Annals of Otolaryngology and Rhinology

Mini Review

Point Mutations Underlying NF1 and NF2 and Increased Risk of Malignancy

Myles Davidson[1], Haupt TS[2], Morris DP[3,4], Shoman NM[3,4], Walling SA[2,4], and Hebb ALO[1,2,4]*

[1]*Department of Psychology, Saint Mary's University, Canada*
[2]*Division of Neurosurgery, Dalhousie University, Canada*
[3]*Division of Otolaryngology, Dalhousie University, Canada*
[4]*Maritime Lateral Skull Base Clinic, Otolaryngology, Neurosurgery and the Stereotactic Radiotherapy Group QEII Health Science Centre, Canada*

***Corresponding author**

Andrea L.O. Hebb, MSc, PhD, RN, Maritime Lateral Skull Base Clinic, Otolaryngology, Neurosurgery and the Stereotactic Radiotherapy Group QEII Health Science Centre, Halifax, Canada; Email: andrea.hebb@dal.ca

Submitted: 12 February 2020

Accepted: 25 February 2020

Published: 27 February 2020

ISSN: 2379-948X

Copyright

© 2020 Davidson M, et al.

OPEN ACCESS

Keywords

- Neurofibromatosis
- Missense mutation
- Frameshift mutation
- Nonsense mutation
- KRAS gene
- Colorectal cancer
- Acoustic neuroma
- Vestibular schwannoma
- Meningioma

Abstract

Neurofibromatosis Type-1 and Neurofibromatosis Type-2 are autosomal dominant tumor suppressor disorders that result from inherited or spontaneous mutations in their respective genes. Neurofibromatosis Type-1 has been attributed to a non-sense mutation in chromosome 17 and Neurofibromatosis Type-2 a point mutation in its gene on chromosome 22. The following discussion briefly reviews point and frameshift mutations and explores the relationship between point mutations and development of malignancies in patients with Neurofibromatosis Type-1 and Neurofibromatosis Type-2.

INTRODUCTION

A point mutation is the change of one base for another in the DNA sequence. Not all point mutations have clinical relevance (silent mutations) due to the redundancy of the genetic code with multiple codons coding for the same amino acid [1]. Missense and non-sense mutations, both point mutations, alter the amino acid sequence and resultant protein often resulting in a distinct clinical phenotype [1,2]. Frameshift mutations occur when one or more nucleotides is inserted or deleted disrupting the normal sequence of codons [3].

Missense mutation

Missense mutations occur when a single base pair in a triplet is substituted for another [1,4]. Unlike a silent mutation where the substitution simply leads to the presence of the same amino acid, the change in the triplet code in a missense mutation leads to the presence of an incorrect amino acid [4]. Accordingly, during protein synthesis, the protein that is created from the mRNA translation process will not be what was initially intended. The well documented condition phenylketonuria (PKU) is a result of a missense mutation. PKU is characterized by the failure of the body to process the amino acid phenylalanine due to a deficiency in the enzyme phenylalanine hydroxylase. A buildup of phenylalanine in the blood stream can lead to neurological damage in a developing child if the disorder goes untreated. There are currently 750 known mutations that can occur to the gene responsible for producing phenylalanine hydroxylase, the majority of which are missense mutations [4].

Frameshift mutation

Frameshift mutations differ in comparison to missense mutations as rather than a base pair substitution in a peptide triplet; frameshift mutations describe the insertion or deletion of one or more base pairs into the amino acid chain. As a result, all the peptide triplets before or after the insertion or deletion are altered and now correspond to different amino acids [3].

The devasting disease Tay-Sachs (GM2 gangliosidosis type1) is the result of a genetic mutation on the *HEXA* gene in humans [3]. Tay-Sachs disease disproportionately affects Jewish children of Ashkenazi descent. It is estimated that most Tay-Sachs cases are caused by the mutation of the *HEXA* allele that causes four base pair insertions on the gene, leading to a frameshift. The result of the frameshift mutation is the introduction of a stop codon and the premature termination of protein synthesis [3]. There is no treatment for Tay-Sachs and the child dies as a result of progressive deterioration of brain function.

