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Mouse models of Inherited Cancer Syndromes

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Abstract

Animal models of cancer have been instrumental in understanding the progression and therapy for hereditary cancer syndromes. The ability to alter the genome of individual mouse cell types in both constitutive and inducible approaches has led to many novel insights into their human disease counterparts. In this review, conventional, conditional and inducible knockout mouse models of inherited human cancer syndromes are presented and insights from the study of these models are highlighted.

Keywords

GEM (Genetically engineered mice); Hereditary Cancer syndrome; Cancer Genetics

INTRODUCTION

Mouse Models and Cancer

Tumorigenesis is a heterogenous and complex process that involves hundreds if not thousands of genetic and environmental factors. These include both cell autonomous processes (i.e, the impact of mutations in the cells that transform into cancer cells), and cell non-autonomous processes involving the tumor niche. Some of the more prominent processes in the tumor niche include adequate oxygenation, nutrition, angiogenesis and immune surveillance, among others. Historically, this complexity has been challenging to tease apart using in vitro systems. Mouse models are instrumental in studying tumorigenesis in a dynamic physiological system and have become an integral part of our approach to understanding the mechanistic basis of tumorigenesis. These processes include the action of oncogenes and tumor suppressor genes, the biology and interaction of host and tumor and potential risk and benefit of chemotherapeutic agents. Because of the ability to manipulate the genome of the laboratory mouse (*Mus musculus*) at the single base pair level, its well annotated genome, small size and ability to breed in captivity, the mouse has become one of the best model systems for the study of tumorigenesis. Because of obvious ethical limitations on our ability to perform studies in human patients, long term prevention studies or drug screening in relatively uncommon diseases such as many cancer genetic syndromes, the mouse has in fact become an indispensable tool in mechanistic, therapeutic and natural history studies of cancer etiology and progression. As we move forward and with the

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development of more sophisticated models we will be able to examine different aspect of cancer biology and develop better therapeutic agents.

Mouse Models of Inherited Cancer Genetic Syndromes

There are estimated to be more than 6,000 Mendelian genetic disorders and more than 50 human familial cancer syndromes.^{1, 2} Many of these diseases are rare, some vanishingly so, but all are aberration in a specific gene, including those that involve tumor suppressor genes (TSG).³ This situation clearly applies to many cancer genetic syndromes, some of which have an evolutionary selection against propagation of mutations in the underlying genes from generation to generation. As described in more detail in the accompanying articles in this issue, inherited cancer genetic syndromes broadly can be defined as diseases that involve germline mutations carried throughout the entire body. Using what are today standard techniques, genetically engineered mice (GEM) can be generated that have the precise germline mutations carried by patients. With this approach not only loss of function mutations can be modeled, but also rare dominant negative, gain of function and mis-function mutations in the same gene can be studied that reflect the operant mechanisms in order to obtain a more complete understanding of allelic heterogeneity in monogenic disorders. Furthermore, many gene interactions as seen in human tumors can only be studied under compound mutant animals by crossing different mutant mice, as well as genetic background effect studies. Modifier genes have been important in human cancer genetics, and mouse models can tease apart the effect of these genes as well.

Gastrointestinal Tumors

Several mouse models have been made to study gastrointestinal neoplasias that arise from familial and sporadic syndromes. Mendelian diseases of colorectal cancer include familial adenomatous polyposis (FAP), Lynch syndrome, *Peutz-Jeghers* syndrome and Cowden syndrome.^{1, 3} (Tables 1 & 2)

Familial Adenomatous Polyposis—FAP is a rare hereditary syndrome characterized by development of hundreds of colonic polyps in the late teens or early twenties. Some of the polyps inevitably transform into colonic carcinomas. Almost all FAP is caused by a mutation in the adenomatous polyposis coli (*APC*) gene. Less frequently, mutations in the Base Excision Repair gene *MYH* can cause an attenuated form of FAP.⁴ To better mimic common mutations found in FAP patients, several *Apc* mutations have been constructed using gene knockout methods besides *Apc*^{min}. *Apc*^{Δ716} contains a truncating mutation at codon 716, and *Apc*^{1638N} contains a truncating mutation at codon 1638.^{5, 6} All three mutations produced different polyp burden on the same background in the small intestine; *Apc*^{min} producing the most polyps of 100 or more and *Apc*¹⁶³⁸ the least number at just around 3.⁷ The polyps were phenotypically indistinguishable from one another in all three mutant models. The advantage of the *Apc*^{1638N} model for FAP is that with a lower polyp burden is these animals have an increased life span and develop more advanced tumors useful for studying tumor progression and metastasis. They are also useful to look at positive synergy with mutations in other candidate tumor suppressors, whereas *Apc*^{Min} are better for testing chemopreventive drugs (e.g. assaying for reduced adenoma burden). A confusing point for these mouse models of *Apc* deficiency is that adenomas form in the small intestine instead of colon as seen more commonly in FAP patients. However, *Apc* mouse models have shed much light on the role of Wnt pathway in the initiation, development and progression of colorectal cancers (CRC). Furthermore, these mouse models have been useful in studying the effect of modifiers of *Apc* mutations and activated WNT signalling. *Apc* models have also been useful in studies on the impact of diet in the process of CRC development. Several modifier of min 1 (Mom) have been identified in mice, that provide insight into epistatic interaction with *APC*. Mutation that affects intestinal adenomas of *Apc*^{min} mice is genes in

archidonic acid pathway have been identified using mouse genetics.⁸ One of these genes is COX-2 gene (*Ptgs2*). The double mutant *Apc*⁷¹⁶;*Ptgs2* has been helpful to interpret the impact of non-steroidal anti-inflammatory (NSAIDS) on mechanism of colon polyp development. The introduction of a cyclooxygenase 1 and 2 (*Cox1* and *Cox2*) mutant in the *Apc*^{min} mice had a pronounced effect on the size and number of intestinal polyps.^{9–11} This mouse model has been very useful to provide a model system for chemoprevention studies, using NSAIDS to treat familial and sporadic polyposis patients.^{12, 13}

