Head and Neck Pathology (2019) 13:516–522
https://doi.org/10.1007/s12105-018-0934-2

CASE REPORT

# *P53* Gene Mutation Identified by Next Generation Sequencing in Poorly Differentiated Neuroendocrine Carcinoma of the Nasal Cavity

**Jason K. Wasserman[1,2,4] · Doaa AlGhamdi[1,2] · John R. de Almeida[3] · Tracy L. Stockley[1,2] · Bayardo Perez-Ordonez[1,2]**

Received: 8 March 2018 / Accepted: 16 May 2018 / Published online: 29 May 2018


## Abstract

Neuroendocrine carcinomas (NECs) are epithelial neoplasms showing morphologic, immunophenotypic or ultrastructural evidence of neuroendocrine differentiation. The 2017 WHO Classification of Head and Neck Tumours classifies NECs into well, moderately and poorly differentiated NECs according to light microscopic features, mitotic rate and presence of tumour necrosis. In this study, we performed next generation sequencing (NGS) using a targeted 161 cancer gene panel on a poorly differentiated NEC of the nasal cavity. The tumour was composed of large cells arranged in poorly formed glands and solid nests. The mitotic count rate was 30/10 HPFs and p53 protein was strongly expressed in all tumour cells. NGS identified a missense mutation, c.764T > G (p.Ile255Ser) in the *TP53* gene with an allele frequency of 85%. This mutation results in an isoleucine to serine substitution and a non-functional protein. No other mutations were identified. These results suggest that *TP53* mutations may drive oncogenesis in poorly differentiated NECs of the head and neck.

**Keywords** Neuroendocrine carcinoma · *TP53* mutation · Next-generation sequencing · Head and neck · Nasal cavity

## Introduction

Neuroendocrine carcinomas (NECs) are malignant epithelial neoplasms showing morphologic, immunophenotypic or ultrastructural evidence of neuroendocrine differentiation. The 2017 WHO Classification of Head and Neck Tumours classifies NECs into well, moderately and poorly differentiated according to microscopic features, mitotic rate and tumour necrosis [1]. Well differentiated NECs have < 2 mitotic figures per 10 high-powered fields (HPFs) and no necrosis; moderately differentiated NECs have ≥ 2 and ≤ 10 mitotic figures per 10 HPFs and/or necrosis; and poorly differentiated NECs have > 10 mitotic figures per 10 HPFs with or without necrosis. The latter category includes small and large cell NECs, which are distinguished based on the cytologic features of the tumour cells. In general, well differentiated NECs are associated with good outcomes while poorly differentiated NECs are almost invariably associated with distant metastases and poor prognosis [2–11]. Moderately differentiated NECs are associated with highly variable clinical behavior, which suggests that this category may represent a heterogeneous group [6, 12].

Our understanding of the clinical and biologic characteristics of NECs of the head and neck may be limited by our reliance on histologic features for the classification of these neoplasms. Evidence from other organ systems suggests that well and poorly differentiated neuroendocrine neoplasms harbor unique molecular signatures and may in fact be distinct biological entities [13]. Few studies have assessed the genetic landscape of neuroendocrine carcinoma in the head and neck so it is unclear if the evidence from other sites applies to the head and neck. In this study, we performed next generation sequencing (NGS) using a targeted 161 gene panel on a poorly differentiated NEC from the nasal cavity in order to investigate possible molecular contributions..

✉ Jason K. Wasserman
bayardo.perez-ordonez@uhn.ca

1 Laboratory Medicine Program, University Health Network, Toronto, ON, Canada

2 Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, ON, Canada

3 Department of Otolaryngology Head and Neck Surgery, Department of Surgical Oncology, University Health Network, Toronto, ON, Canada

4 Department of Pathology, University Health Network, 200 Elizabeth Street, Toronto, ON M5G 2C4, Canada

## Materials and Methods

### Molecular Analysis

DNA and RNA were extracted from formalin fixed paraffin embedded (FFPE) tissue from a tumor resection with cellularity > 30%. Tumor regions were isolated by macrodissection from 10 to 15 unstained sections, and DNA and RNA extracted using a co-isolation method on a automated extractor (Maxwell FFPE kit, Promega, Madison, WI). RNA was converted to cDNA prior to use in NGS. Molecular analysis was performed using 20 ng DNA and 40 ng cDNA with the Onconmine™ Comprehensive Assay v3 (OCAv3; ThermoFisher, Waltham, MA) on the Ion-Torrent™ S5 XL platform (ThermoFisher). The OCAv3 panel includes regions of 161 driver genes, and parallel testing of DNA and RNA (cDNA), enables detection of single nucleotide variants (SNVs), small insertions and deletions, copy number variants (CNVs) and gene fusions in targeted gene regions. Analysis of molecular variants was performed using the Ion Reporter software, with filtering to remove variants below 5% variant allele frequency, low quality variants, known germline polymorphisms, and synonymous variants.

