Embryonic Lethality of Cranial Neural Crest Deletion of Cdc73

Lilia Shen
University of Connecticut - Storrs, liliash19@gmail.com

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Embryonic Lethality of Cranial Neural Crest Deletion of Cdc73

Honors Thesis of Lilia Shen
Advisors: Dr. Jessica Costa-Guda, Dr. Andrew Arnold
Abstract

Hyperparathyroidism-jaw tumor (HPT-JT) syndrome is a rare but damaging disease that is characterized by a plethora of tumors, including parathyroid tumors, renal cysts or tumors, uterine tumors, and ossifying jaw fibromas. The cause of this syndrome can be traced back to a tumor suppressor gene called Hrpt2, now renamed Cdc73, which encodes for the protein product parafibromin. Parafibromin is a part of the Paf1 complex, which interacts with RNA polymerase II, playing a role in transcriptional initiation and elongation. The loss of proper expression of Cdc73 and its protein product parafibromin are implicated in the development of the various types of tumors that are typical of HPT-JT, although the exact mechanisms of tumorigenesis are unclear. In particular, not much is understood about how the loss of Cdc73/parafibromin contributes to the development of ossifying fibromas (OF) of the jaw. OF is a benign bone neoplasm that can affect both the mandible and maxilla, and consists of fibrous tissue in the place of bone. The goal of this research was to deepen the understanding of the role Cdc73/parafibromin plays in the development of OF through creating a mouse model of OF. Using Wnt1 as a Cre driver with Cdc73-floxed mice, Cdc73 loss was targeted to the cranial neural crest of the mouse. However, homozygous knockouts of Cdc73 in the cranial neural crest proved to be embryonic lethal by day 13. Upon investigation of these embryos, the presence of apoptosis was discovered in both the mandible and the midbrain, the latter of which is the likely cause of embryonic lethality. This finding provides further evidence that the normal expression of Cdc73/parafibromin plays an essential role in embryonic development. Heterozygous null mice were viable and healthy, and were followed out to 15 months. Histological analysis of their jaws revealed no development of OF or any
other abnormalities, indicating that the development of these tumors requires biallelic inactivation of \textit{Cdc73} and the amount of time it takes to acquire a second somatic mutation to cause loss of heterozygosity is substantial. Parafibromin was detected throughout the jaw tissue, the presence of which is also consistent with a tumor suppressor model in which the remaining copy of \textit{Cdc73} can produce enough parafibromin in order to maintain normal function.

\textbf{Introduction}

A familial disease inherited in an autosomal dominant manner, hyperparathyroidism-jaw tumor (HPT-JT) syndrome places patients at risk for multiple types of neoplasia. As indicated by the name, patients often present with hyperparathyroidism as a result of the parathyroid tumors developed in this syndrome. These parathyroid tumors are usually parathyroid adenomas; however, what makes this condition particularly aggressive compared to other hereditary causes of hyperparathyroidism is that >15\% of patients afflicted with HPT-JT develop parathyroid carcinomas\textsuperscript{1}, a malignant tumor that can lead to serious clinical manifestations, and is normally extremely rare in the general population. Compared to other types of familial hyperparathyroidism, patients with HPT-JT oftentimes have more severe hypercalcemia\textsuperscript{1} and up to 50\% of patients will also experience kidney or bone disease\textsuperscript{2}. Other presenting symptoms of parathyroid carcinomas include fatigue, weakness, weight loss, anorexia, polyuria, and polydipsia\textsuperscript{2}. The ideal treatment for parathyroid carcinomas is an en bloc resection of the tumor, which if performed successfully, has a 90\% long-term survival rate\textsuperscript{2}. However, incomplete resection increases recurrence rate, usually at the original
site, and subsequent mortality from the long-term consequences of hypercalcemia. In a case study, out of 10 recurrences that occurred in less than 2 years since initial removal of the carcinoma, 9 cases resulted in patient death\textsuperscript{3}. Even for recurrences occurring over 2 years later, 3 out of 8 patients did not survive\textsuperscript{3}, although this is a better survival rate. Overall, the mortality rate for reoccurrences in this case study was 66%. The majority of recurrences also resulted in metastases. Therefore, when not treated successfully or becoming invasive, the prognosis for parathyroid carcinoma can become quite poor.