Lynch syndrome—Mouse models for DNA mismatch repair (MMR) genes *MLH1/MSH2/MSH6/PMS2* have been under investigation for many years; MMR mouse models have been highly valuable in revealing the mechanism of MMR genes in cancer biology.¹⁴ MMR prevents cancer and suppresses tumors through several mechanisms. These include (1) single base substitution repair, (2) insertion/deletion frameshift repair (also called microsatellite instability), (3) anti-apoptosis and (4) suppression of promiscuous homeologous recombination. *MLH1* and *MSH2* mutations are responsible for >90% of all Lynch syndrome, other MMR genes mutations are less deleterious.¹⁵ *Msh2* is an essential part of the *MutS* protein complex and several knockout mouse models of *Msh2* have been generated.^{16–18} Mice have severe life span reduction as a result of aggressive lymphomas, specifically T-cell lymphomas, intestinal tumors and other tumor types as well as sebaceous gland tumors similar to Muir-Torre patients. Biallelic mutation in *Msh2*, *Msh6*, *Mlh1* and *Pms2* exhibits some of the same malignancies seen in humans with biallelic inactivation of the same genes, such as hematological disorders that results in shorter life span.¹⁹ One of the hallmarks of MMR deficiency in mice and in humans is the microsatellite instability (*MSI*) phenotype, reflecting the accumulation of repetitive sequences in the genome. There are, however; differences in the development of the disease in genetically engineered mice (GEM) mice deficient in *Msh2* as compared to human patients, in humans most of the tumor development occurs in the colon and extracolonic cancers including endometrium. For endometrial cancer, MMR deficient mice must be crossed with *Pten* or other tumor suppressor gene knockout mice.²⁰ A recent mouse models that address the difference in tumor development between mice and human where in the mouse model a predominance of tumors are seen in the small intestine as compared to colon in the human patients suffering from Lynch syndrome is the conditional mouse line of *Msh2*^{loxP}; *Vill-cre* mice which directs tumor development to the colon and avoids development of lymphomas.¹⁷ *Msh6* deficient mice show a much later onset of tumor development as compared to *Msh2*^{-/-} mice.²¹ Since the role of *Msh6* in the MMR system is mostly to repair of base substitution and repair of single base IDs, its deficiency does not affect the repair of 2 to 4 base insertion-deletion loops (IDLs), therefore, the mice mostly accumulate base substitutions mutations as opposed to frame shift mutations seen in *Msh2*^{-/-} mice and the phenotype of *MSI* is not seen in tumors from these animals. *Msh6*^{-/-} mouse models show a similar phenotype of cancer onset and progression seen in Lynch syndrome patients with mutations in *MSH6* gene, where most of cancer development and progression occurs at 60 years and older with variable *MSI* phenotypes.^{22, 23} *MSH6* mutation has also been linked to endometrial cancers in Lynch syndrome patients, *Msh6*^{-/-} mice also been reported to develop endometrial cancers.^{21, 24} Mouse model for *Msh3* deficiency show a slight predisposition to cancer development due to moderate repair defects and display a normal life span. *Msh3* deficient mouse cells are not able to efficiently repair only 1 to 4 base IDLs, yet due to the presence of *Msh6* they can efficiently able to repair single-base substitution.²⁵ Similarly, human patients with *MSH3* mutations develop late onset tumorigenesis. The *MutL* homologues, (*MLH* and *PMS* genes) play important roles in DNA excision during repair and acting as molecular scaffold for additional proteins to coalesce. At the heart of the three *MutL* complexes, *Mlh1/Mlh3*, *Mlh1/Pms2* and *Mlh1/Pms1*, lies *Mlh1*. *MLH1* deficiency in human is responsible for shortened life span and a strong predisposition to cancer. *Mlh1* knockout

