European BHD Consortium (EBC) – Fourth Meeting

Present: Lennart Friis-Hansen (University of Copenhagen)
Maurice van Steensel (Maastricht University)
Tijs Claessens (Maastricht University)
Leike Gijezen (Maastricht University)
Eamonn Maher (Birmingham University)
Derek Lim (Birmingham University)
Xiaohong Lu (Birmingham University)
Anne Reimann (Birmingham University)
Lawrence Seabra (Birmingham University)
Mike Nahorski (Birmingham University)
Janine Fenton (Birmingham University)
Ferenc Mueller (Birmingham University)
Matt Rawlings (Birmingham University)
Fred Menko (VU University)
Paul Johannesma (VU University)
Jeroen van Moorselaar (VU University)
Arjan Houweling (VU University)
Marieke Kramer (VU University)
Magnus Nordenskjold (Karolinska Institutet)
Stephane Richard (Hôpital de Bicêtre et Institut de Cancérologie Gustave Roussy)
Sophie Deveaux (Hôpital de Bicêtre et Institut de Cancérologie Gustave Roussy)
Nicolas Kluger (Université Montpellier I)
Laura Schmidt (Urologic Oncology Branch, NCI, Bethesda, NIH).
Ravi Nookala (Cambridge University)
Tom Blundell (Cambridge University)
Andy Tee (Cardiff University)
John Solly (Myrovlytis Trust)
Duncan Azzopardi (Myrovlytis Trust)

Apologies: Thomas van Overeem Hansen (University of Copenhagen)

Date: 16th November 2009

Location: Hallam Conference Centre, London, UK.

Welcome by Eamonn Maher and a brief introduction by all attendees.

1. Birt-Hogg-Dubé syndrome. Gene discovery to folliculin function – an update (Laura Schmidt)

Summary of the discovery of the folliculin gene, and subsequent studies – discover of FNIP 1 and FNIP2, interaction with AMPK, role for FLCN in the mTOR pathway, BHD mouse models, etc.

2. Update on molecular biological studies in BHD (Tijs Claessens)

Update on the work being carried out to determine the mechanism(s) behind fibrofolliculoma development in BHD patients.

3. **Topical rapamycin for fibrofolliculomas – status of the trial (Lieke Gijezen)**

Introduction to the trial. The trial is scheduled to begin in January 2010 and currently has 57 possible patients in the Netherlands.

4. **Experiences of clinical testing for FLCN mutations (Magnus Nordenskojold)**

Comprehensive summary of the clinical and genetic studies of BHD families carried out at the Karolinska Institute.

5. **EBC folliculin mutation database (Derek Lim)**

Introduction to, and description of, the EBC folliculin sequence variation database – www.LOVD.nl/flcn

6. **BHD and colorectal cancer (Mike Nahorski)**

Discussion of possible association between BHD syndrome and incidence of sporadic colorectal cancer. Further investigation required.

7. **Zebrafish studies (Ferenc Mueller)**

Advantages of zebrafish as an animal model and its potential for high throughput screening. Discussion of attempts to generate a BHD model.

8. **Overview of mammalian target of rapamycin (mTOR) and cancer: implications for treatment of Birt-Hogg-Dubé (Andy Tee)**

Introduction to mTOR and its pivotal in several rare genetic conditions, including Tuberous Sclerosis and BHD syndrome. Discussion of possible non-mTOR mediated pathways in BHD syndromes and resultant potential therapies.

9. **Emerging insights into the structural biology of folliculin (Ravi Nookala)**

Discussion of possible structure of FLCN

10. **Activities of the French group (Stephane Richard)**

Brief history of BHD Syndrome in France, with the identification of the first BHD family in 1999. BHD syndrome is now the second most common rare disease diagnosed in France (first is VHL disease) affecting ~35 families and ~120 individuals.

11. **Birt-Hogg-Dube Syndrome: clinical and genetic studies of 10 French Families (Nicolas Kluger)**

Discussion of recent report of French BHD families (Kluger et al, 2009, British Journal of Dermatology)

12. Penetrance and clinical expression in Birt hogg Dube syndrome. A multicenter study in the Netherlands (Arjan Houweling)

Study of the penetrance of fibrofolliculomas, pneumothorax and renal cancer in 24 Dutch families. Analysis of the life time risk for pneumothorax and renal cancer.

13. A possible Danish FLCN founder mutation (Lennart Friis-Hansen)

Discussion of a possible Danish founder mutation IVS9+2T>G. Interested in investigating BHD families elsewhere in the world with Danish origin to provide more data.

14. Discussion of ultrasound versus MRI surveillance for renal cancer in BHD patients (Jeroen van Moorslaar)

Suggestion that that renal surveillance on confirmed BHD patients be carried out with ultrasound only – MRI scan not necessary. Suggestion that renal surveillance be carried out annually and that discovery of small tumours (<1cm) need not trigger surgery for 'a couple of years' because tumour growth rate is ~0.29cm per year, so risk of organ failure or metastasis is small.

15. Prevalence of Birt-Hogg-Dubé syndrome in patients with spontaneous pneumothorax (Paul Johannesma)

Study to assess the prevalence of BHD among patients with spontaneous pneumothorax, and to to evaluate characteristics of patients with demonstrated *FLCN* mutations.

16. Familial trichodiscoma: a syndrome clinically distinct from BHD and not linked to the FLCN locus (Fred Menko)

Summary of data showing that familial multiple trichodiscoma prevalent in the small coastal village of Usk in the Netherlands is not BHD syndrome, despite development of trichodiscomas on the face, and visual similarity (trichodiscomas also develop on ears and arms).

17. Development of a consortium clinical database format for uniform collection of patient data. (Marieke Kramer)

So far, 54 families have been referred to the VU Medical Centre for possible BHD. 24 of these have been confirmed by FLCN sequencing (10 families show clinical BHD but are mutation-negative). Presentation of the current Dutch patient database. Subsequent discussion about how this database could be used to pool data from different European countries.