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REVIEW

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The genomics and epigenetics of olfactory neuroblastoma: A systematic review

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Abstract

Background: Olfactory neuroblastoma (ONB) or esthesioneuroblastoma (ENB) is a rare malignancy of the nasal cavity believed to arise from the olfactory epithelium. The goal of this study was to systematically review the genomics, epigenetics, and cytogenetics of ONB and to understand the potential clinical implications of these studies.

Methods: A systematic literature review was performed for articles published before May 2020 using Cochrane, Embase, Pubmed, and Scopus databases. Inclusion criteria included genomics, cytogenetics, and epigenetics studies on ONB. Exclusion criteria included studies not in English or systematic reviews. Articles and abstracts were reviewed by two independent reviewers to reduce bias during article selection and synthesis of results. Of the 36 studies included in this review, 24 were research articles and 12 were abstracts.

Results: Although recurrent mutations among ONB tumors are uncommon, alterations in *TP53*, *DMD*, *PIK3CA*, *NF1*, *CDKN2A*, *CDKN2C*, *CTNNB1*, *EGFR*, *APC*, *cKIT*, *cMET*, *PDGFRA*, *CDH1*, *FH*, *SMAD4*, *FGFR3* and *IDH2* genes have been reported in several recent studies. In addition, cytogenetic studies revealed that the landscape of chromosomal aberrations varies widely amongst ONB tumors.

Conclusions: The rare character of ONB has limited the sample size available for cytogenetic, genomic, and epigenetic studies and contributes to the limitations of this systematic review. Comprehensive genomic and epigenomic studies with larger cohorts are warranted to validate the initial reports summarized in this review and to identify potential therapeutic targets for ONB.

KEYWORDS
cytogenetics, epigenetics, genomics, olfactory neuroblastoma, tumorigenesis

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1 | INTRODUCTION

Olfactory neuroblastoma (ONB) or esthesioneuroblastoma (ENB) is a rare malignancy of the nasal cavity that likely arises from the olfactory neuro-epithelium.[1] An olfactory epithelial origin is suggested by the tumor anatomical location, morphological features, and characteristic gene expression patterns.[2] ONB was first described in 1924 and named "L'esthesioneuroepitheliome olfactif."[3] Due to lack of information on its histological origin, additional names have since been used including olfactory neurocytoma and others.[4,5] The incidence of ONB is 0.4/million/year, accounting for approximately 2%-3% of nasal cavity tumors.[6,7] To date, no specific risk factors have been identified for ONB.[8] Hyams histologic grading and Kadish, modified Kadish, and Dulguerov staging are traditionally used to clinically characterize the tumor and aid in treatment planning.

The rare character of ONB has limited the sample size available for cytogenetic, genomic, and epigenetic studies. Although multiple manuscripts have identified complex genetic and cytogenetic patterns in ONB, only a subset of reported genomic aberrations were consistent across different studies. While these inconsistencies limit the generalizable conclusions regarding the mutational landscape of this disease, it may indicate that ONB is defined by a set of heterogeneous alterations. Previous cytogenetic studies have reported that deletion on chromosome 11 and gain on chromosome 1p were associated with poor prognosis in ONB.[9] In addition to cytogenetic analysis, various sequencing approaches such as pyrosequencing, and more recently next generation sequencing (NGS), have also been used to explore genomic alterations in patients with ONB. Although the catalogue of somatic mutations in cancer (COSMIC) database as well as other publications in the field of ONB report alterations in *TP53*, *EGFR*, *CTNBB1*, *KIT*, *RET*, *APC*, *FGFR2*, *KDR*, *PDGFRA*, *SMAD4*, *MET*, *CDH1*, *SUZ12*, *PPP6C*, *IKZF1*, *TGFBR2*, *CARD11* and *CDKN2C* genes,[10-12] the fraction of ONB with mutations in these genes that present opportunities for targeted therapy is estimated to be up to 50%.[10]

The goal of this systematic review is to summarize the available ONB cytogenetics, genomics, and epigenetics literature and to suggest potential targetable pathways for precision therapeutics.