### Case Report

The patient was 49-year-old female who presented with a 1-year history of nasal congestion, anosmia, 15-pound weight loss and intermittent epistaxis. The patient had a 30 pack-years history of smoking having quit 4 years before her initial presentation. There was no history of exposure to woodworking, leather or industrial solvents. Endoscopic examination showed a large left-sided nasal mass.

A computed tomography scan of the head and neck revealed a 5.3 × 3.0 × 2.5 cm mass occupying the posterior nasal cavity and spheno-ethmoidal recess with extension to the olfactory grooves and nasopharynx (Fig. 1a, b). Imaging of the chest and abdomen did not reveal any evidence of distant metastases. The patient underwent debulking of the nasal mass for a tissue diagnosis at an outside institution. Post-biopsy imaging demonstrated residual tumour in the posterior nasal cavity and cribriform plate. The patient underwent neoadjuvant chemoradiation with two cycles of high-dose cisplatin and a radiation dose of 50 Gy followed by planned surgical resection. The tumour demonstrated a modest response to neoadjuvant therapy (Fig. 1c, d) and underwent endoscopic endonasal resection of the residual tumour with negative margins.

Microscopically the tumor cells were arranged in poorly formed glands and solid nests (Fig. 2a). The glands contained pale luminal mucin but no intracytoplasmic mucin. The tumour was composed of large cells with ample cytoplasm, finely dispersed chromatin and inconspicuous nucleoli (Fig. 2b). The background demonstrated necrotic debris and hemorrhage. The mitotic rate was 30/10 highpower fields and abnormal forms were easily identified. Patchy involvement of surface epithelium by tumour cells was also identified. No residual tumor was identified on follow-up imaging (Fig. 1e, f) and at the time of this report, the patient has been disease free for 14 months.

Immunohistochemical stains showed that the tumor cells were diffusely positive for pan-keratin AE1/AE3 (Fig. 3a), CK18, CK19, and synaptophysin (Fig. 3b). There was focal expression of chromogranin (Fig. 3c), CD56 (Fig. 3d), p63, and CD117. No staining was noted for CK7, CK20, CK5/6, CD5, CDX2, S100, glial fibrillary acidic protein (GFAP) or CD30. A stain for *p53* showed diffuse and strong nuclear expression (Fig. 3e). The proliferative index as measured by Ki-67 was approximately 70% (Fig. 3f). A PAS stain did not reveal any intracytoplasmic mucin. A diagnosis of poorly differentiated NEC was made.

Next generation sequencing performed on representative sections from the tumour identified a TP53 mutation, c.764T > G (p.Ile255Ser; I255S) with a variant allele frequency of 85% (Fig. 4). The mutation results in an isoleucine to serine substitution and a non-functional protein. The I255S mutation is found in exon 7 of TP53, within the DNA binding domain encoded by exons 5–8 [14].

## Discussion

In this study, a *TP53* gene mutation I255S was identified using NSG in a poorly differentiated NEC of the nasal cavity. Our data is consistent with two previous reports, which each identified a *TP53* gene mutation in NECs arising from the maxillary sinus and parotid gland, respectively, using polymerase chain amplification [10, 15]. Our report is different, however, in that, NGS is able to sequence hundreds of known cancer associated genes simultaneously, and this allowed us to more fully profile the genetic landscape of this NEC. Somewhat surprisingly, we found that out of the 161 targeted gene regions analyzed, the *TP53* I255S was the only variant of potential clinical relevance after filtering to remove known polymorphisms and synonymous variants (see "Materials and Methods"). This result suggests that *TP53* gene mutations may play a significant role in the oncogenesis and progression of NECs in the head and neck.

The *TP53* gene is prototypical tumour suppressor and the most frequently mutated gene in human cancer [16]. Mutations in *TP53* cause dysregulation in a variety of cellular processes including cell cycle arrest, apoptosis, senescence,