mice do not have MMR capacity, therefore, due to the high rate of base substitution, as well as small insertions and deletions in mono- and dinucleotide repeats, these mice have high mutator phenotype in their tissue and tumors, similar to *Msh2*^{-/-}. Mice deficient in *Mlh1* also have shortened life span and high degree of predisposition for cancer development.^{26–29} Combined mutation of *Mlh1* and *Msh2* do not change the tumor suppressor phenotype, consistent with the idea that they both participate in the same complex. (M. Liskay, personal communication) Tumor spectrum of *Mlh1*^{-/-} mice includes T-cell lymphomas, intestinal adenomas, and adenocarcinomas, as well as skin tumors.¹⁹ *PMS2* deficiency in humans is associated with Lynch syndrome as well as Turcot syndrome, a rare genetic condition which also predisposes patients to both multiple adenomatous colon polyps and brain tumors.³⁰ *Pms2*^{-/-} mice exhibit different disease progression, they show a milder mutator phenotype, an increase in mutation frequency at mononucleotide repeat tracts, but they do not develop any intestinal or brain adenomas, rather they mostly develop lymphomas and sarcomas with a delayed onset.^{29, 31} Recently characterized *Mlh3* gene deficiency has been shown to have similar effects as *Pms2* deficiency in mice and human patients suffering from Lynch syndrome.^{32–34} One major difference between *Pms2*^{-/-} and *Mlh3*^{-/-} deficiencies is that *Mlh3*^{-/-} mice do develop small intestinal adenomas and adenocarcinomas as well as extra-gastrointestinal tumors, including lymphomas, basal cell carcinomas of the skin. Similar to *Msh3* and *Msh6* combined inactivation mimics *Msh2*^{-/-}, combined inactivation of *Pms2* and *Mlh3* increase the level of mutator phenotype to that of *Mlh1*^{-/-}. Thus, *Mlh3*^{-/-}*Pms2*^{-/-} mice display similar disease development and progression as *Mlh1*^{-/-} mice.^{25, 32} From these mouse models, it has become clear that *Pms2* and *Mlh3* and *Msh3* and *Msh6* have redundant roles in repair and tumor suppression functions and it is the most likely reason penetrance is lower in patients deficient in any one of these genes.^{21, 25} Recently reported *Pms2*-cre mouse model, where a cell division-activated Cre-lox system for stochastic recombination of loxP-flanked loci is used, this system better mimics spontaneous mutation that occurs in cancer..³⁵

MMR deficiency in mice results in both DNA repair and DNA damage response defect, where both of these mechanisms are important in suppression of tumorigenesis. To study the role of each mechanism, knock-in mouse models have been generated where the mice carrying a recurrent mutation in a gene will render DNA repair mechanism null. *Msh2*^{G67A} (*Msh2*^{GA}) was one of the first knock-in mutant model with separation-of-function mutation similar to *MSH2* missense mutation seen in patients.^{36–38} As predicted, this mutant lost its DNA repair capability, but retained its DNA damage response and *MEFs* from these mice responded to cisplatin, 6-thioguanine, and MNNG.³⁷ Mouse model of *Mlh1*^{G67R} causing a separation of function in the *Mlh1* protein; the DNA damage repair is impaired while DNA damage response including apoptotic response to cisplatin remained intact in the *Mlh1*^{G67R/G67R} mice. These mice displayed strong cancer predisposition similar to *Mlh1*^{-/-}, however, they developed fewer intestinal adenomas.³⁹ More than 250 different germline mutations have been identified in *MLH1* patients.⁴⁰ These new mouse models of different missense mutations which can elicit different phenotype and more importantly different response to therapy are promising in terms of tailored therapy for variances that exist in patients.

Somatic DNA Mismatch Repair Inactivation—Inflammatory bowel disease (IBD) including Ulcerative colitis and Crohn's disease has been linked to the development of cancer.⁴¹ Immune system has been shown to play an important role in colonic inflammation. Several mouse models with deletion of immune-specific genes such as those for *IL-2*, *IL-10*, T-cell receptor (TCR) chains, major histocompatibility and complex (MHC) class II molecules have been generated.¹⁰ These mice have a strong predisposition for developing colorectal adenocarcinomas. *IL-2* and *IL-10* defective mice display immune system aberrations as well as IBD similar to humans.^{42, 43} *MUC2*, a secretory mucin in the

intestinal mucosa, and mice made deficient of *Muc2* become prone to inflammation and subsequently develop intestinal adenomas and invasive adenocarcinomas.^{44, 45} *Gia2* knockout mouse develops spontaneous colitis and non-polypoid, right sided, multifocal CRCs with mucinous histology and a Crohn's-like inflammatory infiltrate. *Gia2*^{-/-} mice is the first mouse model of somatically acquired MMR deficiency due to inflammation through the *Mlh1* promoter repression.^{46, 47} It is noteworthy that these mice also show MSI phenotype as the result of *Mlh1* repression. Treatment of *Gia2*^{-/-} mice with histone deacetylase inhibitor (HDACi) decreases colitis and relieves epigenetic repression of *Mlh1* expression.⁴⁶ IBD mouse models are important as gastrointestinal inflammation is considered to be a strong risk for developing colorectal cancer. Suberoylanilide hydroxamic acid, SAHA is an HDACi that is currently being used in the treatment of cutaneous T-cell lymphoma (CTCL) and is in clinical trial for other cancers; the use of this compound could be extended to treatment of IBD and associated diseases.^{48–50}