2 | MATERIALS AND METHODS

2.1 | Search of publications

A systematic review was conducted following the guidelines of the preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement. We conducted a systematic literature search using Cochrane, Embase, Pubmed, and Scopus databases. Articles published before May 2020 were included in the review. The key words used for the search included Esthesioneuroblastoma, Olfactory Neuroblastoma, nasal glial heterotopia, nasal glioma, neuroblastoma, nose glioma, olfactory esthesioneuroblastoma, olfactory neuroblastomas, paranasal sinus-nasal cavity, nasal glial heterotopia, olfactory, genomics, genetics, epigenomic, pharmacogenomics, phylogenomic, epigenetic, epigenetics, miRNA, histone, methylation, acetylation, and epigenesis.

2.2 | Selection criteria

PubMed, Cochrane, Embase, and Scopus search results were selected as they provided the most comprehensive literature search for the topic. Duplicate articles were removed using Covidence. The title and abstract of all potentially relevant studies were screened for their contents ensuring adherence to the following inclusion and exclusion criteria for the systematic review.

Inclusion criteria:

i. Cytogenetic studies on clinical samples for ONB patients
ii. Genomics studies on clinical samples of ONB patients
iii. Epigenetics studies on clinical samples of ONB patients

Exclusion criteria:

i. Studies without full text
ii. Studies not published in English
iii. Review articles

2.3 | Data extraction

Data was extracted from all the eligible studies for systematic review. Experimental data involving study design, sample type, and experimental technique was collected from the research articles exploring genetic make-up of patients using various genomics and cytogenetic techniques. Cytogenetic and genomic alterations as well as epigenetic data were extracted from all previous studies.

2.4 | Quality assessment

Two independent reviewers critically assessed the content of all the studies included in this systematic review. A total of 115 abstracts were categorized into three groups: "yes," "no," and "maybe"; where "yes" indicated abstracts deciphering genetic and cytogenetic changes, "no" stood for abstracts depicting that study was a review article or was not published in English, whereas "maybe" defined studies focused on head and neck cancers or other cancers of the sinonasal cavity. Among the 115 screened abstracts, 79 were found to be unrelated and were excluded. The full texts of the remaining 36 studies were screened and marked as "yes" and "no." This time, "yes" indicated studies that explored genetics and cytogenetics of ONB tumors, and "no" was assigned to the studies focusing on head and neck as well as sinonasal cancers that did not include ONB samples. Of the 36 studies, 24 research articles and 12 abstracts were included in this review. These 24 studies were directly related to ONB. The 12 abstracts included in our overview were published in