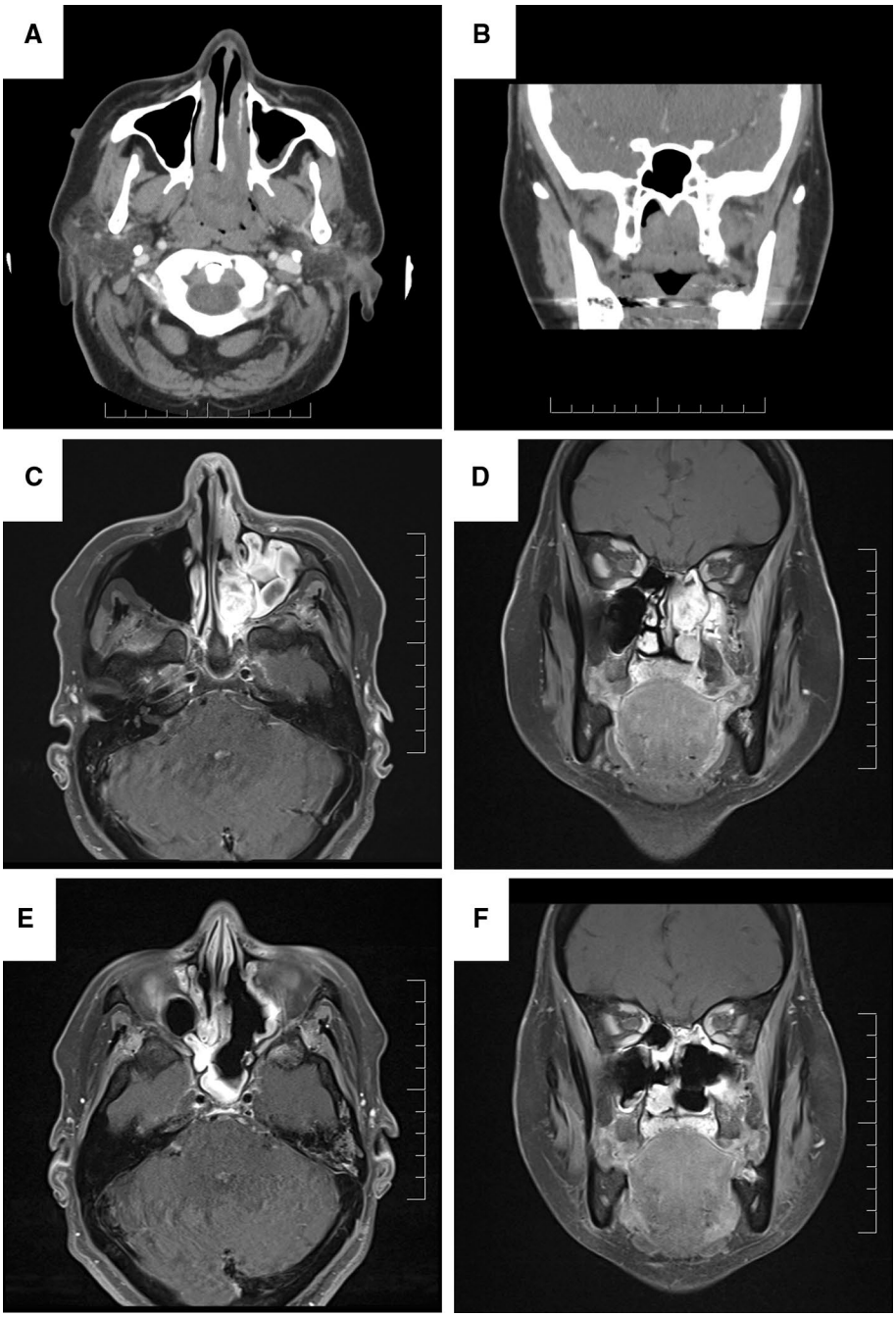


**Fig. 1** Representative preoperative (**a** and **b**), post radiation (**c** and **d**), and post debulking resection images (**e** and **f**). Axial (**a**) and coronal (**b**) CT images showing the tumour in the posterior aspect of the left inferior turbinate and pterygopalatine fossa region with extension to the nasopharynx prior to biopsy and debulking. Axial (**c**) and coronal (**d**) magnetic resonance images with contrast of the same tumour after treatment with pre-debulking radiotherapy showing regrowth of the tumour in the posterior ethmoid region. Axial (**e**) and coronal (**f**) magnetic resonance images taken 6 months after surgical resection of the tumour showing no residual or recurrent disease and healing left nasal cavity

DNA repair, and metabolism [17]. The *TP53* gene contains 12 exons but the majority of clinically relevant mutations occur in exons 4 through 9. These exons are known to encode for amino acids that form the central DNA binding core domain [18]. Common mutations in this region result in a protein that is unable to bind DNA thereby preventing transcription of p53-regulated genes. The *TP53* I255S mutation in this report results from a T to G missense mutation located on exon 7. According to the catalogue of somatic mutations in cancer (COSMIC), this point mutation has been previously described in 14 occurrences in a variety of cancers arising from the lung, endometrium, esophagus, breast, bone, brain, oral cavity, and bladder [19]. The I255S mutation has also been reported in ten occurrences as a somatic mutation in the IARC *TP53* database (two occurrences thyroid, two mouth, and one each in corpus uteri, bladder, brain, ovary, breast, lung). Because the p53 protein functions as a tetramer, the presence of a non-functional protein effectively inhibits the activity of the remaining wild-type proteins [20]. The lack of p53 activity results in increased protein production through disinhibition of a negative-feedback loop. Ultimately, the protein accumulates