Peutz-Jeghers Syndrome—Peutz-Jeghers syndrome (PJS) is autosomal dominant disease with variable inheritance caused by germline mutation in *LKB1/STK11*.⁵¹ *LKB1/STK11* is a serine/threonine kinase and considered to be a tumor suppressor gene. PJS is characterized by hamartomatous polyposis of the gastrointestinal tract, mostly in the small intestine with a strong predisposition to malignancy including mammary tumors and mucocutaneous pigmentation.⁵² *LKB1/STK11* null mutation in mice is lethal and *Lkb1/Stk11* heterozygous mice exhibit similar phenotype to PJS patient as they develop gastrointestinal hamartomatous without wild-type allele inactivation.^{53–56} Furthermore, heterozygous mutation of *Lkb1* is sufficient for the development of gastrointestinal hamartomas that exhibited histological features similar human PJS patients.⁵³ This mouse model has showed that biallelic inactivation is not necessary for hamartoma development and therefore, it is plausible that *LKB1* LOH would result in malignant transformation of hamartomas along with other mutations.⁵⁶ Since, mice's lifespan is too short to allow for the inactivation of wild-type allele and any further genetic hits necessary for progression to malignancy as seen in *LKB1* inactivation in humans. A second proposed mechanism for *LKB1*'s tumor suppression capability is that since it is involved in the *p53* dependent apoptosis and decreased level of *LKB1* protein would suppress growth arrest and apoptosis which will lead to accumulation of somatic mutations.⁵³ For example, the Wnt pathway is not activated in *Lkb1*^{+/-} hamartomas, however; *LKB1* LOH adenomatous lesions showed B-catenin mutation, suggesting that mutation in the Wnt pathway is also important for the progression of hamartomas to carcinomas along with *LKB1* LOH.⁵⁶

Breast Cancer

Several genes with germline mutations have been implicated in the development of breast cancer, i.e. *BRCA1*, *BRCA2*, *PTEN* (Cowden Disease) *TP53*, and *STK11/LKB1* (Peutz-Jeghers syndrome).^{1, 57} (Table 3)

Germline mutation in *BRCA1* and *BRCA2* has been conferred to increase the rate of breast cancer and ovarian cancer.⁵⁸ The risk for other cancers in germline mutations of these two genes are still under investigation. The limitations of homozygous *Brca1/2* mice have been embryonic lethality and the lack of sporadic tumors. Conditional mouse models for *BRCA1* targeted to the breast epithelial has been made, these models have been able to shed light on the mechanism of the breast tumor initiation and progression. To date ten conventional *Brca1* knockout models each carrying a different mutation has been generated and none of the heterozygous mice have been able to recapitulate the human heterozygous *BRCA1* germline mutation which results in mammary tumor development.⁵⁹ Conditional *Brca1* alleles and *Brca2* alleles have been generated, each displaying a different phenotype. The mice were crossed to either MMTV-*Cre* (mouse mammary tumor virus long terminal repeat)

active in many tissue or WAP-*Cre* (whey acidic protein) active only in the mammary epithelial cells and generated transgenic lines.⁶⁰ *Brca1* conditional female mice showed abnormal development of the mammary gland, where as *Brca2* female mice showed reduced ductal side branching in the mammary tissue.^{61–63} Mammary tumorigenesis did occur in these mice but with long latency period, tumors showed genomic instability and altered *Trp53* expression.⁶⁴ Human breast cancer with inactivation of *BRCA1* commonly exhibit *p53* mutation as compared to sporadic tumors.^{65, 66} Genetic interaction between *BRCA1/2* and the *p53* pathway studies have been possible in mouse models for the *Brca1/2* inactivation and *p53* heterozygosity. For example, the *MMTV-Cre; Brca^{co/co}; p53^{+/-}* mouse, closely mimic those *BRCA1* associated carcinogenesis that are associated with *p53* mutations.^{67, 68} Importantly, in humans *BRCA1*-associated breast tumors fall in the high grade invasive ductal carcinomas (IDCs) that lack the expression of estrogen receptor (ER), progesterone receptor (PR), and ERBB2/HER2, which is referred to as 'triple-negative' tumors.^{69, 70} The tumors from these mice were negative for ER α , showed genomic instability at the chromosomal level tested by aCGH (comparative genomic hybridization) and SKY (spectral karyotyping).⁶⁴ Association of *p53* and *Brca1* in mammary tumor development has also been shown using *K-14-Cre* which is active in skin, salivary gland and mammary-gland epithelium. Female mice in this model showed aneuploidy, solid carcinomas with ER α negative, highly proliferative and poorly differentiated and contact uninhibited tumors.^{71, 72} Progesterone receptor (PR) Similar to *Brca1*, *Brca2* homozygous mutant is embryonic lethal. To better mimic mammary gland specific tissue affect of the *Brca2* inactivation, a knock-out using *Wap-cre* and conventional truncated mutants have given researchers the insight to the development of *Brca2* null tumors.^{73, 74} Female mice in the conditional model developed non-metastatic carcinomas, and tumors from the mice displayed aneuploidy and genomic instability with long latency period. The latency period was reduced when mice were crossed to heterozygous *p53*.⁷⁵ Histochemical analysis showed the tumors to be ErbB2/neu negative and usually ER α and cyclin D1 positive.^{64, 74, 76} Together, these results from *BRCA1/2* and *Trp53* mice indicate a cooperate associations of *BRCA* and *p53* in cellular maintenance.