TABLE 1 Summary of reported cytogenetic alterations

Author	Type of alteration	# of patients	Reported alterations
Bockmühl et al, 2004[9]	Loss/gain—frequency of alteration > 50% of cases or pronounced deletion/gain defined by ratio profile that exceeded the threshold of 0.5	12	*Loss*: 1p21-31, 1q24-q32, 2q22-q32, 3p/q, 3p12-p14, 4p/q, 4p13-p15, 5p14, 5q, 6q14-q23, 9p, 9q22-q33, 10p/q, 10q26, 12p11.2-p12, 12q21, 13q, 13q21-q23, 18q, 21q21 *Gain*: 1p34, 1q12, 1q23-q31, 7p21, 7q11.2, 7q31, 9p23-p24, 11q13, 14q, 14q32.2, 16p11.2, 16q, 16p13.3, 17p13, 17q11-q22, 17q12, 17q21-q24, 17q24-q25, 17q25, 19, 19p/q, 20p, 20q, 20q13, 22q11.2, 22q13 *Loss associated with worse prognosis or metastasis*: 4p/q, 5p/q, 6q, 7q31-q32, 9p, 11p/q, 11p12-p14, 15q21 *Gain associated with worse prognosis or metastasis*: 1p32-34, 1q12, 2p22-p24, 8q, 20q
Castañeda et al, 1991[40]	Ploidy	1	Near pseudotetraploid, chromosome 5 present in multiples of eight
Guled et al, 2008[24]	Loss/gain—frequency of alteration > 20% of cases	13	*Loss*: 2q31.1, 2q33.3, 2q37.1, 4p13, 5q31.2, 6p12.3, 6p21.33, 6p22.1, 6q16.3, 6q21, 6q22.1, 15q11.2-q24.1, 15q13.1, 18q12.2-q12.3, 19q12, 19q13.11, 19q13.32, 19q13.43, 22q11.23, 22q12.1, 22q11.1-q11.21, Xp/q *Gain*: 1p36.31, 1p35.3, 4p12-p15.31, 4p16.2-p16.3, 4q12, 4q21.22-q22.1, 4q27-q35.2, 5q34, 5q35.1-q35.3, 6p12.3, 7q11.23, 7q21.11, 9p13.3, 10p12.31, 12q23.1, 12q24.31, 13q, 13q14.2-14.3, 13q31.1, 13q34, 15q13.3, 16q12.1, 20p/q, 20p13.3-p12.2, 20q11.21-q11.23, 20q13.32-q13.33, 21q, 22q12.1, Xp/q
Holland et al, 2007[41]	Loss/gain—G-banding	1	*Loss*: 1p12-p21, 1p22-p32, 1p31-p33, 2q31-q33, 2q37, 3p11-p13, 3p12-p14, 3p25, 3q25, 3q26, 6p21, 6q12-q14, 6q22-q24, 10q26, 11q23, 15q26, 20q11.1-q12, 21q22, 22q13 *Gain*: 1q25-q32, 1q25-q41, 16p13.3, 16q13-q22, 17p12, 17p13, 17q25
Holland et al, 2007[41]	Loss/gain—SNP array karyotyping	1	*Loss*: 2q37.3, 3p21.3, 3q27.2, 4p12, 4q31.3, 7q36.1, 8q24.3, 10p26.11, 11p11.2, 12q24.31, 14q32.33, 16p11.2, 21q22.11 *Gain*: 2q14.3, 3p21.3, 6q25.3, 6q27, 7q11.21, 7q11.23, 7q36.1, 7q36.3, 8p11.21, 9p13.3, 10q11.23, 11p14.1, 11q15.3, 11q23.3, 11q24.3, 13q12.11, 13.q33.3, 13q34, 14q32.31, 15q12, 15q13.1, 16p11.2, 16p13.11, 17q12, 17q21.31, 17q25.3, 19q13.42, 20q13.31, 21q22.3, 22q13.1, 22q13.31, 22q13.33
Jin et al, 1995[42]	Ploidy—G-banding of short-term culture	1	Hyperdiploid karyotype with unbalanced structural rearrangements
Kristensen et al, 1991[43]	Ploidy	1	polyploidy, aneuploidy and marker chromosomes
Lopez-Hernandez et al, 2018[44]	Loss/gain	11	*Loss*: 1p, 2p25.1-14.3, 3, 4, 5q, 13q14.3-q21.1, 16p12.3, 22q12.2-12.3 *Gain*: 1q, 3q, 4p14-13, 4q13-31, 6p, 7p, 7q11.23-33, 9p24, 11p14.3-p12, 11q13.4-q14.2, 12p, 12q, 14q, 16q23.3-24.3, 17q22-25, 18q, 20
Mezzelani et al, 1999[15]	Gain	5	*Gain*: (1/5 patients) 8p/q
Riazimand et al, 2002[45]	Loss/gain	3	*Loss*: (3/3 patients): 4q, (2/3 patients): 13q, (1/3 patients): 6p Gain: (3/3 patients): 8q24.1, 15q25, 19p/q, 22q, (2/3 patients): 1p32, 9q34.1, (1/3 patients): 10q24.3

(Continues)

TABLE 1 (Continued)