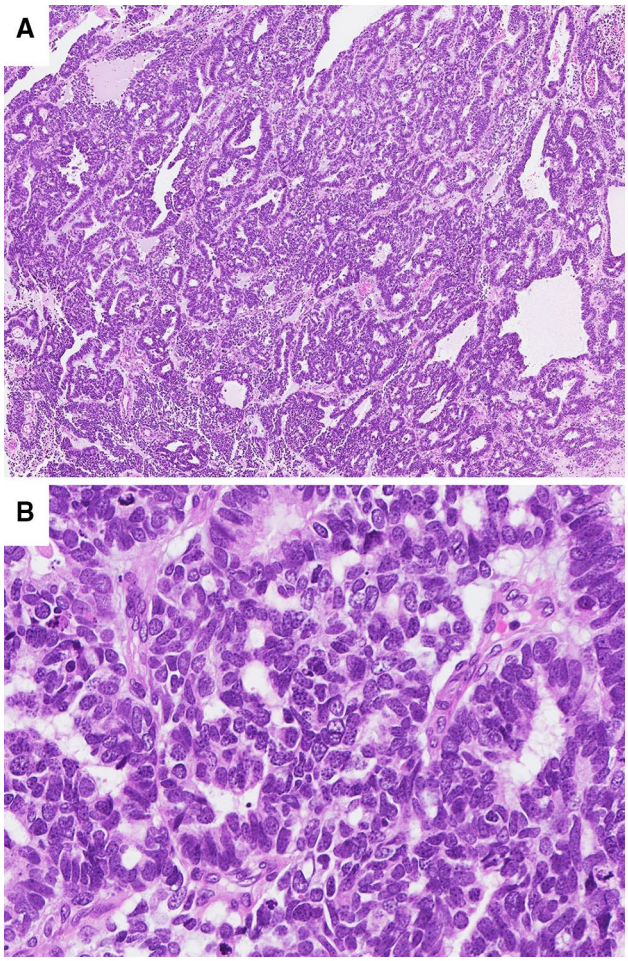


**Fig. 2** Representative images of a poorly differentiated neuroendocrine carcinoma. **a** The tumour was composed of cells arranged in poorly formed glands and nests. Some of the glands contained pale mucin. **b** The tumour was composed large cells with ample cytoplasm, finely dispersed chromatin, and inconspicuous nucleoli

in the nucleus where it can be visualized by standard immunohistochemical methods.

A growing body of evidence suggests that mutations in *TP53* are a hallmark of poorly differentiated neuroendocrine neoplasms independent of site of origin. As early as 1996, Brambilla and colleagues used immunohistochemistry to show to *TP53* was overexpressed in neuroendocrine tumours in the lung [21]. Subsequent studies have shown that the *TP53* gene is consistently mutated in both small and large cell NECs of pulmonary origin [22–24]. In the gastrointestinal tract, *TP53* gene mutations have been described in NECs arising from the colorectum and pancreas [25, 26]. More recently, *TP53* gene mutations have been described in small cell NEC of the prostate [27, 28]. There have been only two previous studies to describe a *TP53* gene mutation in neuroendocrine carcinoma of the head and neck [10, 15]. Franchi and colleagues described a mixed large cell NEC and squamous cell carcinoma of the maxillary sinus and used PCR to show that only the neuroendocrine component harbored a mutation in *TP53* [15] Similarly, Nagao and colleagues used PCR to identify a *TP53* mutation in a poorly differentiated neuroendocrine carcinoma of the parotid gland [10].

The near ubiquity of *TP53* mutations in poorly differentiated NECs is consistent with the concept that loss of p53 protein expression is an early event and a driver of oncogenesis in this tumour type. Indeed, in patients with small cell NECs of the lung, the same *TP53* mutations have been detected in tumour cells and the adjacent morphologically normal bronchial epithelium [29]. Moreover, in lung, pancreatic, and prostate models of small cell NECs, knocking down the expression of p53 protein has been shown to induce the development of tumours that look and behave like their clinical counterpart [27, 30, 31]. These results are consistent with the notion that p53 acts as a 'defender' of genomic integrity and that loss of functional p53 results in genomic instability and the accumulation of other driver mutations which drive tumour progression. Functional p53, however, also acts directly to activate pathways that limit cell growth and the early loss of p53 protein would help explain the hyperproliferative state that both defines and characterizes high-grade NECs [32].

The current WHO classification of head and neck neuroendocrine carcinoma was modeled after the system used for pulmonary NECs in that it relies primarily on the appearance of the tumor and mitotic rate of the tumour to establish a diagnosis and grade [33]. This classification system suggests that all three grades exist on a continuum, which is reflected in the mitotic rate. Recent genetic studies, however, suggest instead that neuroendocrine neoplasms are best dichotomized into "well differentiated" and "poorly differentiated" malignancies based on unique molecular alterations. Well differentiated neuroendocrine tumors in the lung and gastrointestinal tract (carcinoid and atypical carcinoid) display lower somatic mutation rates (< 1 per million base pairs) and frequently demonstrate inactivation of genes affecting histone methylation (*MEN1*) by multiple mechanisms and SWI/SNF complex subunit mutations [34–38]. In contrast, "poorly differentiated" neoplasms display a high rate of somatic mutations and the vast majority harbor mutations in both *RB* and *TP53* [22]. Our results provide additional evidence that *TP53* mutations may play a central role in the development and progression of poorly differentiated NECs in the head and neck.