The utility of mouse model for mechanistic studies again becomes clear, as investigation of *Brca1* and 2 mutant mice clearly have showed activation of *Cdkn1a*, *p21* and *p53*, which were analyzed in greater detail to study the associations in compound mutant animals generated by cross breeding.^{77–80} The *Brca1* and 2 mouse models not only have been instrumental in understanding the disease mechanism of breast cancer but they have been valuable in testing of novel therapeutics. Current mouse models have shortcomings in validation studies where the tumors in these mice do not completely mimic the human *BRCA1/2* tumors, that being said the models have proven to be useful in the study of external factors involved in breast cancer such as hormone dependency of *BRCA1*. A corollary has existed between estrogen and its receptor alpha in the *Brca1* associated mammary tumors. Paradoxically, majority of human defective *BRCA1* breast cancers are ER α negative compared to sporadic tumors.⁸¹ Using mouse models it has been shown that ER α is highly expressed in the precancerous mammary glands, however; its expression lessens as cancer progresses.⁸² The *Brca1/p53* conditional models have been valuable in preclinical studies of the PARP1 poly-(ADP-ribose)-polymerase-1 inhibitor.⁸³ PARP-1 is important in repair of single strand DNA breaks via the base excision repair pathway and since the HR pathway is defective in *Brca* deficient cells, these cells would not be able to repair any DNA damage and be marked for cell death due to the accumulation of damaged DNA. *Brca1/p53* mouse model has also been used in a study where progesterone antagonist (mifepristone) prevented mammary tumorigenesis; this could be used as a chemopreventive therapy.⁸⁴

In summary, the *Brca/2* mouse models have been very useful in studying the mechanisms of *BRCA/2* tumor suppression. *Brca1* truncation mutants have become important in understanding the role of *Brca1*'s functional domains in the maintenance of the genome and tumor suppression. Improvement on the current *Brca1* mouse model would be to generate models to study the role of genetic reversion in therapy resistance. And *Brca1* mutation that are similar to known pathogenic *BRCA1* mutations such as *BRCA1*^{C64G}. A knock-in model of *BRCA1*C64G (BAC transgene) into homozygous mutant mice was not able to rescue embryonic lethality where the normal *BRCA1* was able.^{85, 86}

Cowden Syndrome—Cowden syndrome (CS) is a rare genetic disorder characterized by development of hamartomas of the mucous membrane with increased risk of progression to cancer of the breast, thyroid, endometrium. Genetic mutation of the *PTEN* gene is responsible for this syndrome. *PTEN* is a tumor suppressor and most human tumors display LOH of this gene.⁷⁸ *PTEN* encodes a protein with dual-specificity phosphatase that negatively regulates the cell survival signaling of PI3K/Akt. Mutations in *PTEN* are found in many cancers including breast and colorectal cancers. *Pten* homozygous mutant mice are embryonic lethal, and heterozygous mutant animals developed lymphomas, dysplastic intestinal polyps, endometrial complex atypical hyperplasia, prostatic intraepithelial neoplasia, and thyroid neoplasms but not the same malignancies seen in germline *PTEN* mutation in human, such as neoplasia of skin, breast and brain or hamartomas.^{87–90} Moreover, consistent with the model that *Pten* is a tumor suppressor, loss of the wild-type allele was frequently observed in mouse lymphomas. Conditional *Pten* mouse models have been used in the study of mammary tumor progression by using MMTV-*Cre*. Mutant mice exhibited an increase in ductal branching and increased mammary epithelial cell proliferation.⁹¹ These data suggest that conditional *Pten* knockout mice will be a useful model system for the study of endometrial, prostate, and thyroid cancer in the context of tissue specific *cre* transgenes.

Familial Endocrine and Neural Tumor Syndromes

Germline mutation of several genes can result in endocrine or neural cancers. These include neurofibromatosis (*NF1* and *NF2*), Multiple endocrineneoplasia (*MEN1*), Retinoblastoma (*RB*), Paraganglioma (*SDH*), and *PRKARIA* (Carney complex) among others.^{1, 57} (Table 4)

Neurofibromatosis (1 and 2)—Neurofibromatosis result from loss of two genes, neurofibromatosis type 1 (*NF1*) and type 2 (*NF2*), it is a common inherited disorder of the nervous system with a strong predisposition to cancer. *NF1* mutation results in the development of astrocytomas and peripheral nerve sheath tumors while *NF2* mutation causes schwannomas and meningiomas.^{92, 93} The two genes are very distinct, *NF1* gene product is neurofibromin and *NF2* encodes merlin.⁹³ Mouse model of this disease has been developed to identify the mechanism of tumor suppression capabilities of these genes and to develop therapeutics. Mouse models of *NF1* have included targeted mutation in the *Nf1* gene, in this model the homozygous mutant mice showed embryonic lethality and analysis heterozygous animals has yielded important insight into the loss of *Nf1*. *Nf1*^{+/-} mice are more prone to developing tumors with LOH.^{94, 95} *Nf1*^{-/-} chimeric mice, where a subset of cells in the mouse is *Nf1*^{-/-}, these animal developed neurofibromas, similar to plexiform neurofibromas seen in patients with *NF1* mutation.⁹⁶ Several knockout conditional models have been generated; these mice only developed growth abnormalities and failed to develop significant tumors.^{97, 98} It has been suggested that besides the absence of *Nf1* as a tumor suppressor gene, other genetic mutations must occur for the development of brain tumors.⁹³ Also cell non-autonomous processes are important in the development of the tumors, when Schwann cells were made null for *Nf1* in the setting of *Nf1* heterozygosity (i.e., *Krox-cre*; *Nf1*^{loxP/-}), the mice developed schwannomas with 100% penetrance.^{99–101} When *NF1*^{+/-}

mice are bred with any tumor suppressor gene mutant mice i.e. $p53^{+/-}$, they developed malignant tumors.^{96, 102} Two different models for *Nf2* targeted mutation have been reported and the tumor spectrum of the animals was different from *NF2* patients.^{93, 103, 104} However, conditional *Nf2* knockout models crossed with *P0-cre* (myelin protein zero promoter) showed similar features seen in *NF2* patients, including schwann cell hyperplasia, schwann cell tumors, cataracts, and cerebral calcifications.^{93, 105}