Along with parathyroid adenomas and carcinomas, >15% of patients with HPT-JT can also develop renal tumors, including Wilms’ tumors, hamartomas, and carcinomas\textsuperscript{4}. About 75% of female patients who develop HPT-JT also find themselves with benign or malignant tumors of the uterus\textsuperscript{5}. Finally, about 30% of HPT-JT patients develop ossifying fibromas of the jaw, benign neoplasms that can manifest in the mandible or maxilla.

Patients with HPT-JT often present first with an ossifying fibroma of the jaw\textsuperscript{6}. In fact, OFs can be found in HPT-JT patients that show no evidence of the characteristic parathyroid tumors or hyperparathyroidism\textsuperscript{7}. Ossifying fibromas (OF) are tumors in the bone that consist of a highly cellular fibrous tissue, either calcified tissue that resembles bone, cementum, or a varying amount of both. The mandible is the most commonly affected site, and although an OF can present at any position throughout the mandible, it presents most frequently inferior to the premolars and molars\textsuperscript{8}. This concurs with the conventional belief that OFs are thought to originate from the periodontal ligament, which surrounds the tooth-bearing areas of the jaws. The peak age for the development of OF appears to be in the middle-aged range of adulthood, between 20 to 40 years of age\textsuperscript{8,9}. 
OF seems to show a predominance towards females, who are up to five times more likely to develop this neoplasm than their male counterparts\textsuperscript{9}.

A characteristic of OF that distinguishes it from other types of fibrous lesions or dysplasia is a well-defined growth pattern. The slow-growing, progressive expansion of the bone is marked by smooth, relatively well-demarcated radiographic borders\textsuperscript{8,9}. In most cases, the growth tends to be round with concentric outgrowth that is approximately regular in all directions\textsuperscript{8}. OFs can also appear to be irregular in shape, especially if they are recurrent or if they grow very rapidly in a short period of time. In these cases of a recurrent OF or of aggressive local growth, the tumors can encompass the entire jaw bone, appearing as one large, irregularly shaped mass\textsuperscript{8}.

OFs are benign neoplasms; however, they can grow large enough to cause damage to the surrounding tooth-bearing areas of the jaw as well as general cosmetic concerns such as visible outgrowths of the jaw and facial asymmetry for patients who are afflicted. The expansion of the tumor can lead to tooth displacement and even resorption of tooth roots\textsuperscript{8}. Often times, the lamina dura is also missing from the displaced teeth. Left untreated, an OF will continue to expand and can become severely disfiguring to the face\textsuperscript{6}. If severe enough, the displacement caused by a particularly large OF can hinder an afflicted patient’s ability to take in food. Treatment of OF requires radical surgery involving complete excision of the tumor along its well-demarcated lines\textsuperscript{8}. Larger tumors may require resection with an additional small margin\textsuperscript{9}. Though capable, the vast majority of OFs do not recur after being surgically removed as long as the resection is complete.
The development of HPT-JT has been genetically linked to a tumor-suppressor gene called \textit{Hrpt2}, now renamed \textit{Cdc73}. This gene was identified in chromosome 1q24-q32\textsuperscript{1}, and encodes a protein product called parafibromin. Germline mutations in \textit{Cdc73} that are expected to produce loss of function in parafibromin through truncation or premature stops have been reported, lending evidence that this gene plays a significant role in the pathogenesis of HPT-JT. Additional inactivating mutations in conjunction with already present germline mutations have also been reported in the parathyroid tumors of certain kindreds afflicted with HPT-JT\textsuperscript{1,10}. This advent of loss of heterozygosity provides evidence that the development of HPT-JT requires biallelic inactivation of \textit{Cdc73} in order to manifest, a clear marker of a tumor-suppressor mechanism of pathogenesis. Such inactivating mutations were not detected in adjacent non-tumor tissue or in patients who are not afflicted with HPT-JT\textsuperscript{1}, suggesting that the mutations in \textit{Cdc73} were directly related to the pathogenesis of HPT-JT.