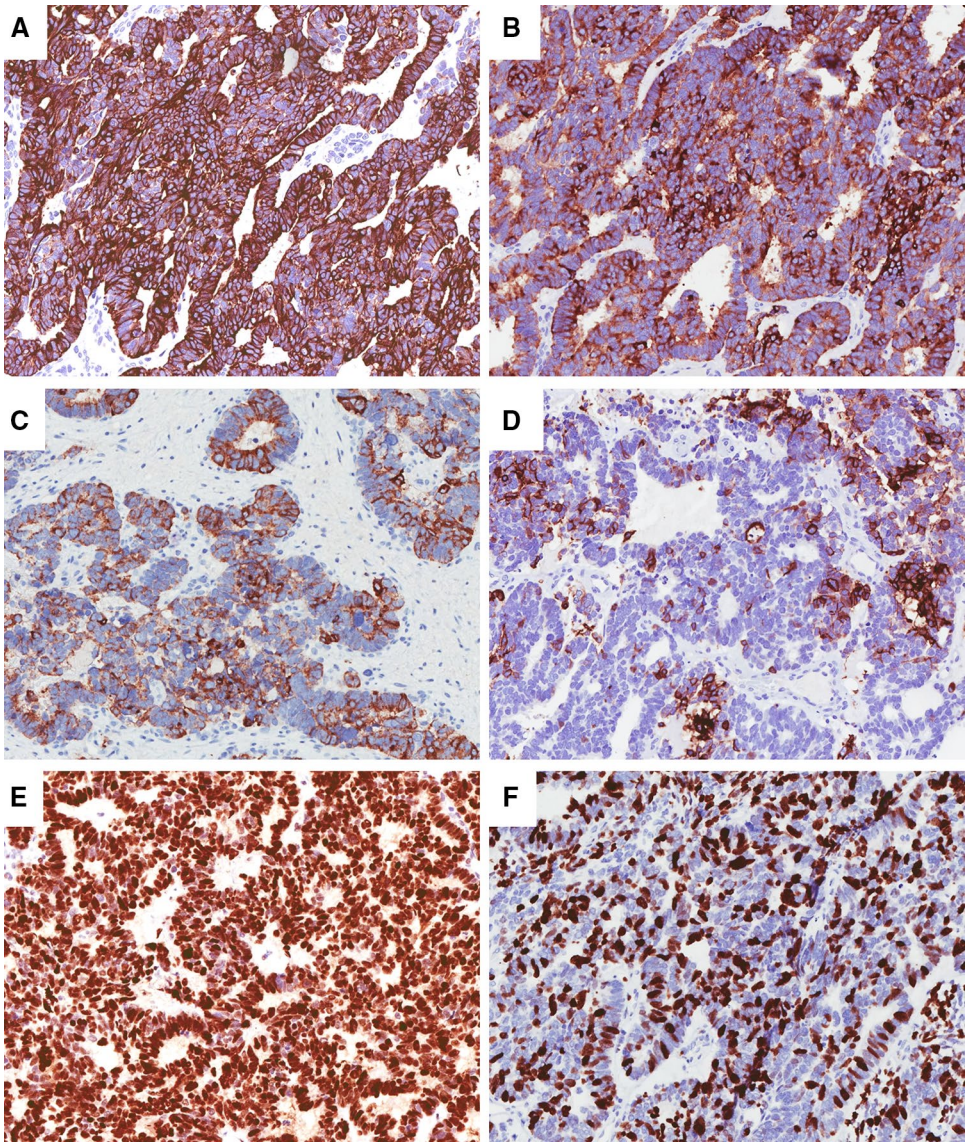


**Fig. 3** Representative immunohistochemical stains. **a** Pan-keratin AE1/AE3. **b** Synaptophysin. **c** Chromogranin. **d** CD56. **e** p53. **f** Ki-67