Multiple endocrineneoplasia (MEN1)—Multiple endocrineneoplasia (*MEN1*) is an autosomal dominant inherited disorder, characterized by predisposition to pituitary adenomas, parathyroid hyperplasia, and pancreatic endocrine tumors.¹⁰⁶ *MEN1* gene encodes the tumor suppressor menin. *Men1*^{-/-} mice are embryonic lethal and heterozygous mutant mice exhibit similar phenotype to human *MEN1* phenotype.¹⁰⁷ To further study the role *Men1* in pancreas, conditional knockout *Men1* mice were generated where they developed adenomas.¹⁰⁸ These *Men1* mouse models are able to offer means for elucidating the role of menin in tumor suppression and possible development of therapeutics.

Retinoblastoma (RB)—Loss of the retinoblastoma gene causes familial retinoblastoma in children. *RB1* gene is a “tumor suppressor” and based on Knudson’s “two hit” model of inheritance, one inactive allele results in 90% incidence of retinoblastoma in children and as well as a 10% incidence of osteosarcomas and soft-tissue sarcomas.^{3, 109} Loss of *RB-1* gene has also been reported in breast, lung and bladder carcinomas.¹¹⁰ Different mouse models have been generated with targeted deletion of *Rb1*, since *Rb1* gene is required for embryonic development 12–15 days post gestation, one of the first models for *Rb1* inactivation was made by introducing a termination codon in the exon 3 of the gene resulting in a mutant allele. This mouse did not develop any retinoblastoma or retinomas, the mice did develop pituitary tumors.¹¹¹ One of the reasons set forth for the lack of similarity between the mouse and human cancer resulting from loss of *Rb1* is that other family member (i.e. *p107* and *p130*) of *Rb1* gene has a compensatory effect in mice. To address this problem a mouse model defective both in *Rb1* and *p107* was generated. The SJ-RBL (St. Jude retinoblastoma mouse) mouse model showed an increase proliferation in the retinal progenitor cells. When SJ-RBL mice were crossed with $p53^{+/-}$ mice, animals lacking *Rb1*, *p107* and *p53* developed aggressive metastatic retinoblastoma.¹¹² These models can be used to further analyze the mechanism of tumorigenesis caused by *Rb1* loss and more importantly to test for any potential therapeutics. It is important to note that *p53* gene mutations have not been detected in patients with retinoblastoma.

Paraganglioma (SDH)—Paraganglioma is an autosomal dominant disease caused by a germline mutation in the mitochondrial succinate dehydrogenase (*SDH*). *SDH* has a role in both tricarboxylic acid cycle and the electron transport chain. It is one of the first proteins in the metabolic process linked to tumorigenesis, both in (PGL) and pheochromocytomas (PC). Recently, a conventional knockout mouse model was generated by the removal of exon3 of *Sdh* and crossed with a knockout *H19*, a modifier gene of *Sdh* tumorigenesis. Only heterozygous animals were studied due to embryonic lethality of the homozygous mutant. The animals did not show hyperplasia nor developed any paragangliomas. This data was surprising since the *SDH* mutation has high penetrance in humans.¹¹³ One of the reasons set forth for this disparity is that the chromosomal organization of genetic elements, locus of the gene in human’s is on chromosome 11 and also has the main locus for imprinted genes, while in the mouse the two loci are on different chromosomes and it seems that the loss of both elements is required for the development of disease, this also could be the reason that PGL nor PC have not been detected in mice.¹¹³ The next generation of humanized mouse models would be able to introduce BAC containing the two loci to better model the chromosomal organization seen in humans.

Carney Complex—Carney complex is an autosomal dominant neoplasia syndrome caused by inactivating mutation in *PRKARIA*, the gene which encodes the type 1A regulatory subunit of protein kinase A. It is characterized by spotty skin pigmentation, myxomatosis, endocrine tumors, and schwannomas.^{99, 114} Both conventional and conditional mouse model for this disease have been generated to better understand the mechanism of the disease. The spectrum of tumors that developed in these animals overlapped what has been seen in Carney complex patients, specifically, schwannomas, bone tumors, and thyroid neoplasms, confirming the validity of this mouse model.⁹⁹

Familial Hematopoietic Tumor Syndromes

Hematopoietic cancers could rise from germline mutation in *TP53* (Li-Fraumeni syndrome), *AT* (Ataxia telangiectasia), *BLM* (Bloom Syndrome) and *FACA* (Fanconi anemia).^{1, 3} (Table 5)

Li-Fraumeni Syndrome—Li-Fraumeni Syndrome (LFS) is a rare autosomal dominant familial cancer syndrome that is caused by mutation in the *Tp53* gene and confers a predisposition to a variety of tumors with early onset of disease.⁵⁷ *p53* plays a critical role in the DNA damage response, by delaying the progression of the cell cycle which would either proceeds to DNA repair or apoptosis. Transgenic mice carrying a *Tp53* mutant allele display an increased incidence of osteosarcomas, soft tissue sarcomas, adenocarcinomas of the lung and adrenal and lymphoid tumors similar to patients with LFS.^{115, 116} Germline *Tp53* deletion or conditional mutation of *Tp53* mouse model have resulted in a different spectrum of tumors, moreover, the latter has shown to closely mimic carcinomas seen in human cancers, this is attributed to the fact that point mutations could render a gene hypomorphic or neomorphic and this would more accurately resembles the genetic mutation seen in human tumors.¹¹⁷ Mouse models are important in the study of pleiotropic genes such as *Tp53*, as they associate with many other genes and animal models are the best system to dissect their interactive role in tumorigenesis.