Author	Type of alteration	# of patients	Reported alterations
Sorensen et al, 1996[13]	Translocation	6 + 2 cell lines	t(11;22) (q24;q12)
Szymas et al, 1997[46]	Loss/gain	1	*Loss*: 5q, 16p/q, 18p/q, 17p, 19p/q, Xp/q *Gain*: 1q, 4p/q, 8p/q, 11p/q, 14p/q, 17q
Valli et al, 2015[27]	Loss/gain—frequency of alteration ≥ 3/11 samples	10 (11 samples)	*Loss*: Yp11.31, Yp11.2, Yq11.21-q11.23 *Gain*: 2p/q, 5p/q, 6p/q, 7p/q, 11p/q, 13p/q, 14p/q, 15p/q, 16p/q, 17p/q, 18p/q, 19p/q, 20 p/q, 22p/q, Xp/q, Yp/q
VanDevanter et al, 1991[47]	Gain—short term culture	1	*Gain*: 8p/q
Lazo de la Vega et al, 2017[21]	Loss/gain	18	*Loss*: 1p/q, 3p/q, 8p/q, 12p/q *Gain*: 5p/q, 7p/q, 11p/q, 20p/q
Weiss et al, 2012[48]	Loss/gain/amplification	1	*Loss*: 5q15, 6 p25.1, 7p15.3, 7p21.3, 11q24.2, 19p12, 21q.1 *Gain/amplification*: 5p15.33, 7p13, 8p, 8q24.3, 9q22.31, 9q34.3, 16q22.1, 16q24.3
Whang-Peng et al, 1987[49]	Translocation, loss/gain	1 cell line	t(2;14)(p25;p12), t(8;17)(q12;p12), t(11;22)(q24;q12) *Loss*: 18p/q *Gain*: 12p/q, del(8)(q12)

conferences and meetings and explored the genetic and cytogenetic makeup of ONB patients.

3 | RESULTS

3.1 | Cytogenetic landscape of ONB patients

Cytogenetic changes in ONB patients were studied by using different techniques but were limited in number. Initial research hypothesized that a (11;22) (q24;q12) translocation suggested that ONB was related to Ewing Sarcoma.[13,14] However, a later study analyzing 5 ONB tumors could not identify the EWS gene rearrangement by FISH or the Ewing sarcoma-associated MIC2 antigen by immunohistochemistry.[15] Furthermore, an additional study that performed RT-PCR on two ONB specimens did not identify *EWS-FLI1* or *EWS-ERG* translocations,[16] suggesting that ONB is not a member of the primitive peripheral neuroectodermal tumor-Ewing's group.[2,14-16]

In a later study of 22 patients, comparative genomic hybridization identified deletion of chromosome 3p and high copy number amplifications on 17q in 90%-100% of tumors analyzed.[9] However, despite the high frequency of these chromosomal changes, cytogenetic studies have ultimately revealed that ONB tumors are cytogenetically complex and the landscape of chromosomal aberrations varies widely. The inconclusive reports may stem from the very small number of cases analyzed, with many of the cytogenetic studies having been carried out on only a single patient. The list of detected chromosomal aberrations is summarized in Table 1. While these cytogenetic alterations can potentially be used as predictive and prognostic biomarkers, their biological relevance remains to be validated.

3.2 | Genetic landscape of ONB patients

Compared to cytogenetic approaches, exploring the genome by high throughput NGS technologies provides a more detailed view of the tumor genome at the nucleotide level. As ONB is rare, there are no large genomic studies to date, with the largest genomic study conducted in a cohort of 41 ONB specimens.[10] Among the 41 tumors, 28 harbored genomic alterations. The study reported *TP53* gene as the most commonly altered along with genomic alterations in *PIK3CA*, *NF1*, *CDK2NA* and *CDKN2C* genes. Genetic changes in *TP53* were detected in the DNA binding domain of this tumor suppressor gene, and 17% of patients carried splice site, missense (P278S, R248W, G245C and P278R) and truncation (P190del) alterations. It was also observed that 7% of tumors in this study had alterations in *PIK3CA* (missense mutations at positions E545Q and E542K) and truncation alterations in *NF1*, *CDKN2A*, and *CDKN2C* genes.[10] Another case report has also documented the presence of a *TP53* missense mutation and *CDKN2C* loss-of-function alteration in a patient with ONB.[17] Notably, the gain of function alteration detected in *PIK3CA* gene were located in the accessory domain, which has been suggested to be associated with substrate presentation according to the Single Nucleotide Polymorphism Database (dbSNP).