The protein product of \textit{Cdc73}, parafibromin, is composed of 531 amino acids and is predominately found in the nucleus\textsuperscript{11}. It has been identified as a part of the Pafl complex, and involved in processes such as transcription elongation and posttranscriptional events, such as 3’ end processing\textsuperscript{11,12}. Parafibromin can also associate with the large subunit of RNA polymerase II in the process of transcription. This interaction is contingent on a C-terminal domain on the protein, which is commonly affected by 80% of clinically relevant mutations in \textit{Cdc73}. These mutations result in premature truncations that can delete more than half of this C-terminal domain on parafibromin, hindering its normal function to regulate transcription. Down regulation of parafibromin has also been shown to increase entry into the S phase of cell division\textsuperscript{12},
spawning a theory that parafibromin has the ability to inhibit the cell cycle, although the mechanism by which it does this is unknown. This however, concurs with the idea that \textit{Cdc73} is a tumor suppressor gene—the loss of normal function of parafibromin can leave cell division unchecked, leading to the development of the typical cancerous growths seen in HPT-JT.

Given \textit{Cdc73}/parafibromin’s significant role in the development of HPT-JT, mouse models in which normal \textit{Cdc73}/parafibromin expression have been knocked out have been created in an effort to study the mechanisms of tumorigenesis in HPT-JT, albeit to varying degrees of success. In conventional knockouts of \textit{Cdc73}, wild-type and heterozygote adult mice were viable and fertile but homozygote mice were not, showing embryonic lethality as early as embryonic day 6.5\textsuperscript{13}. Heterozygote adult mice of conventional \textit{Cdc73} knockouts were able to develop parathyroid tumors including parathyroid adenomas, parathyroid carcinomas, and other atypical parathyroid adenomas, representative of the tumors found in HPT-JT\textsuperscript{14}. Female heterozygotes developed uterine neoplasms as well, another hallmark of HPT-JT\textsuperscript{14}. Their wild-type counterparts did not develop tumors of any kind. Both these parathyroid and uterine tumors showed a reduction, or even a complete lack of normal nuclear expression of parafibromin\textsuperscript{14}, again concurring with the tumor suppressor role of \textit{Cdc73}. OFs were not found in the heterozygote conventional knockouts; however, they did have an increased mandibular cell proliferation rate\textsuperscript{14}, which may represent a possible early phase with potential for tumorigenesis in the future.

In addition to conventional models, a conditional knockout of \textit{Cdc73} specific to the parathyroid has also been created by mating \textit{Cdc73}-floxed mice with transgenic PTH-
Cre mice, localizing the loss of *Cdc73* to the parathyroid. Unlike the conventional knockout model, both heterozygous and homozygous mice with knockouts of *Cdc73* restricted within the parathyroid were viable. Within these mice, which either had one or both alleles of *Cdc73* deleted in the parathyroid, >40% displayed parathyroid tumor development\(^\text{14}\). Similarly, their wild-type counterparts did not develop any tumors. The previously described conventional knockout of *Cdc73*, and this parathyroid-specific knockout provide a model with which to investigate the molecular basis of tumorigenesis in HPT-JT.

Despite the successful creation of mouse models for the parathyroid tumors and uterine tumors seen in HPT-JT, there has been a lack of mouse models for OFs in HPT-JT and little is known about how the loss of *Cdc73* and its protein product parafibromin contributes to the development of these jaw tumors, which have not been studied so extensively as the other characteristic tumors of the syndrome. A few somatic and germline mutations have been discovered in sporadic OFs\(^\text{15}\); however, whether these cases are related to HPT-JT cannot be determined, and it is not necessarily revealing of how mutations in *Cdc73* contribute directly to the development of the tumor. Therefore, the aim of this project was to model OF in mice in the hopes of discovering some ideas about the mechanism of OF tumorigenesis following the loss of *Cdc73*/parafibromin.

**Materials/Methods**

**Animals**

In order to produce a transgenic mouse model for OF, *Cdc73*-floxed mice were crossed with *Wnt1*-Cre mice, generating offspring that were Cre-positive and
heterozygous for the LoxP sites surrounding the target gene. These mice were then crossed again with Cdc73-floxed mice to produce offspring that was both Cre-positive and homozygous for Cdc73 LoxP sites, effectively knocking out the gene. The use of Wnt1 as a Cre driver localizes Cdc73 deletion to the craniofacial bones. Wnt1 expression occurs in migrating neural crest cells, which arise in the midbrain and hindbrain, and proliferate into the frontonasal, maxillary, and mandibular prominences\textsuperscript{16}. Therefore, homozygous Cdc73 deletion is restricted to the jaw of the mouse.