Ataxia telangiectasia—Ataxia telangiectasia (AT) is a human autosomal recessive disorder with a wide spectrum of clinical manifestations including progressive cerebellar ataxia, oculocutaneous telangiectasia, lymphoid tumors and various other abnormalities including cell-cycle checkpoint defects and chromosomal instability.³ AT is caused by mutation in the *ATM* gene, a Ser/Thr protein kinase and a member for phosphoinositide 3-kinase (PI3K) - related protein kinase (PIKK) family.¹¹⁸ Mouse model of AT was created using gene targeting techniques, homozygous mutant mice displayed similar neurologic dysfunction, growth retardation, defects in T lymphocyte maturation, extreme sensitivity to gamma-irradiation, and chromosomal abnormalities as seen in AT patients.¹¹⁹ Heterozygous mutant animals did not display tumor phenotype, however; *ATM* knock-in (*Atm*^{ΔSRI}) heterozygous mice harboring an in-frame deletion corresponding to the human 7636del9 mutation showed an increased in risk of tumor development.^{120, 121}

Bloom Syndrome—Bloom syndrome is a rare autosomal recessive genetic disorder with a predisposition for early onset of hematopoietic, head and neck cancers.³ *BLM* is a human homologue of the *E. coli* RecQ helicase and has many potential roles in the pathways of DNA repair and replication. *Blm* null mice (*Blm*^{3m/3m}) have a 5-fold increased risk of developing cancer as compared to *Blm* heterozygous mice (*Blm*^{3m/+}); animals mostly developed hematopoietic cancers similar to those in BS syndrome.^{122, 123} Irradiated *Blm* deficient mice show accelerated malignancies and a better model for recapitulating numerous features of the human disease specifically the broad spectrum of hematologic malignancies.^{123, 124}

Fanconi Anemia—Fanconi anemia is an autosomal recessive disorder caused by mutation in the *FANCA* gene. Disease features include congenital abnormalities, early onset bone marrow failure and increased risk of developing myelodysplasia (MDS), acute myeloid leukemia (AML), solid tumors, and cellular sensitivity to mitomycin C and ionizing radiation.^{3, 57} Mouse model for *Fanca* deficiency did not show developmental abnormalities, and hematological changes in young mice only included a slight decrease in the platelet count and slight increase in the erythrocyte mean cell volume, but did not progress to anemia. However, similar to FA patients both female and male mice showed impaired fertility and more importantly the embryonic fibroblasts from these knockout animals displayed spontaneous chromosomal instability and were hyper-responsive to the effect of mitomycin C.¹²⁵

Familial Kidney Tumor Syndromes

Familial kidney tumor syndrome has been linked to several genes, VHL (Von Hippel-Lindau), c-MET (hereditary papillary renal cancer), BHD (Birt-Hogg-Dubé) and others.^{126, 127} (Table 6)

Von Hippel-Lindau Syndrome—VHL is a rare autosomal dominant syndrome where germ-line *VHL* mutation results in hemangioblastomas, precancerous, cavernous hemangiomas of the liver and renal cysts and renal cell carcinomas.¹²⁷ Conventional heterozygous mutant mice (*Vhl*^{+/-}) and *Vhl* conditional knockout mice (*actin-cre* as a transgene) showed multiple organ and extensive vascularized tumors similar to those seen in humans with VHL mutation.^{128, 129} However, the mice did not develop the spectrum of disease seen in patients.¹³⁰ It has been suggested that the difference is most likely due to lack of modifier gene inactivations. This model could be better tested in a targeted deletion of *Vhl* floxed allele in kidney-specific *Cre* transgenic mouse.

Hereditary papillary renal cancer

Hereditary papillary renal cancer (HPRC) is an autosomal dominant with variable penetrance that rises from a mutation in the c-Met oncogene which codes for a membrane bound receptor with an intracellular tyrosine domain.¹³¹ Homozygous mutant mice are embryonic lethal. Mice targeted mutations in the murine met-locus were generated. The different mutant lines developed unique tumor spectrum which included carcinomas, sarcomas, and lymphomas. Majority of the tumors from these mice displayed non-random duplication of the mutant met allele; this phenomenon has also been seen in HPRC patients. This shows that different mutations effect downstream signaling.¹³²

BHD (Birt-Hogg-Dubé)—Birt-Hogg-Dubé (BHD) syndrome is a rare autosomal dominant genetic disorder characterized by mutation in the BHD tumor suppressor gene, associated with a risk of developing kidney cancer. BHD gene encodes folliculin, a protein that may interact with the energy- and nutrient-sensing AMPK-mTOR signaling pathways.¹³³ *Bhd* homozygous mutant mice are embryonic lethal and heterozygous mice develop kidney cysts and solid tumors with age. Kidney tumors from *Bhd*^{+/-} mice show activation in mTORC1 and mTORC2 similar to human BHD mutant kidney tumors.^{133, 134} From these mice studies, the PI3K-AKT-mTOR pathway was linked to kidney tumor from human BHD patients. Human BHD tumors analyzed showed PI3K-AKT-mTOR activation, regardless of the type of BHD mutation.¹³⁴ Furthermore, inhibitors of mTORC1 and mTORC2 are potential therapeutic agents for BHD-associated kidney cancer.