Gallia et al found deletions involving the dystrophin (DMD) locus in 12 of 14 (86%) of ONB tumors analyzed in their study.[18] Alterations in DMD gene were detected in both exonic region as well as 5′UTR. DMD has been identified as a tumor suppressor in other tumor types.[19] Interestingly, one of the two tumors that did not display alterations in the Xp21.1 locus, showed a somatic homozygous deletion in *LAMA2*, bringing the number of ONBs with deletions of genes involved in the development of muscular dystrophies to 13 of 14 (93%).[18]

TABLE 2 Summary of genomic alterations

Author	Type of alteration	# of patients	Genes
Cha et al, 2016[17]	Mutations	1	*TP53* (missense), *CDKN2C* (loss of function)
Classe et al, 2018[12]	Insertion/deletion	27	*CDKN2A*, *CTR9*
	Stop/gain		*RB1*, *TP53*
	Non-synonymous SNV		*ARID1A*, *BRCA2*, *BRIP1*, *CHD7*, *DNMT3A*, *DNMT3B*, *EXO1*, *FZD9*, *GLI2*, *GLI3*, *HERC2*, *IDH2*, *KDM2B*, *KIT*, *KMT2A*, *KMT2C*, *KMT2D*, *LEF1*, *MSH3*, *NAA10*, *NUMA1*, *RBBP4*, *SMARCA4*, *SMARCC1*, *SMC2*, *TOPBP1*, *TP53*, *XRCC1*, *YWHAE*
Gallia et al, 2018[18]	Deletions	14	*Dystrophin*, *LAMA2*
Gay et al, 2017[10]	Short variants, truncations, and rearrangements	41	*ARID1A*, *ARID2*, *ATM*, *AXL-ARHGEF* fusion, *BCOR*, *CDKN1B*, *CDKN2C*, *CTCF*, *CTNNB1*, *DAXX*, *IDH2*, *KDM5C*, *LRP1B* deletion, *NF1*, *NRAS*, *PBRM1*, *PIK3CA*, *PIK3R2*, *PTCH1*, *PTEN*, *SMARCA4*, *TET2*, *TNFAIP3*, *TP53*, *TSC1*,
	Focal copy number alterations		Amplification: *BCL2L1*, *BCL2L2*, *CDK6*, *HGF*, *FGF14*, *GNAS*, *IRS2*, *KIT*, *MDM4*, *MYC*, *PIK3C2B*, *RICTOR* Loss: *ARID2*, *CDKN2A*, *CDKN2B*, *CDKN2C*, *FAF1*, *MLH1*, *NF1*, *PTPRD*, *TP53*, *RB1*,
	Non focal amplifications		*ARFRP1*, *AURKA*, *FGF10*, *FGFR4*, *FLT4*, *GATA6*, *LYN*, *PDGFRB*, *RICTOR*, *SRC*, *TOP1*, *ZNF217*,
Kim et al, 2017[50]	Recurrent and/or pathogenic somatic mutations	6	*ANKHD1*, *ARHGEF9*, *ATM*, *CNOT10*, *CSDM1*, *DCTN1*, *ITSN1*, *LMTK2*, *MACF1* (recurrently mutated), *MAP2K1*, *MMRN2*, *MYOCD*, *RCE1*, *RORB*, *SDCCAG8*, *ZNF471*
	Inter-chromosomal in-frame fusion gene		*DHRS2-GSTM2* (recurrent in two samples)
Topcagic et al, 2018[20]	Mutations	15	*APC*, *c-KIT*, *CTNNB1*, *FH*, *SMAD4*, *TP53*,
	Variants of unknown significance		*CDH1*, *cMet*, *EGFR*, *PDGFRA*,
Lazo de la Vega et al, 2017[21]	Mutations	18	*CTNNB1*, *KMT2A*, *KMT2C*, *PTEN*, *TP53*
	Copy number alterations		Loss: *CDKN2A*, *CDKN2B* Gain: *FGFR3*, *CCND1*
	Frameshift insertion		*DCC*, *RNF213*
Wang et al, 2016[51]	Missense mutations	1	*EGFR*, *FGFR2*, *KDR*, *RET*
Weiss et al, 2012[48]	Insertion/deletions /gain/loss	1	Deletions: *ARID4B*, *CCDC120*, *CYP4A22* Insertions: *KCNA10*, *OBSCN*
	Gene mutations		*KDR*, *MAP4K2*, *MYC*, *NLRC4*, *SIN3B*, *TAOK2*, *TP53*,