**Timed Pregnancies**

After it was discovered that homozygous knockouts of Cdc73 in the jaw resulted in embryonic lethality, timed pregnancies were performed instead in order to assess the morphology of the homozygous knockout embryos before they were resorbed in utero, as well as to perform chemical staining to assay for apoptosis throughout the embryonic
tissue. Euthanization of the mother was generally performed at approximately embryonic day 11-13. Embryos were harvested, genotyped, and then embedded into paraffin blocks to be sectioned for further chemical and histological analysis.

**Immunohistochemistry**

The location and presence of apoptotic cells throughout the embryonic tissue of the homozygous cranial neural crest *Cdc73* knockouts was assessed by immunohistochemical (IHC) staining techniques.

The primary antibody used was Cleaved Caspase-3 (Asp175) (5A1E) Rabbit mAB, an antibody specific to cleaved caspase-3, a protein involved in cell death. Caspases play an integral role in cellular apoptosis, but normally exist as inactive enzymes within the cell. During the signaling process for apoptosis, initiator caspases cleave effector caspases such as caspase-3, thereby activating it so it can carry out its function of proteolytically degrading intracellular proteins and organelles, ultimately leading to the death of the cell. Therefore, the presence of cleaved caspase-3 indicates that apoptosis has occurred in the cell. Slides were incubated with the antibody

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**Figure 3: IHC Diagram.** Immunohistochemical staining techniques utilize a primary antibody that binds to the protein of interest. The secondary antibody binds to the primary antibody, and has an enzyme attached that can generate a colored product when substrate is introduced, identifying the presence of the desired protein.
overnight, before being treated with a secondary antibody, ImmPRESS Anti-Rabbit IgG, that contained an enzyme that could produce a colored product. DAB Chromogen was used as a substrate, which was converted by the enzyme into the brown colored staining indicative of a cell positive for cleaved caspase-3. After the IHC staining was complete, the slide was counterstained with hematoxylin, observed under a light microscope, and scored for instances of positive staining using the table shown below.

<table>
<thead>
<tr>
<th>% positive cells</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;10%</td>
<td>10-25%</td>
<td>25-50%</td>
<td>50-75%</td>
<td>&gt;75%</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Positive structures</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Neither</td>
<td>Nuclei only</td>
<td>Cytoplasm only</td>
<td>Both</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intensity of staining</th>
<th>-</th>
<th>+</th>
<th>++</th>
<th>+++</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absence of staining</td>
<td>Absence of staining</td>
<td>Weak</td>
<td>Moderate</td>
<td>Intense</td>
</tr>
</tbody>
</table>

*Figure 4: IHC Scoring Chart.* Slides were scored for the percentage of positive cells, the location of staining within the cell, and the intensity of the staining based on the scale shown above.

**Jaw Prep for Heterozygous Null Mice**

Heterozygous null mice are positive for the Cre driver and heterozygous for LoxP sites flanking the gene Cdc73, meaning they only have one copy of Cdc73 in their craniofacial bones. These heterozygous null mice were followed out to 15 months, and were viable and healthy. Their jaws were harvested, embedded into paraffin blocks, and sectioned for histological analysis and immunohistochemical staining. For histological analysis, a hematoxylin and eosin (H&E) stain was performed. IHC staining for heterozygous null mice jaws was also done. It utilized the Parafibromin (2H1) antibody
in order to assess for the presence of the protein within the tissue. The antibody was incubated for an hour only in order to reduce the amount of background staining as it was a mouse-on-mouse antibody. After the IHC was complete, slides were also counterstained with hematoxylin. Slides were scored using the same scale used for the IHC staining of the homozygous knockout embryos.

Results

The number of observed births from initial crosses is summarized in Figure 5. As can be seen from the table, there were live births obtained of all the listed genotypes except for the homozygous cranial neural crest knockouts, identified as Cre+ F/F in the table. It is statistically unlikely for there to be absolutely no live births of the homozygous cranial neural crest knockouts as the correct ratio over time for these listed genotypes (from top to bottom as shown in the table) should be approximately 2:1:2:1. However, the actual observed ratio was 1:1:1:0, indicating that the homozygous cranial neural crest knockouts are embryonic lethal, therefore resulting in the lack of live births and the skewing of the actual genotype ratio.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Number of Live Births</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cre- F/+</td>
<td>24</td>
</tr>
<tr>
<td>Cre- F/F</td>
<td>27</td>
</tr>
<tr>
<td>Cre+ F/+</td>
<td>21</td>
</tr>
<tr>
<td>Cre+ F/F</td>
<td>0</td>
</tr>
</tbody>
</table>