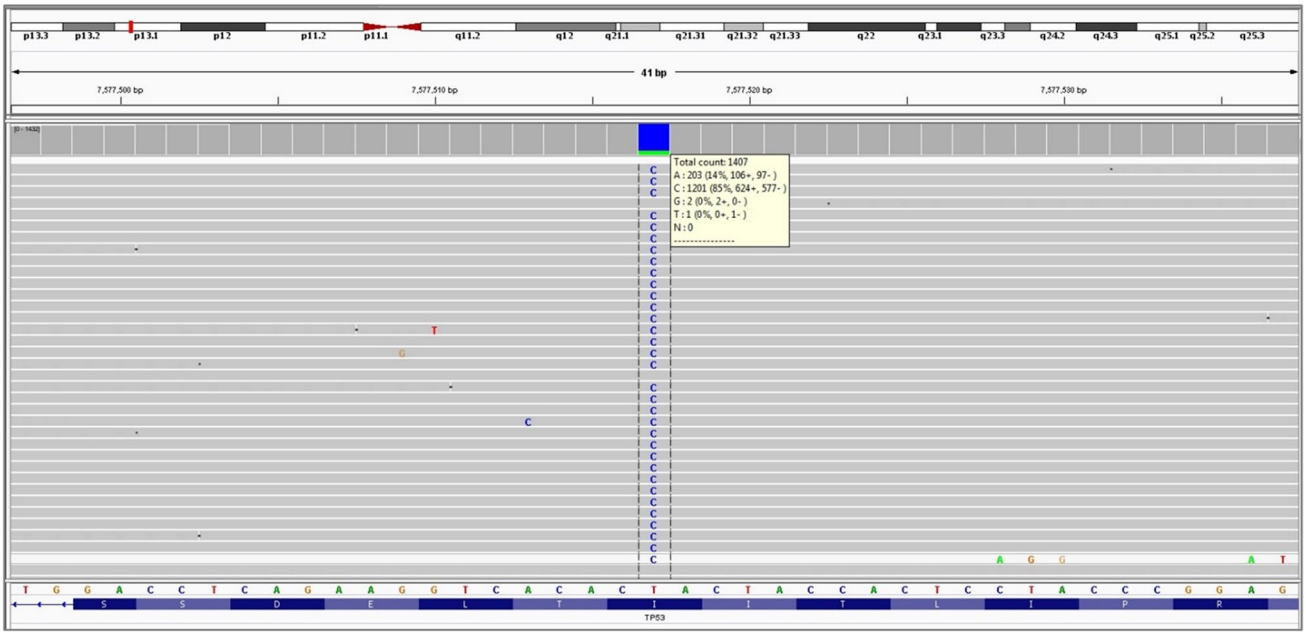


**Fig. 4** View of a subset of next generation sequencing (NGS) reads aligned to the reference genome (human hg19 reference) at the site of the TP53 c.764T>G (p.Ile255Ser) variant using integrated genome viewer (IGV) software. The read count details are shown in the yellow box, with the total reads at the c.764 position of 1407 reads, of which 203 (14%) of reads contain the reference A allele and 1201 (85%) contain the variant C allele

## Compliance with Ethical Standards

**Conflict of interest** All authors declare that no conflict of interest exists related to this work.

**Informed Consent** Informed consent was obtained from the individual included in the study.

## References


1. El-Naggar AK, Chan JKC, Rubin Grandis J, Takata T, Slootweg PJ. International Agency for Research on C. WHO classification of head and neck tumours. Lyon: International Agency for Research on C; 2017
2. Bapat U, Mackinnon NA, Spencer MG. Carcinoid tumours of the larynx. Eur Arch Otorhinolaryngol. 2005;262:194–7.
3. Casas P, Bernaldez R, Patron M, Lopez-Ferrer P, Garcia-Cabezas MA. Large cell neuroendocrine carcinoma of the parotid gland: case report and literature review. Auris Nasus Larynx. 2005;32:89–93.
4. Chetty R, Shah KA, Perez-Ordonez B. Large cell neuroendocrine carcinoma of the head and neck. Am J Surg Pathol. 2012;36:1102–3.
5. Duvall E, Johnston A, McLay K, Piris J. Carcinoid tumour of the larynx. A report of two cases. J Laryngol Otol. 1983;97:1073–80.
6. Kao HL, Chang WC, Li WY, Chia-Heng Li A, Fen-Yau Li A. Head and neck large cell neuroendocrine carcinoma should be separated from atypical carcinoid on the basis of different clinical features, overall survival, and pathogenesis. Am J Surg Pathol. 2012;36:185–92.
7. Kawaratani H, Tsujimoto T, Yoshikawa M, Kawanami F, Shirai Y, Yoshiji H, Morita K, Fukui H. Large cell neuroendocrine carcinoma presenting with neck swelling in the submandibular gland: a case report. J Med Case Rep. 2013;7:81.
8. Kusafuka K, Abe M, Iida Y, Onitsuka T, Fuke T, Asano R, Kamijo T, Nakajima T. Mucosal large cell neuroendocrine carcinoma of the head and neck regions in Japanese patients: a distinct clinicopathological entity. J Clin Pathol. 2012;65:704–9.
9. Lewis JS Jr, Spence DC, Chiosea S, Barnes EL Jr, Brandwein-Gensler M, El-Mofty SK. Large cell neuroendocrine carcinoma of the larynx: definition of an entity. Head Neck Pathol. 2010;4:198–207.
10. Nagao T, Sugano I, Ishida Y, Tajima Y, Munakata S, Asoh A, Yamazaki K, Muto H, Konno A, Kondo Y, Nagao K. Primary large-cell neuroendocrine carcinoma of the parotid gland: immunohistochemical and molecular analysis of two cases. Mod Pathol. 2000;13:554–61.
11. Weinreb I, Perez-Ordonez B. Non-small cell neuroendocrine carcinoma of the sinonasal tract and nasopharynx. Report of 2 cases and review of the literature. Head Neck Pathol. 2007;1:21–6.
12. Wenig BM, Hyams VJ, Heffner DK. Moderately differentiated neuroendocrine carcinoma of the larynx. A clinicopathologic study of 54 cases. Cancer. 1988;62:2658–76.
13. Swarts DR, Ramaekers FC, Speel EJ. Molecular and cellular biology of neuroendocrine lung tumors: evidence for separate biological entities. Biochim Biophys Acta. 2012;1826:255–71.
14. Levrero M, De Laurenzi V, Costanzo A, Gong J, Wang JY, et al. The p53/p63/p73 family of transcription factors: overlapping and distinct functions. J Cell Sci. 2000;113:1661–70.

