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NF1 – Neurofibromatosis type 1

NIHR BioResource – Rare Diseases study project

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Summary

Neurofibromatosis type 1 (NF1) is a multisystem autosomal dominantly inherited tumour predisposition neurocutaneous syndrome characterised by pigmentary skin changes and benign nerve sheath tumours (neurofibromas).

NF1 affects around 1 in 1/1900–2500 live births (Huson et al, 1989, Evans et al, 2010, Uusitalo et al, 2015) and significantly reduces life expectancy primarily due to the development of Malignant Peripheral Nerve Sheath Tumours (MPNST) in around 10% of affected people, but also gliomas and other malignancies including breast cancer (Evans et al., 2011).

The National Institutes of Health (NIH) defined diagnostic criteria* in 1987 (National Institutes of Health Consensus Development Conference, 1987) and these have largely remained unchanged also including bone dysplasia and Lisch nodules as criteria (Anderson and Gutmann, 2015, Gutmann et al., 1997). For such a large gene containing 58 coding exons (Shen et al., 1996) little is still known about domains outside the GTPase-activating protein-related domain (GRD) domain which is thought to be the main region associated with tumour suppression through down-regulation of the oncogene ras (Anderson and Gutmann, 2015, Ferner, 2007).

There are substantial risks of neurological deficits including cognitive impairment, epilepsy, spinal cord compression, cerebrovascular disease, and multiple sclerosis (Ferner, 2007). There are only a few genotype-phenotype correlations with certain missense mutations and an in frame deletion causing mild disease and a range of missense mutations in codons 844-848 (Koczkowska et al 2018) and whole gene deletions causing more severe disease. Generally there is wide variation in families making the likelihood of genetic modifiers high. The difficulties in early detection makes identifying biomarkers in blood a priority for MPNST.

Recruitment Criteria

Inclusion

Patients can be recruited to the NIHR BioResource if they meet diagnostic criteria (below) or have an identified pathogenic variant in NF1.

The diagnostic criteria for NF1 are met in an individual if two or more of the following are found (except pigmentary only criteria with no genetic confirmation):

- ≥6 cafe-au-lait macules
  - >5 mm, prepubertal individuals; >15 mm, postpubertal individuals
- ≥2 neurofibromas of any type or 1 plexiform neurofibroma
- Freckling in the axillary or inguinal region
- Optic glioma
- ≥2 Lisch nodules (iris hamartomas)
- Distinctive osseous lesion sphenoid wing dysplasia, pseudoarthrosis
- A first-degree relative (parent, sibling, or offspring) with NF1 by the above criteria

**NIH 1987, NF1 Criteria. Neurofibromatosis. NIH Consensus Statement 1987 Jul 13-15;6(12):1-19. https://consensus.nih.gov/1987/1987Neurofibramatosis064html.html*