Classe et al screened DNA extracted from 14 ONB samples and matched germline DNA from blood or adjacent normal tissue by whole exome sequencing and found that 21.4% of patients carried single nucleotide alterations in the *TP53* gene, with 7.14% of these mutations reported to be stop-gain, resulting in a premature transcription termination.[12]

Topcagic et al, have retrospectively analyzed 23 ONB patient samples by using targeted DNA sequencing, in situ hybridization and gene fusion assays.[20] DNA sequencing of 15 patient samples was carried out; that included a panel of 46 genes in 10 cases, and an extended panel of 592 genes by NGS in 5 cases. In these 15 patients, the study detected alterations in *TP53* (H214Y, c673-1G>T and T155_V157del), *CTNNB1* (S33_H36del), *EGFR* (Q276R and T572R), *APC* (A1474T), *cKIT* (G565V), *cMET* (L1321I), *PDGFRA* (V546L), *CDH1* (D756Y), *FH* (K477dup) and *SMAD4* (N468fs) genes.[20] Among the 15 patients analyzed in this study, 20% exhibited missense mutation, single nucleotide variation or deletion in DNA binding domain of the *TP53* gene.[20]

Lazo de la Vega et al, studied 20 ONB samples using targeted multiplexed PCR based NGS. While no recurrent alterations were detected in their study, copy number alterations affecting chromosomes 5, 7, 11 and 20 were identified in a subset of patients.[21] In two tumors, co-amplification of *CCND1* at 11q13 and *FGFR3* at 4p16 was observed, resulting in potential driver oncogenic event. CCND1 is a core cell cycle regulator that is frequently overexpressed in many solid tumors including head and neck cancers. Missense mutation V272M in DNA binding domain of *TP53* gene was detected in one patient. *PTEN* gene exhibited nonsense mutation Y16X in one patient,

resulting in a truncated PTEN protein which is unable to inhibit the PIK3/mTOR pathway.[21] Although there was little overlap of genetic alterations identified by different studies, most of the genomic studies have reported the *TP53* gene as frequently mutated in ONB patients, suggesting that a complex signaling network regulated by p53 can be a potential therapeutic target (Table 2).

Several studies have also detected *IDH2* gene alterations in ONB samples sequencing. However, the true frequency of *IDH2* aberrations remains controversial. For example, Dogan et al, screened 9 ONB samples using targeted exome sequencing and none of these ONB samples showed alterations in *IDH2*.[22,23] In contrast, Classe et al, have detected R172 *IDH2* mutation in 16.7% of ONB specimens,[12] which were further validated by pyrosequencing. Gay et al, screened 41 patients and reported two missense mutations, R172S and R172T, in different patients each carrying one alteration.[10] Various studies have reported short variants, truncations, rearrangements, focal copy number alterations and non-focal number alterations in a variety of other genes, but at much lower frequency (Table 2).