15. Franchi A, Rocchetta D, Palomba A, Degli Innocenti DR, Castiglione F, Spinelli G. Primary combined neuroendocrine and squamous cell carcinoma of the maxillary sinus: report of a case with immunohistochemical and molecular characterization. Head Neck Pathol. 2015;9:107–13.
16. Levine AJ, Oren M. The first 30 years of *p53*: growing ever more complex. Nat Rev Cancer. 2009;9:749–58.
17. Aylon Y, Oren M. New plays in the *p53* theater. Curr Opin Genet Dev. 2011;21:86–92.
18. Cho Y, Gorina S, Jeffrey PD, Pavletich NP. Crystal structure of a *p53* tumor suppressor-DNA complex: understanding tumorigenic mutations. Science. 1994;265:346–55.
19. Forbes SA, Beare D, Boutselakis H, Bamford S, Bindal N, Tate J, Cole CG, Ward S, Dawson E, Ponting L, Stefancsik R, Harsha B, Kok CY, Jia M, Jubb H, Sondka Z, Thompson S, De T, Campbell PJ. COSMIC: somatic cancer genetics at high-resolution. Nucleic Acids Res. 2017;45:D777-D783.
20. Milner J, Medcalf EA, Cook AC. Tumor suppressor *p53*: analysis of wild-type and mutant *p53* complexes. Mol Cell Biol. 1991;11:12–9.
21. Brambilla E, Negoescu A, Gazzeri S, Lantuejoul S, Moro D, Brambilla C, Coll JL. Apoptosis-related factors *p53*, Bcl2, and Bax in neuroendocrine lung tumors. Am J Pathol. 1996;149:1941–52.
22. Clinical Lung Cancer Genome P, Network Genomic M. A genomics-based classification of human lung tumors. Sci Transl Med. 2013;5:209ra153.
23. Rekhtman N, Pietanza MC, Hellmann MD, Naidoo J, Arora A, Won H, Halpenny DF, Wang H, Tian SK, Litvak AM, Paik PK, Drilon AE, Socci N, Poirier JT, Shen R, Berger MF, Moreira AL, Travis WD, Rudin CM, Ladanyi M. Next-generation sequencing of pulmonary large cell neuroendocrine carcinoma reveals small cell carcinoma-like and non-small cell carcinoma-like subsets. Clin Cancer Res. 2016;22:3618–29.
24. Takahashi T, Nau MM, Chiba I, Birrer MJ, Rosenberg RK, Vinocour M, Levitt M, Pass H, Gazdar AF, Minna JD. *p53*: a frequent target for genetic abnormalities in lung cancer. Science. 1989;246:491–4.
25. Takizawa N, Ohishi Y, Hirahashi M, Takahashi S, Nakamura K, Tanaka M, Oki E, Takayanagi R, Oda Y. Molecular characteristics of colorectal neuroendocrine carcinoma; similarities with adenocarcinoma rather than neuroendocrine tumor. Hum Pathol. 2015;46:1890–900.
26. Yachida S, Vakiani E, White CM, Zhong Y, Saunders T, Morgan R, de Wilde RF, Maitra A, Hicks J, Demarzo AM, Shi C, Sharma R, Laheru D, Edil BH, Wolfgang CL, Schulick RD, Hruban RH, Tang LH, Klimstra DS, Iacobuzio-Donahue CA. Small cell and large cell neuroendocrine carcinomas of the pancreas are genetically similar and distinct from well-differentiated pancreatic neuroendocrine tumors. Am J Surg Pathol. 2012;36:173–84.
27. Li Z, Sun Y, Chen X, Squires J, Nowroozizadeh B, Liang C, Huang J. *p53* Mutation directs AURKA overexpression via miR-25 and FBXW7 in prostatic small cell neuroendocrine carcinoma. Mol Cancer Res. 2015;13:584–91.
28. Tan HL, Sood A, Rahimi HA, Wang W, Gupta N, Hicks J, Mosier S, Gocke CD, Epstein JI, Netto GJ, Liu W, Isaacs WB, De Marzo AM, Lotan TL. Rb loss is characteristic of prostatic small cell neuroendocrine carcinoma. Clin Cancer Res. 2014;20:890–903.
29. Wistuba II, Berry J, Behrens C, Maitra A, Shivapurkar N, Milchgrub S, Mackay B, Minna JD, Gazdar AF. Molecular changes in the bronchial epithelium of patients with small cell lung cancer. Clin Cancer Res. 2000;6:2604–10.