Figure 5: Table of Live Births Observed. Cre+ indicates the presence of the Wnt1-Cre driver while Cre- indicates the lack of it. F/F indicates a mouse that is homozygous for LoxP sites on Cdc73. F/+ indicates a mouse that is heterozygous for LoxP sites on Cdc73. No live births of homozygous cranial neural crest knockouts (Cre+ F/F) were observed.

The homozygous cranial neural crest knockouts of Cdc73 that were harvested from embryonic day 13 and beyond, were oftentimes smaller with gross morphological abnormalities than embryos of the wild-type and heterozygous genotypes. It is likely that
these embryos have already begun to become resorbed in utero after their death in the womb. Therefore, embryonic lethality in this line of knockout mice must’ve occurred at approximately embryonic day 13.

IHC staining on the harvested homozygous knockout embryos with an antibody for cleaved caspase-3 revealed positive staining in various locations throughout the embryonic tissue. A certain level of apoptosis is typically associated with an embryo in development and can be considered normal. Therefore, not all cases of staining were considered to be significant. Instead, the focus was more on locating apoptosis in places of the tissue where the Cre driver, Wnt1, is known to be expressed, as these tissues would be the site of Cdc73/parafibromin loss following the knockout. With these considerations, positive staining revealed the presence of apoptosis in the mandible and the midbrain, the two primary locations where Wnt1 proliferates during development and where normal Cdc73/parafibromin expression would’ve been lost.

Heterozygous null mice were healthy and viable, but it was still pertinent to assess whether or not they had shown any development of OF over their lifetimes. Histological analysis after an H&E stain of the jaw bones from heterozygous null mice, followed out to 15 months, were completely normal and did not show any signs of OF or any morphological abnormalities.
Figure 7: IHC Staining Results for Cleaved Caspase-3. Positive (brown) staining was found in the midbrain area of a homozygous Cdc73 cranial neural crest knockout at embryonic day 11-11.5, indicating the presence of apoptosis. Scores: % positive cells – 1, positive structures – 3, intensity of staining – +++.

Figure 8: H&E Stain of Jaw Bone. Jaw from a heterozygous null mice, followed out to 15 months, shows that the tissue is healthy and does not exhibit any development of OF or morphological abnormalities.
Finally, IHC staining with an antibody for parafibromin was also performed on these jaw sections from heterozygous null mice. The bone tissue was fragile and did not handle staining procedures well, resulting in lifting, folding, and sometimes even completely washing off of bone tissue from the slide. Positive staining did occur in the bone; however it was more difficult to observe and did not produce as clear results as staining elsewhere. The majority of the positive staining was observed fairly ubiquitously throughout the surrounding epithelial and muscular tissue of the jaw, most notably in the periodontal ligament of the tooth-bearing areas.

![Image of IHC staining results for parafibromin. Positive (brown) staining for parafibromin was found in the periodontal ligament of the tooth-bearing areas of the jaws in heterozygous null mice. Scores: % positive cells – 4, positive structures – 3, intensity of staining – ++.]

**Discussion**

The original aim of this project was to develop a mouse model for the OFs seen in HPT-JT as a method of studying the mechanisms of development of this specific tumor.
The homozygous cranial neural crest knockouts of Cdc73 were discovered to be embryonic lethal, similar to conventional knockouts of Cdc73, which meant the study of tumorigenesis of OFs was not possible using this model. However, analysis of these homozygous cranial neural crest knockouts and their heterozygous null counterparts does have some important implications.

The homozygous cranial neural crest knockouts were lethal by embryonic day 13, which is longer than previous conventional knockouts of Cdc73. Conventional knockouts of Cdc73 have been embryonic lethal as early as embryonic day 6.5 with lethality likely occurring at the hatching stage or implantation stage. In conventional knockouts, wild-type and heterozygous Cdc73 blastocysts were able to attach to the plate in vitro while homozygous blastocysts failed to attach and thus were unable to continue growing, suggesting that their inability to implant was what directly caused the lethality. The cranial neural crest knockouts were able to remain viable for longer due to the timing of the knockout. This model utilizes Wnt1 as a Cre driver, and the expression of Wnt1 begins at approximately embryonic day 9.5, effectively knocking out the Cdc73 gene starting only from this time point forward. Therefore, this allows the cranial neural crest knockouts to bypass the failure of conventional knockouts to implant because normal expression of Cdc73 still remains at embryonic day 6.5.

