Aim of Poster

The aim of this poster is to develop a deeper understanding of the mechanisms which cause neurofibromatosis type 1 on a cellular level and also explore the clinical manifestations which may arise from this disorder. Specifically, a focus will be placed behind the biology of peripheral neurofibromas.

An Introduction to NF-1

- NF-1 is an inheritable multisystem neurocutaneous disorder which affects the skin, nervous system, and eyes (Johnson Hopkins Medicine, 2018). NF-1 is characterized as an autosomal dominant disorder and is the most prevalent neurocutaneous syndrome affecting every 1 in 2,600-3,000 individuals (Rasuli, 2020).
- NF-1 mainly affects cells derived from the neural crest e.g., Schwann cells, melanocytes and fibroblasts (Trainor et al., 2014).
- NF-1 is the result of predisposing mutations occurring at the NF-1 gene locus which has the name 17q11.2 (Trainor et al., 2014).
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Genetic Cause of NF-1

- NF-1 is the result of predisposing mutations occurring at the NF-1 gene locus which has the name 17q11.2 (refer table 1). The gene product, neurofibromin, is a GTP-ase-activating protein that suppresses the Ras-pathway (Bergoug et al., 2020). • Mutations in the genetic code of the NF-1 gene result in nil production or inhibited function of the neurofibromin protein leading to elevated Ras-GTP levels. Raised levels of active Ras stimulate Raf, MEK and ERK kinases which are responsible for cell growth, proliferation and differentiation (Kang et al., 2019).
- Abnormalities of the NF-1 gene thus result in dysplasia and neoplasia leading to tumour formation (Rasuli, 2020).

Clinical Manifestations of NF-1

- The clinical manifestations of NF-1 can be identified by 3 main stages, where the manifestations are progressive with each stage (refer figure 2) (BMJ, 2018).
  - Stage 1 [Features] – this stage involves the manifestations which are directly correlated to the mutation of the NF-1 gene. Examples include café-au-lait macules, neurofibromas, vertebral dysplasia.
  - Stage 2 [Consequences] – this stage involves symptoms derived from stage 1 manifestations. For example, scoliosis is a derived from vertebral dysplasia.
  - Stage 3 [Complications] – this stage involves symptoms derived from stage 2 manifestations. For example, scoliosis leading to spinal cord compression.

Table 1: Types of pathogenic variants in the NF-1 gene with potential to disrupt normal synthesis of the gene product, neurofibromin leading to neurofibromatosis type 1 (Rubinstein, 2005).

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Notes</th>
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<tbody>
<tr>
<td>Small deletion</td>
<td>Removal of a small number of DNA bases, usually leading to failure of protein production.</td>
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<tr>
<td>Premature &quot;stop&quot; mutation</td>
<td>Changing the genetic instructions to insert an amino acid in a sequence that causes production of the protein to stop.</td>
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<td>Deletion of multiple exons</td>
<td>Can result in either shortening of the protein or complete loss of function.</td>
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<tr>
<td>Amino acid substitution</td>
<td>May alter the structure or function of the protein.</td>
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<tr>
<td>Small insertion</td>
<td>Has similar impact as a small deletion.</td>
</tr>
<tr>
<td>Mutation of an intron (encoding section of a gene)</td>
<td>Interferes with the splicing process, resulting in an abnormal protein, or no protein produced at all.</td>
</tr>
<tr>
<td>Deletion of entire gene</td>
<td>Complete gene deletion results in no protein product from that gene copy.</td>
</tr>
<tr>
<td>Chromosome abnormality</td>
<td>A rearrangement of the structure of a chromosome, cannot disrupt a gene, such as NF1.</td>
</tr>
<tr>
<td>Alteration of the T-untranslated region</td>
<td>Unclear if changes that follow the coding sequence of the NF1 gene are truly mutations or incidental changes.</td>
</tr>
<tr>
<td>Large insertion</td>
<td>Has similar impact as large deletions.</td>
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Pathophysiology and Pathogenesis of Neurofibromatosis Type 1 (NF-1): A Focus on Peripheral Neurofibromas
Brandon Truong, Faculty of Health and Medical Sciences, University of Adelaide

Biography of Peripheral Neurofibromas

- The formation of benign and malignant tumours increases in incidence throughout the life of an individual with NF-1 (Seminog, 2015).
- Peripheral neurofibromas are benign peripheral nerve sheath tumours which can present under the skin or deeper regions of the body and nerve roots exiting the central nervous system.
- These tumours form centrally within the nerve are made up of a unique combination of Schwann cells, fibroblasts, disrupted perineurial cells and mast cells (refer figure 3) (Ortonne et al., 2018).
- Schwann cells have been identified as the primary tumour cell of NF-1-associated neurofibromas due to nil discovery of NF-1 alleles in these cells and their neural crest origin (Maertens et al., 2006).
- There are three types of peripheral neurofibromas all of which are neoplasms of Schwann cells:
  - Cutaneous/dermal neurofibromas (cNF) – present as soft discoloured lumps on the skin. (Tonsgard, 2006).
  - Plexiform neurofibromas (pNF) – located superficially and on minor nerves and large nerves. May convert into malignant peripheral nerve sheath tumours (Dombi et al., 2007).
  - Nodular neurofibromas (nNF) – present as distinct, hard and tender lumps that grow under the dermis which may enlarge. nNF may be precancerous tumours (Miedtken, 2017).
- These tumours can present as clinically harmless or may compress surrounding nerves and tissues leading to damage (Brazier, 2018).

Figure 1: Diagram depicting (a) a healthy single nerve fascicle and (b) the composition of a single nerve fascicle in neurofibromas (Parrinello, 2009).

Figure 2: Progression of clinical manifestations of neurofibromatosis type 1. Clinical manifestations worsen from left to right (Gutmann, 2017).

Figure 3: Diagram depicting (a) a healthy single nerve fascicle and (b) the composition of a single nerve fascicle in neurofibromas (Parrinello, 2009).
References


Kang, E. et al. (2019) "Phenotype categorization of neurofibromatosis type I and correlation to NF1 mutation types", Journal of Human Genetics, 65(2), pp. 79-89. doi: 10.1038/s10038-019-0695-0.


