they can be applied using the ACMG framework.

- 11:20 Setting the scene for variant interpretation: transcripts, annotation and moving from build GRCH37 to GRCH38 including MANE initiative
  Dr Sarah Bowdin
  Cambridge University Hospitals, UK

- 11:50 Population data: gnomAD, ExAC, constraint and PEXT scores
  Dr Kaitlin Samocha
  Postdoctoral Fellow, Wellcome Sanger Institute, UK

- 12:20 Computational and predictive data. In silico tools including splice tools. Strength and limitations
  Prof Andrew Wilkie
  University of Oxford, UK

12:50-14:00 **Lunch**

14:00-14:40 **Session 1 cont: Tools for variant interpretation**

- 14:00 Functional data
  Prof David FitzPatrick
  MRC Human Genetics Unit, University of Edinburgh, UK

14:20 Segregation data
Prof Andrew Wilkie
University of Oxford, UK

14:40-15:15 **Session 2: The ACMG framework**
During this session, you will understand how to apply your learning from sessions 1 and 2 to the ACMG framework (incorporating the ACGS updates) as a structure to facilitate variant interpretation.

Prof Sian Ellard
University of Exeter, UK

15:15- 15:45 **Session 3: Tools used in DECIPHER**
During this session, you will be introduced to the DECIPHER online resource which integrates variant interpretation tools and the ACMG framework to facilitate and record MDT variant discussion.

Dr Julia Foreman
DECIPHER Project Manager, Wellcome Sanger Institute, UK

15:45-16:15 **Afternoon tea**

16:15-18:00 **Session 4: Putting it into practice – Workshop 1**
In this first workshop, you will learn how to access the various variant interpretation tools and databases discussed during the day and apply your learning to interrogate genomic variation.

Decipher Team
Wellcome Sanger Institute, UK

18:00-18:45 **Free time**

18:00-18:45 **Opportunity for trainees to have tutorial discussions based on content covered during the day**

Dr Sarah Bowdin
Cambridge University Hospitals, UK
and
Prof Kate Tatton-Brown
ICR/St George's University, UK

18:45-19:30 **Pre dinner drinks**

19:30 **Buffet dinner**

Thursday 30 January 2020

Variant interpretation

09:00-09:10 **Introduction to Day 2**

09:10-10:30 **Session 5: Putting it into practice – Workshop 2**
In this second workshop, you will revise the concepts learnt during day 1 and apply the tools to increasingly complex rare disease genomic variants.

Decipher Team
Wellcome Sanger Institute, UK

10:30-11:00 **Coffee**

11:00-11:40 **Session 6: Risk estimation and penetrance**
In this session, you will be introduced to risk estimation and penetrance, and the role of genomics in diagnosis and screening.

11:00 Risk estimation in genomic medicine: understanding diagnostic and screening tests – the importance of prior risk and penetrance
Prof Andrew Read
University of Manchester, UK

11:20 Introduction to the tolerated population variation calculator
Dr Nicola Whiffin
Research Fellow, Imperial College London, UK

11:40-13:00 **Session 7: Workshop 3**
In this session, you will evaluate phenotype and genotype data using DECIPHER ACMG variant classifier, citation tool and clinical fit tool. Each centre to bring 5 illustrative cases. Work in teams to prepare cases for tomorrow morning's MDT discussion.

Decipher Team
Wellcome Sanger Institute, UK

13:00-14:00 **Lunch**

14:00-15:30 **Session 8: Cardiac genetics: Talk and Workshop 4**
In this session, you will learn why the interpretation of cardiac genetic variants differs from rare disease variant interpretation and how the ACMG criteria (and component tools/databases) can be applied to cardiac genetic variants.

Application of ACMG to cardiac genetics
Prof James Ware
Imperial College London, UK

Workshop
Prof James Ware
Imperial College London, UK
with
Dr Kate Thomson
Oxford University Hospitals, UK

15:30-16:00 **Afternoon tea**

16:00-18:00 **Session 9: Cancer genetics: Talk and Workshop 5**
In this session, you will learn why the interpretation of cancer genetic variants differs from rare disease variant interpretation and how the ACMG criteria (and component tools/databases) can be applied to cancer genetic variants.

Application of ACMG to cancer genetics
Prof Clare Turnbull
Cancer Lead, Genomics England, UK

Workshop
Prof Clare Turnbull
Cancer Lead, Genomics England, UK
with
Dr Marc Tischkowitz
University of Cambridge, UK
and
Dr Patrick Tarpey
Cambridge University Hospitals, UK

18:00-18:30 **Free time**

18:00-18:30 **Opportunity for trainees to have tutorial discussions based on content covered during the day**

Dr Sarah Bowdin
Cambridge University Hospitals, UK
and
Prof Kate Tatton-Brown
ICR/St George's University, UK

18:30-19:15 **Pre dinner drinks**

19:15 **Course Dinner**

Friday 31 January 2020

Multidisciplinary interpretation of the genome

09:00-10:45 **Session 10: Integrating phenotype and genotype for safe practice in genomic medicine**

This session will focus on the importance of interpreting a genotype in the context of phenotype and how MDMs can facilitate the robust interpretation of genomic variation.

09:00 Next-generation phenotyping and the link between genotype and phenotype – LGMDE threads
Prof David FitzPatrick
MRC Human Genetics Unit, University of Edinburgh, UK

09:20 Aggregating data to build knowledge
Dr Helen Firth
Cambridge University Hospitals, UK

09:40 GEL data and portals
Dr Richard Scott
Rare Disease Lead, Genomics England, UK

10:00 MDM working for the Genomic Medicine Service:
Lightning talks from each of the hubs (up to 7 talks)

10:45-11:15 **Morning coffee**

11:15-13:00 **Session 11: Future frontiers – beyond single gene variants in the coding sequence**

In this session, you will learn about new mechanisms of disease and techniques to interrogate the non-coding space.

11:15 How mutations lead to disease – concepts of dominance and recessivity – lessons from craniosynostosis and other disorders
Prof Andrew Wilkie
University of Oxford, UK

11:40 How mutations lead to disease: the role of chromatin associated proteins
Prof David FitzPatrick
MRC Human Genetics Unit, University of Edinburgh, UK

12:05 Interrogating the non-coding space
Prof Matt Hurles
Head of Human Genetics, Wellcome Sanger Institute, UK

12:30 Splicing
Prof Diana Baralle
University of Southampton, UK

12:55 Mutations in UTR's as a cause of disease
Dr Nicola Whiffin
Research Fellow, Imperial College London, UK

13:15-14:15 **Lunch**

Session 12: Future directions – therapeutics
In this session, you will hear how our increasing understanding of the genomic architecture of cancer and rare disease is driving the development of gene-directed therapies and the realisation of personalised medicine.

14:15 Rare disease and therapeutics
Prof Clara van Karnebeek
University of Amsterdam, The Netherlands

15:00 Mutational signatures in cancer therapeutics
Dr Serena Nik Zainal
University of Cambridge, UK

15:45-16:00 Course summary and wrap-up
Dr Helen Firth
Cambridge University Hospitals, UK

16:10 **Coach departs to Cambridge train station and city centre**