3.3 | Epigenetic landscape of ONB

Currently, epigenetic data on ONB are very limited and focus predominantly on DNA methylation. Capper et al, carried out a microarray-based methylation profiling of 66 ONB samples and distinguished four unique subgroups within the histopathological diagnosis of ONB.[11] A total of 64% of ONB tumors were used to define the "core ONB" genome-wide methylation profile, while a total of 7 samples formed a second group with global hypermethylation features that were also associated with R172 *IDH2* hotspot mutations in all cases. The third group consisted of only 4 tumors with a high level of overall methylation but absence CpG island methylation and lacking *IDH1* or *IDH2* mutations. The group was heterogeneous and did not fit any of the above inclusion criteria.

The unique methylome profile of ONB was further confirmed in a study by Dogan et al, in a series of sinonasal tumors that included ONB, using a DNA methylation microarray. While only 4 ONB samples were included, they formed a distinct cluster based on a semi-supervised hierarchical clustering analysis.[23]

4 | DISCUSSION

The current review systematically summarizes the genetic, cytogenetic, and epigenetic alterations that have been previously reported in ONB. Although heterogeneous chromosomal instability in ONB were predicted by various studies, more cytogenetic alterations were observed in high grade tumors in comparison to low grade malignancies,[24] which is not surprising and has been previously observed in other cancers, such as cutaneous squamous cell carcinoma.[25] Loss of 3p was found to be the most common chromosomal alteration among patients with ONB and this alteration has been reported to be associated with resistance to chemotherapy or radiotherapy in other settings.[9,26] Additional studies have predicted metastasis and poor prognosis in patients with deletion in chromosome 11 and gain on chromosome 1p.[9,24] While frequent cytogenetic alterations were detected in all chromosomes besides 8 and 20, Valli et al, reported that neither Kadish stage nor Hymans grade was significantly associated with any of the cytogenetic alterations detected in their study.[27] One cytogenetic study that analyzed primary and recurrent malignancies, found that there were decreased trisomies and increased number of partial gains in relapsed tumor in comparison to the primary disease.[27] Patients exhibiting aneuploidic alterations have been treated with energy and proteotoxic stress-inducing compounds such as AICAR (5-aminoimidazole-4-carboxamide riboside), 17-AAG (17-allylamino-17-demethoxy-geldanamycin) and chloroquinone, however, the applicability of these treatment modalities to ONB requires further investigation.[28] More importantly, platinum-based agents were reported to be efficient against cancer cells with heterogeneous chromosomal instability,[29] suggesting that platinum-based chemotherapy may be an effective approach in treating this disease among the patients with chromosomal instability. In fact, cisplatin has shown efficacy as induction chemotherapy for ONB.[30]

Although comprehensive molecular profiling for patients with advanced and metastatic disease can be useful in designing defined therapeutic strategies, sequencing of ONB has been limited by low sample sizes due to rarity of the disease. The COSMIC database and published studies have reported alterations in a large number genes, including *TP53*, *EGFR*, *CTNNB1*, *KIT*, *RET*, *APC*, *FGFR2*, *KDR*, *PDGFRA*, *SMAD4*, *MET*, *PIK3CA*, *NF1*, *CDKN2A*, *CDH1*, *SUZ12*, *PP6C*, *IKZF1*, *TGFBR2*, *CARD11*, *CDKN2C*, *SND1*, *cMET* and *CREB3L1*, with subset of these genes being either known tumor drivers or tumor suppressors. For example, alterations in cKIT and PGDFRA have been implicated in the pathogenesis of gastrointestinal tumors. Tyrosine kinase inhibitors such as Imatinib, have been investigated in patients with gastrointestinal stromal tumors harboring the gain-of-function mutations in aforementioned genes,[31] and may be considered for treating ONB patients given the high frequency of cases harboring such alterations. Gay et al have reported mutations in genes associated with mTOR, CDK and growth factor signaling pathways.[10] Inhibitors of these pathways have been used in various cancers including breast, head and neck, lymphoma, and lung cancer.[32,33]