Nonsense mutation

In a nonsense mutation, a base pair in a triplet code is replaced, but rather than leading to the presence of another amino acid, this replacement leads to the insertion of a stop codon [5]. A stop codon is a ribosomal signal the mRNA has completed the translation process and no more amino acids are required

to create the protein. Due to the presence of a stop codon at an unintended location in the amino acid chain, protein synthesis is halted prematurely resulting in a truncated protein [5].

NEUROFIBROMATOSIS

Neurofibromatosis Type-1 (NF-1) and Type-2 (NF-2) are autosomal dominant disorders known to be associated with both missense and nonsense mutations on chromosome 17 and 22 respectively [5-7]. NF1 and NF2 are both associated with malignancy through different oncogene signaling pathways [8]. Worldwide NF affects 1 in 3000 individuals worldwide (Children's Tumor Foundation; https://www.ctf.org).

NF1

Colorectal cancer is one of the primary causes of death in the western world and is the second deadliest cancer known, having a five-year survival rate of only 50 percent [9]. Like several other cancers, its origin is thought to be from the activation of the *KRAS* gene, a known oncogene. The NF1 gene is a negative regulator of *KRAS*. It governs hydrolysis of KRAS-GTP to KRAS-GDP [10]. Given that the *KRAS* gene is responsible for cell growth and maturation, mutations to this gene can lead to the over activity of cell growth and the formation of cancerous tumors. It is thought that missense mutations in codons 12 and 13 of the *KRAS* gene are responsible for one-quarter of all cancers, and almost half of all colorectal cancer cases [9,10].

Metastatic colorectal cancer refers to cancerous tumors in the colon or rectum that break away from their initial site and move elsewhere in the body [11]. Monoclonal antibodies against the epidermal growth factor receptor (anti-EGFR) are thought to be an effective way to combat metastatic colorectal cancer. When the cancerous tumors are caused by mutations on the *KRAS* gene, however, anti-EGFR has been deemed ineffective. Accordingly, *KRAS* testing recommendations in Canada have been modified to ensure that patients with colorectal cancer stemming from a KRAS mutation are treated with effective regimes. In 2011, a panel of Canadian gastrointestinal medical oncologists, molecular geneticists, and pathologists met in Montréal to discuss amendments to the testing and treatment protocols for colorectal cancer. Based on the best available literature, the panel concluded that amendments must be made regarding indications and timing for testing, sample requirements, recommendations for reporting requirements, and acceptable turnaround times [11].

NF2

NF2 is relatively uncommon and affects around 1 in 25000 people. Patients with NF2 present with bilateral vestibular schwannomas (acoustic neuromas) and have frequent clinical features such as neurological lesions, eye lesions, skin lesions which tend to have more serious symptoms in children [12-18]. Loss of function of a tumour suppressor protein (Merlin) results in bilateral vestibular schwannomas in patients with NF2 as well as an increased incidence of intracranial and intraspinal meningiomas. While bilateral vestibular schwannomas are the most common intracranial tumors associated with NF2, meningiomas are the second most common, occurring in over 50% of patients [19]. Up to 60% of sporadic meningioma's exhibit inactivation of NF2 by somatic mutation, epigenetic inactivation, or allelic loss of chromosome 22q [20].

NF2 mutations and merlin inactivation occur in spontaneous schwannomas and meningiomas. Overall, there are two primary types of sporadic meningiomas: tumors with or without the inactivated NF2 gene. As NF2-related meningiomas increase in grade, there is an increased level of chromosomal instability [19]. NF2-associated schwannomas exhibit NF2 inactivation and merlin expression is absent [21]. Merlin's tumor suppressor activity is three-fold. It is related to its contact inhibition of proliferation. Merlin normally functions to reduce the availability of receptor tyrosine kinases (RTKs) at the plasma membrane. Merlin is a negative regulator of the Hippo pathway in meningiomas and inhibits the activation of PI3K by binding phosphatidylinositol 3-kinase enhancer-L (PIKE-L). Phosphoinositide 3-kinase (PI3K)/AKT signaling is involved in the regulation of cell growth and proliferation. High-grade meningiomas showed higher levels of phosphorylated AKT compared to benign tumors, showing that the PI3K/AKT/mTOR pathway is associated with merlin-driven meningiomas [20]. Meningiomas may be of benign histology (WHO grade 1), increased mitotic activity (WHO grade II) or anaplastic (WHO grade III) with demonstrable brain infiltration [20,22]. In addition, it has been reported that patients with NF2 may have an increased risk of cancers, as a result of downstream effects of loss of merlin on oncogenic signaling pathways including RAS [23].

