Germline Pathogenic Variant Carriers: FLCN

Management Guidelines for Healthcare Professionals

General information

- Germline pathogenic variants (GPV-including class 4 likely pathogenic and class 5 pathogenic variants) in the FLCN gene are associated with Birt-Hogg-Dube syndrome (OMIM 607273) and follow an autosomal dominant inheritance pattern.
- FLCN heterozygotes (carriers) are at increased risk of renal cancer, lung cysts, spontaneous pneumothoraces and fibrofolliculomas.
- All histological sub-types of renal cancer can occur, but oncocyti/chromophobe subtype is most characteristic. Multifocal or bilateral tumours are frequently reported, but metastatic disease is rare.
- An association with colorectal polyps/cancer has been previously suggested, but remains unproven.
- An association with increased melanoma risk has been suggested, but further confirmation is required.

Associated risks

<table>
<thead>
<tr>
<th>Risk</th>
<th>Percentage</th>
<th>Age of Onset</th>
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<tbody>
<tr>
<td>Renal cancer</td>
<td>≈30% lifetime risk</td>
<td>≈50 years</td>
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<tr>
<td>Fibrofolliculomas</td>
<td>≈40% risk by age 30 years</td>
<td>Nearly complete penetrance by age 70 years</td>
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<tr>
<td>Lung cysts</td>
<td>≈75-85% lifetime risk</td>
<td>≈35 years</td>
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<tr>
<td>Pneumothoraces</td>
<td>≈30% lifetime risk</td>
<td>≈35 years</td>
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</tbody>
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Management recommendations*

Surveillance

- Annual renal surveillance age 18-70 years by MRI or renal USS (only with an experienced renal ultrasonographer). If an indeterminate lesion is identified on USS, further imaging with MRI is advised. Renal lesions should be monitored by MRI and Urology input.
- Surveillance beyond 70 years can be considered following discussion with the patient and consideration of other co-morbidities.
- Refer to local Clinical genetics for recommendations on organisation of renal cancer surveillance.
- Baseline lung high resolution CT scan at age 20 years or at diagnosis if diagnosis >20 years.
- Consider respiratory team referral if lung cysts identified or co-existing lung disease.
- Bowel surveillance with colonoscopy should only be offered where there is a family history of bowel cancer (See BSG recommendations).

Skin management

- Consider referral to Dermatology if skin lesions (fibrofolliculomas or trichodiscomas) present.
- Treatment for cosmetic reasons may be considered e.g. with shaving or laser ablation.

Lifestyle advice

- Provide information on the benefits of smoking cessation, minimising alcohol intake and maintaining a healthy weight to lower the chance of getting cancer.
- Exposure to large ambient pressure differences could predispose to pneumothorax in BHD patients. There is no evidence against commercial air travel, but individuals who are pilots, fly in unpressurised aircraft or are deep-sea divers, should be referred to a respiratory clinician for advice.
- Anaesthetists should be informed of the diagnosis of BHD before surgery requiring general anaesthetic.

Family matters

- Refer to clinical genetics for discussion of predictive genetic testing in at-risk family members.
- Predictive testing is normally considered from around the age at which surveillance starts.
- Refer to clinical genetics for discussions on reproductive options.

*If clinical criteria for BHD are reached according to European BHD Consortium criteria (Menko et al. 2009), but FLCN GPV not identified, surveillance in proband as above can be offered. For first degree relatives of proband over 18 years, offer clinical assessment +/- imaging for diagnostic purposes and offer ongoing assessment if clinical diagnosis of BHD made. Also consider re-assessment of skin at older age for individuals without FLCN GPV but have one other clinical feature of BHD e.g. lung cysts/basal lung cysts or RCC with typical BHD histology (i.e. chromophobe, hybrid mixed chromophobe-oncocytoma).

References

- https://www.ukcgg.org/information-education/ukcgg-consensus-meetings/

Patient resources

- Birt-Hogg-Dubé syndrome foundation : https://bhdsyndrome.org/