The findings of the current review and data extracted from COSMIC database suggest that *TP53* is the most frequently mutated gene in ONB.[10,12,17,20,21,34] Known alterations in *TP53* include stop/gain, short variants, truncations, rearrangements and SNPs in the DNA binding domain. These alterations are commonly associated with loss of protein function and have been reported to be involved in driving tumorigenesis of various tumor types, including breast, lung, colorectal and other solid malignancies. In general, ~50% of human cancers carry a loss of function mutation resulting in abolished or reduced p53 protein function.[35] *TP53* gene mutations are associated with multiple oncogenic processes, such as loss of cell cycle arrest, apoptosis, inhibition of angiogenesis and metastasis, DNA repair, as well as inhibition of mTOR signaling axis. The enhanced number of alterations in TP53 among patients with ONB can pave the path for designing new

therapies focused on restoring or enhancing the p53 tumor suppression activities. Various molecules including nutlins, MI series, RO5693, PRIMA-1, and RITA have been developed for treatment of cancers with *TP53* mutations. Nutlins function by targeting negative regulators of p53 protein, MI series function by reactivation of p53 by p21 mediated cell cycle arrest, whereas PRIMA-1 binds to p53 by Michael addition after getting converted into methylene quinuclidinone (MQ), and its binding at cysteine residues induces apoptosis in tumor cells. Another molecule, COTI-1, induces DNA damage signaling. Many of these molecules are in the preclinical phase, except for two compounds APR-246 and COTI-2 that have progressed to clinical trials.[36] None of these approaches have been tested in ONB patients. Of note, tumors harboring *TP53* alterations may respond better to WEE kinase inhibitors that function by acting against G2-M checkpoint regulators of the cell cycle, WEE1 and CHK1.[37]

While epigenetics research in ONB is recently emerging, it has already demonstrated a promising practical implementation in clinical practice, as ONB harbors unique genome-wide methylation profiles in comparison with other sinonasal malignancies.[11] A pattern of global hypermethylation was described in a subgroup of ONB tumors that harbor R172 *IDH2* hotspot mutations, corroborating the complex interplay between genomic and epigenomic regulation. It has been previously described that IDH mutations lead to neomorphic enzymatic activity, and acute myeloid leukemia patients that harbor IDH mutations also demonstrate a hypermethylation phenotype.[38] This represents an attractive area for pharmaceutical targeting, as in vitro data using IDH2 R140Q expression in TF-1 cells that reflects global hypermethylation of clinical acute myeloid leukemia, was reversed by an IDH2 small molecule inhibitor, AGI-6780.[39] It is likely that additional epigenetic regulatory mechanisms such as miRNAs and long non-coding RNAs play a role in the onset, progression, and ultimately therapeutic response of ONB, but those remain yet to be determined.

The rare character of ONB has limited the sample size available for cytogenetic, genomic, and epigenetic studies and contributes to the limitations of this systematic review. Furthermore, the exclusion criteria included studies not in English or without full text which may have limited the scope of articles reviewed. Given its rarity, studies characterizing the landscape of genomic alterations in ONB are still limited, and targeted therapies are lacking for this disease. Thus, additional studies with larger sample sizes are warranted to further advance our understanding of the molecular processes underlying the progression of ONB. An increase in available molecular data will assist in detecting potential correlations between changes in the ONB specific genetic landscape and a clinical course of the disease. Furthermore, alterations specific to high grade and low grade ONB may be used for designing novel therapeutic approaches aiming to improve the overall survival of patients with this rare but aggressive disease. As the number of fully sequenced ONB cases continues to grow, comprehensive, well-powered molecular analyses will allow international collaborative networks to correlate the genomic and epigenomic profiles with clinical outcomes and create a map of novel targets for therapeutic exploitation. Not only will this significantly improve our understanding of ONB pathogenesis, but also allow us to guide targeted therapies and potentially adopt these techniques in the routine diagnostic work-up of our patients.

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CONFLICT OF INTEREST

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