NF2, like NF1, has also been associated with increased colorectal cancer, albeit through inactivation of the Merlin gene. In a recent study, over 50% of colorectal carcinoma samples lacked one functional copy of the NF2 gene. The proportional fraction of merlin that was phosphorylated (deactivated) was higher in tumors compared to normal mucous tissue [21].

A multidisciplinary team, including but not limited to an otolaryngologist, audiologist, neurosurgeon, neurologist, nurse and geneticist usually follows NF-2 patients because of multisystem complications that occur. NF2 patients tend to be followed and monitored on an annual basis for tumor's; follow up can involve a history, physical exam, ophthalmologic and hearing evaluation, MRI's of the spine and brain [8].

MARITIME LATERAL SKULL BASE CLINIC

The Maritime Lateral Skull Base Clinic provides coordinated care through Otolaryngology, Neurosurgery and the Stereotactic Radiotherapy Group to patients with unilateral or bilateral vestibular schwannomas (also called acoustic neuromas) and a range of other lateral skull base tumours. Our program is unique in Canada in allowing members from all disciplines to formulate management decisions in the same clinic. NF2 Clinics is dedicated to patients with Neurofibromatosis Type 2 in collaboration with Medical Genetics, Radiology, Nova Scotia Hearing and Speech as well as Ophthalmology are held every second month. The MLSBC currently follow over 30 patients with NF2. Neurofibromatosis Society of Nova Scotia (http://www.nfsns.org) in collaboration with the Children's Tumor Foundation (https://www.ctf.org) provides education and support to patients and their families' diagnoses with NF1 and NF2.

CONCLUSION

Genetic mutations can result in clinically significant events in childhood and early adulthood. NF1 and NF2, once grouped

together, are now recognized as having distinct presentations. The NF1 and NF2 phenotypes are highly variable, ranging from mild manifestations of the disease in some individuals to very severe forms in others. Identification of specific cellular pathways promoting disease burden may provide evidence for the development of novel therapies and/or the implementation of available chemotherapeutic drugs.