30. Gazdar AF, Savage TK, Johnson JE, Berns A, Sage J, Linnoila RI, MacPherson D, McFadden DG, Farago A, Jacks T, Travis WD, Brambilla E. The comparative pathology of genetically engineered mouse models for neuroendocrine carcinomas of the lung. J Thorac Oncol. 2015;10:553–64.
31. Glenn ST, Jones CA, Sexton S, LeVea CM, Caraker SM, Hajduczok G, Gross KW. Conditional deletion of *p53* and Rb in the renin-expressing compartment of the pancreas leads to a highly penetrant metastatic pancreatic neuroendocrine carcinoma. Oncogene. 2014;33:5706–15.
32. Akeno N, Miller AL, Ma X, Wikenheiser-Brokamp KA. *p53* suppresses carcinoma progression by inhibiting mTOR pathway activation. Oncogene. 2015;34:589–99.
33. Travis WD, Brambilla E, Burke A, Marx A, Nicholson AG, International Agency for Research on C. WHO classification of tumours of the lung, pleura, thymus and heart. Lyon: International Agency for Research on C; 2015
34. Swarts DR, Claessen SM, Jonkers YM, van Suylen RJ, Dingemans AM, de Herder WW, de Krijger RR, Smit EF, Thunnissen FB, Seldenrijk CA, Vink A, Perren A, Ramaekers FC, Speel EJ. Deletions of 11q22.3-q25 are associated with atypical lung carcinoids and poor clinical outcome. Am J Pathol. 2011;179:1129–37.
35. Swarts DR, Van Neste L, Henfling ME, Eijkenboom I, Eijk PP, van Velthuysen ML, Vink A, Volante M, Ylstra B, Van Criekinge W, van Engeland M, Ramaekers FC, Speel EJ. An exploration of pathways involved in lung carcinoid progression using gene expression profiling. Carcinogenesis. 2013;34:2726–37.
36. Fernandez-Cuesta L, Peifer M, Lu X, Sun R, Ozretic L, Seidal D, Zander T, Leenders F, George J, Muller C, Dahmen I, Pinther B, Bosco G, Konrad K, Altmuller J, Nurnberg P, Achter V, Lang U, Schneider PM, Bogus M, Soltermann A, Brustugun OT, Helland A, Solberg S, Lund-Iversen M, Ansen S, Stoelben E, Wright GM, Russell P, Wainer Z, Solomon B, Field JK, Hyde R, Davies MP, Heukamp LC, Petersen I, Perner S, Lovly C, Cappuzzo F, Travis WD, Wolf J, Vingron M, Brambilla E, Haas SA, Buettner R, Thomas RK. Frequent mutations in chromatin-remodelling genes in pulmonary carcinoids. Nat Commun. 2014;5:3518.
37. Iwakawa R, Takenaka M, Kohno T, Shimada Y, Totoki Y, Shibata T, Tsuta K, Nishikawa R, Noguchi M, Sato-Otsubo A, Ogawa S, Yokota J. Genome-wide identification of genes with amplification and/or fusion in small cell lung cancer. Genes Chromosom Cancer. 2013;52:802–16.
38. Scarpa A, Chang DK, Nones K, Corbo V, Patch AM, Bailey P, Lawlor RT, Johns AL, Miller DK, Mafficini A, Rusev B, Scardoni M, Antonello D, Barbi S, Sikora KO, Cingarlini S, Vicentini C, McKay S, Quinn MC, Bruxner TJ, Christ AN, Harliwong I, Idrisoglu S, McLean S, Nourse C, Nourbakhsh E, Wilson PJ, Anderson MJ, Fink JL, Newell F, Waddell N, Holmes O, Kazakoff SH, Leonard C, Wood S, Xu Q, Nagaraj SH, Amato E, Dalai I, Bersani S, Cataldo I, Dei Tos AP, Capelli P, Davi MV, Landoni L, Malpaga A, Miotto M, Whitehall VL, Leggett BA, Harris JL, Harris J, Jones MD, Humphris J, Chantrill LA, Chin V, Nagrial AM, Pajic M, Scarlett CJ, Pinho A, Rooman I, Toon C, Wu J, Pinese M, Cowley M, Barbour A, Mawson A, Humphrey ES, Colvin EK, Chou A, Lovell JA, Jamieson NB, Duthie F, Gingras MC, Fisher WE, Dagg RA, Lau LM, Lee M, Pickett HA, Reddel RR, Samra JS, Kench JG, Merrett ND, Epari K, Nguyen NQ, Zeps N, Falconi M, Simbolo M, Butturini G, Van Buren G, Partelli S, Fassan M,, Khanna KK, Gill AJ, Wheeler DA, Gibbs RA, Musgrove EA, Bassi C, Tortora G, Pederzoli P, Pearson JV, Waddell N, Biankin AV, Grimmond SM. Australian Pancreatic Cancer Genome I. Whole-genome landscape of pancreatic neuroendocrine tumours. Nature. 2017;543:65–71.