Clinical Dermatology

UCD CHARLES INSTITUTE SEMINAR SERIES

UCD School of Medicine
Scoil an Leighis UCD
Charles Institute of Dermatology

Of spots and stripes

Attendees at UCD's Charles Institute Seminar Series recently heard a presentation from ***Prof Veronica Kinsler*** *of University College London on mosaic disorders of the skin*

The Charles Institute, Ireland's national dermatology research and education centre, played host to a range of guest speakers who covered a variety of topics ranging from skin cancer to psoriasis, among others. The series, which was sponsored by RELIFE (part of the A.Menarini group), was designed to provide expert advice from a range of distinguished national and international experts in their respective fields and was chaired by Prof Desmond Tobin, Full Professor of Dermatological Science at UCD School of Medicine and Director of the Charles Institute of Dermatology. The seminars were broadcast to attendees with a special interest in dermatology in other locations, who accessed the talks remotely via an audio-visual link.

Attendees at the series recently heard a presentation from Prof Veronica Kinsler, Professor of Paediatric Dermatology and Dermotogenetics at Great Ormond Street (GOS) Hospital for Children and UCL GOS Institute of Child Health, and group leader at the Francis Crick Institute in London, where she runs the Mosaicism and Precision Medicine laboratory. Against the backdrop of her ongoing work in providing new understandings of the causes and treatment of these disorders using a personalised medicine approach, Prof Kinsler delivered a talk titled 'Of Spots and Stripes: Understanding Mosaic Disorders of the Skin'.

Prof Kinsler explained that within the past decade, technological advances have provided unprecedented insights into the genetic basis of many birthmarks, proving their 'mosaic' basis and leading to a new understanding of the associated cutaneous and non-cutaneous features, in the hope that this could lead to the development of new targeted therapies for these previously-untreatable diseases.

Prof Veronica Kinsler

Basic principles

Prof Kinsler told the attendees that there are some "basic principles" that are extremely helpful when a patient presents with these conditions. "What we have come to realise, since understanding that this is a single cell that is 'hit' by a mutation during embryonic development, is that these are the factors that influence what we see in the phenotype," she explained. "Mosaic disorders have been difficult to define and understand in the past because their phenotype is influenced by more than just the gene involved. Other facts influencing the phenotype are the cell type affected by the mutation, germline variation between individuals, the pattern of gene expression, the exact mutation and very importantly, the timing of the mutation.

"The earlier the mutation happens in development, the more potent those cells are, and the more offspring those cells will have, all carrying the mutation."

Prof Kinsler provided an overview of work she has conducted with her team on stripes, and spoke about "an inflammatory, linear, verrucous, epidermal naevus (ILVEN). These conditions present as linear in appearance and can be either present at birth or can appear in the first year or two after birth, but they can occasionally present slightly later.

"It is extremely difficult to treat. In fact, as part of diagnostic criteria that were proposed in 1985, resistance to treatment is actually one of the things that is listed as a criterion."

Genetic causes

"We hypothesised that this condition probably has multiple different genetic causes," Prof Kinsler continued. "Our work on ILVEN shows that it is a mosaic disorder, probably involving many genes. I think this explains all the arguments in the literature over the years about histology and pathogenesis." The case presented went on to receive a targeted therapy directed at the pathway dysregulated by the genetic cause, and resulted in dramatic and sustained clinical improvement. "This is also a nice demonstration that molecular dissection, although it can be painstaking, can really help in terms of new potential therapies for individual patients."

Prof Kinsler presented some data from a study conducted by herself and her colleagues on spontaneous lightening of congenital melanocytic naevi (CMN), including case studies from study participants, and explained that spontaneous lightening often occurs. "We found that the final colour of a congenital melanocytic naevus is significantly associated with the final colour of the participant's normal skin [colour]," she said. "However, the CMN is often very dark at birth, which is totally separate from the final colour, so the final colour of the CMN is totally unrelated to the CMN colour in the first three months of life.

"This is important, because quite a lot of people had previously thought that the colour at birth matters and have tried to lighten it via surgical intervention," Prof Kinsler continued. She presented case studies of patients who had undergone dermabrasion, laser and curettage treatments, including several cases where only part of the naevus had been treated. "What we have shown is that parts of the CMN that initially had lightening after these treatements re-pigmented to the genetically-determined colour, and those areas which were untreated gradually lightened to that same genetically-determined colour." Removing the top layers does not ultimately alter the final colour of the CMN and can also result in significant scarring, she pointed out.

Mutations

During a lively Q&A session following the presentation, Prof Tobin touched on the fact that mutations that cause mosaics occur at a single-cell level. "The consequence of that can be that you can end up on the pathway to tumourigenesis, but you also have a non-tumorigenic phenotype from the same single cell. Bearing that in mind, what along the way drives movement away from just a pattern in a static cell, to a carcinogenic risk?"

Prof Kinsler responded: "That's a great question. Mosaic mutations causing skin disease are often oncogenic mutations, well-described in cancers, but are not sufficient to cause cancer on their own. In development, they do what cancer genes do — they regulate differentiation and cell division, and produce the congenital phenotype.

> *[...] Our work on ILVEN shows that it is a mosaic disorder, probably involving many genes. I think this explains all the arguments in the literature over the years about histology and pathogenesis*

"But very often, these patients do also have a risk of cancer."

Speaking to the ***Medical Independent*** (***MI***) following her presentation, Prof Kinsler spoke about the supports available for these patients in terms of how birthmarks may affect their psychological wellbeing. "We provide psychological support via the hospital, but the bulk of it is done by the wonderful support groups for these conditions — for example, Caring Matters Now (***www.caringmattersnow.co.uk***), or Naevus International (***www.naevusinternational.com***)," she said. "Not all the conditions have support groups though, and we also rely on the charity Changing Faces."

Prof Kinsler also touched on the CMN Exhibition, 'How Do You C Me Now', which aimed to challenge public perception through photographic exhibitions of both children and adults with CMN. Many of the people in the photographs had never revealed their naevus before, so the exhibition was also aimed at improving the confidence of the participants.

Prof Kinsler concluded by telling ***MI*** her take-home message from the presentation for medical professional colleagues: "If you think it is mosaic and you don't know what it is or what to do with it in terms of investigation, refer it to us or to another centre which deals with mosaic cases and we can hopefully help."

RELIFE has had no input into the content of this article or series of seminars