REFERENCES

1. Chaudhary P, Naganathan AN, Gromiha MM. Prediction of change in protein unfolding rates upon point mutations in two state proteins. Biochim Biophys Acta. 2016; 1864: 1104-1109.
2. Raamsdonk LM, Teusink B, Broadhurst D, Zhang N, Hayes A, Walsh MC, et al. A functional genomics strategy that uses metabolome data to reveal the phenotype of silent mutations. Nat Biotechnol. 2001; 19: 45-50.
3. Lew RM, Burnett L, Proos AL, Delatycki MB. Tay-Sachs disease: current perspectives from Australia. Appl Clin Genet. 2015; 8: 19-25.
4. Réblová K, Kulhánek P, Fajkusová L. Computational study of missense mutations In phenylalanine hydroxylase. J Mol Model. 2015; 21: 70.
5. Wallace MR, Marchuk DA, Andersen LB, Letcher R, Odeh HM, Saulino AM, et al. Type 1 neurofibromatosis gene: identification of a large transcript disrupted in three NF1 patients. Science. 1990; 249: 181-186.
6. Sainz J, Huynh DP, Figueroa K, Ragge NK, Baser ME, Pulst SM. Mutations of the neurofibromatosis type 2 gene and lack of the gene product in vestibular schwannomas. Hum Mol Genet. 1994; 3: 885-891.
7. Rouleau GA1, Merel P, Lutchman M, Sanson M, Zucman J, Marineau C, et al. Alteration in a new gene encoding a putative membrane-organizing protein causes neuro-fibromatosis type 2. Nature. 1993; 363: 515-521.
8. Evans DGR, Salvador H, Chang VY, Erez A, Voss SD, Schneider KW, et al. Cancer and Central Nervous System Tumor Surveillance in Pediatric Neurofibromatosis 1. Clin Cancer Res. 2017; 23: e46-e53.
9. Dinu D, Dobre M, Panaitescu E, Bîrlă R, Iosif C, Hoara P, et al. Prognostic significance of KRAS gene mutations in colorectal cancer--preliminary study. J Med Life. 2014; 7: 581-587.
10. Ahlquist T, Bottillo I, Danielsen SA, Meling GI, Rognum TO, Lind GE, et al. RAS signaling in colorectal carcinomas through alteration of RAS, RAF, NF1, and/or RASSF1A. Neoplasia. 2008; 10: 680-686.
11. Aubin F, Gill S, Burkes R, Colwell B, Kamel-Reid S, Koski S, et al. Canadian Expert Group consensus recommendations: KRAS testing in colorectal cancer. Curr Oncol. 2011; 18: e180-e184.
12. Parry DM, Eldridge R, Kaiser-Kupfer MI, Bouzas EA, Pikus A, Patronas N. Neurofibromatosis 2 (NF2): clinical characteristics of 63 affected individuals and clinical evidence for heterogeneity. Am J Med Genet. 1994; 52: 450-461.
13. Mautner VF, Lindenau M, Baser ME, Hazim W, Tatagiba M, Haase W, et al. The neuroimaging and clinical spectrum of neurofibromatosis 2. Neurosurgery. 1996; 38: 880-885.
14. Evans DG, Huson SM, Donnai D, Neary W, Blair V, Newton V, et al. A clinical study of type 2 neurofibromatosis. Q J Med. 1992; 84: 603-618.
15. Bosch MM, Boltshauser E, Harpes P, Landau K. Ophthalmologic findings and long-term course in patients with neurofibromatosis type 2. Am J Ophthalmol. 2006; 141: 1068-1077.
16. Ragge NK, Baser ME, Klein J, Nechiporuk A, Sainz J, Pulst SM, et al. Ocular abnormalities in neurofibromatosis 2. Am J Ophthalmol. 1995; 120: 634-641.
17. MacCollin M, Mautner VF. The diagnosis and management of neurofibromatosis 2 in childhood. Semin Pediatr Neurol. 1998; 5: 243-252.
18. Mautner VF, Lindenau M, Baser ME, Kluwe L, Gottschalk J. Skin abnormalities in neurofibromatosis 2. Arch Dermatol. 1997; 133: 1539-1543.
19. Dewan R, Pemov A, Dutra AS, Pak ED, Edwards NA, Ray-Chaudhury A, et al. First insight into the somatic mutation burden of neurofibromatosis type 2-associated grade I and grade II meningiomas: a case report comprehensive genomic study of two cranial meningiomas with vastly different clinical presentation. BMC Cancer. 2017; 17: 127.
20. Sungho Lee, Patrick J. Karas, Caroline C. Hadley, James C. Bayley V, A. Basit Khan, Ali Jalali, et al. The Role of Merlin/NF2 Loss in Meningioma Biology. Cancers (Basel). 2019; 11.
21. Petrilli AM, Fernández-Valle C. Role of Merlin/NF2 inactivation in tumor biology. Oncogene. 2016; 35: 537-548.
22. Joachim T, Ram Z, Rappaport ZH, Simon M, Schramm J, Wiestler OD, et al. Comparative analysis of the NF2, TP53, PTEN, KRAS, NRAS and HRAS genes in sporadic and radiation-induced human meningiomas. Int J Cancer. 2001; 94: 218-221.
23. Garcia-Rendueles ME, Ricarte-Filho JC, Untch BR, Landa I, Knauf JA, Voza F, et al. NF2 Loss Promotes Oncogenic RAS-Induced Thyroid Cancers via YAP-Dependent Transactivation of RAS Proteins and Sensitizes Them to MEK Inhibition. Cancer Discov. 2015; 5: 1178-1193.

Cite this article

Davidson M, Haupt TS, Morris DP, Shoman NM, Walling SA, et al. (2020) Point Mutations Underlying NF1 and NF2 and Increased Risk of Malignancy. Ann Otolaryngol Rhinol 7(1): 1232.