Instead, lethality of the homozygous cranial neural crest knockouts was likely caused by the presence of apoptosis in the midbrain, and thus a failure to develop properly. Wnt1 begins proliferation in the midbrain and the hindbrain, effectively knocking out Cdc73 in those areas of the developing embryo as well. The lack of Cdc73 expression in the midbrain and the subsequent apoptosis that accompanies provides
further evidence that normal expression of \textit{Cdc73}/parafibromin plays a critical role in development. In an inducible knockout of \textit{Cdc73}, injection of tamoxifen at embryonic day 10.5 leads to a significant delay in the development of the central nervous system and the embryos die rapidly afterwards \textsuperscript{13}. It is likely that a similar phenomenon is occurring in this cranial neural crest knockout model as well, especially because expression of \textit{Wnt1} producing the knockout begins at around the same time. The loss of \textit{Cdc73} expression during this time period is associated with elevated levels of apoptosis in the midbrain that become embryonic lethal, implying that proper \textit{Cdc73} expression is required for development, including in the nervous system.

The jaws harvested from 15-month-old heterozygous null cranial neural crest knockouts were histologically normal with no sign of OF development. The fact that these mice did not develop any jaw tumors indicates that tumorigenesis likely requires biallelic inactivation of the \textit{Cdc73} gene. This is consistent with the tumor-suppressor role of \textit{Cdc73}, as one copy of the gene is apparently sufficient to sustain normal function within the jaw tissue and prevent the development of tumors. Immunohistochemistry results for parafibromin showed the presence of the protein within the jaw tissue, most significantly in the periodontal ligament, the believed origin of OF. Nuclear staining of parafibromin in this region indicates that these mice, despite having lost one allele of \textit{Cdc73}, were still able to produce enough functional protein to maintain normal activity and stave off tumor development. Nuclear staining was more difficult to observe in the bone tissue as it did not adhere to the slide as well as other surrounding tissue did during the staining procedure and so, did not always produce clear results. The relative low quantity of cells in the bone matrix itself also made staining difficult to pinpoint.
However, staining was still occurring in some cases and the presence of functional parafibromin in the bone itself also provides evidence for *Cdc73* as a tumor suppressor, and that the inactivation of one allele is not enough to cause tumors.

For the future, further studies will need to be performed in order to produce a successful mouse model that can be used to study the specific mechanisms of tumorigenesis for OF. The importance that *Cdc73* and parafibromin expression plays in embryonic development makes it particularly challenging in creating a successful mouse model, especially one targeted for the study of jaw tumors. However, the embryonic lethality of the cranial neural crest knockouts of *Cdc73* at least provides additional evidence that *Cdc73* is required for development, and its specific role in embryogenesis can become an important area of study. The heterozygous null knockouts reaffirm *Cdc73*’s role as a tumor suppressor, and suggests that the development of tumors can occur only when both copies of the gene become nonfunctional. The fact that these heterozygous null knockouts did not develop tumors or any other histological abnormalities for the entire time that they were followed for 15 months can be seen as a reflection of the time it takes to acquire an additional inactivating mutation that causes the loss of the last copy of the *Cdc73* gene. Loss of heterozygosity is a common phenomenon that causes cancer when the last copy of a tumor suppressor gene becomes subject to an inactivating mutation. However, loss of heterozygosity is rarer in HPT-JT compared to other familial types of hyperparathyroidism, and can suggest that in tumors characteristic of HPT-JT, alternative mechanisms aside from loss of heterozygosity may be at play.
The study of OF is especially vital as it has not been so extensively studied as the other tumors of HPT-JT, such as the parathyroid adenomas. While there have been mouse models successfully produced that show the development of parathyroid and uterine tumors, there has not been one made for the jaw tumors. The creation of mouse models, particularly for OF now, is of utmost importance for elucidating the possibly myriad ways in which tumorigenesis can occur and is key to diversifying the knowledge of such a unique and still mysterious syndrome.
References