Familial Skin Cancer Syndromes

Genetic diseases of skin arises from germline mutation ins *WRN* (Werner syndrome), *XP* (xeroderma pigmentosum), *PTCH1* (Nevoid basal cell carcinoma) and *CDKN2A*(familial melanoma) genes.^{1, 57} (Table 7)

Werner Syndrome—Werner syndrome is an autosomal recessive disorder with manifestation of premature aging, genomic instability and onset of age related diseases including myocardial infraction and malignancies.⁵⁷ *WRN* gene is a member of Rec-Q like subfamily of DNA helicases. *Wrn* deficient mouse model was generated to further study the cause of the disease.¹³⁵ At cellular level the fibroblast from the *Wrn* deficient mice exhibited reduced proliferation and early saturation arrest similar to the fibroblast of WS patients. Spontaneous mutation in the *HPRT* locus was found in WS patient's immortalized cell lines, murine ES cells from deficient mice displayed a higher resistant colony count to purine analog, 6-thioguanine. The deficient mice, at organismic level, did not show any signs of premature aging or increased tumor development.¹³⁵ A mouse model of *WRN*^{-/-} in a *p53*^{-/-} background was able display shorter life span and to recapitulate many of the phenotype of WS.¹³⁶ The reasons set forth as to why we see a better phenotype in the second mouse model, is either because *Wrn* and *p53* have been shown to interact physically and therefore they might have cooperative roles in maintaining genomic integrity; or is that *p53*^{-/-} allows for a more accelerated aging where the phenotype becomes evident.¹³⁶

Xeroderma pigmentosum—Xeroderma pigmentosum (*XP*) is a rare autosomal recessive disease characterized by lack of UV-induced DNA damage repair due to mutation in the nucleotide excision repair pathway (NER). *XP* patients show extreme sensitivity to sunlight and have a 1000-fold increased risk of developing skin cancer. Mouse model with a mutation in the *Xpa* gene renders the NER pathway defective and develops skin tumors when exposed to UV light. Mutant animals also show high susceptibility to genotoxic carcinogens, which makes them attractive for studying carcinogens.^{137–139} A compound mice of *Xpa* and *p53* (*Xpa*^{-/-}/*p53*^{+/-}) developed tumors earlier than the homozygous mutant (*Xpa*^{-/-}), which makes them a better model for short term carcinogenesis studies.¹⁴⁰

Nevoid basal cell carcinoma—Nevoid basal cell carcinoma syndrome (NBCCS) is an autosomal dominant disorder caused by a mutation in the *PTCH1* (Protein patched homolog 1) gene which encodes the receptor for sonic hedgehog pathway.^{3, 57} NBCCS is characterized by developmental abnormalities and a predisposition to cancers such as basal cell carcinomas, and tumors display LOH, suggesting that *PTCH1* could be a tumor suppressor gene.^{78, 141} Heterozygous mutant mice develop skeletal abnormalities and medulloblastomas, but they do not develop basal cell carcinoma, thus; haploinsufficiency is sufficient for mice to develop medulloblastomas.^{142–144}

Familial Melanoma—Germline mutations in *CDKN2A* which encodes two cell cycle inhibitory proteins, *p16INK4a* and *P14ARF* (*p19Arf* in mice) has been implicated in the development of melanoma as well as other tumors.¹⁴⁵ Mice deficient in *p16Ink4a* are susceptible to developing spontaneous and carcinogen induced tumors without the loss of *p19Arf*.^{146, 147} This model shows that loss of one tumor suppressor protein is sufficient for the development of carcinoma.

“Humanized” mice

Mouse models of human disease have not been able to recapitulate all aspect of human disease; this is due to the disparate biology of human and mice especially difference at chromosomal level, however; cancer mouse models have been essential since most of human cancer biology is difficult to study clinically. To improve on the current mouse

models, the next generation of humanized mouse models can be generated by inserting human genes as well as non-coding elements of human gene into the mouse genome in order to assess the affect of non-coding elements in cancer biology. Genome wide association (GWA) studies have identified many non-coding variants that could affect gene expression, and splicing processes that could have dramatic affect on the biology of disease. Since introns and many non-coding elements contain GWA risk variants but have low evolutionary conservation, in future investigators may have to knock in whole introns are large genomic regions in order to make appropriate models of the human disease. Humanized animal model will be able to bridge the gap between preclinical studies and therapeutic benefits. Differences in the telomere length can play a role in the neoplastic process, therefore, crossing of Terc knockout mouse that lacks the RNA subunit of telomerase with existing mice.¹⁴⁸ Finally difference in drug metabolism and xenobiotic receptor (XR) in mice and human can be addressed by crossing mice to existing mouse models with human cytochrome p450 as well expressing XR.¹⁴⁹

Conclusion and Future Studies

Mouse models have been important in supporting essential roles of genes, early embryonic lethal genes are indicative of the important role of genes play in development. It is evident through these different animal models presented here that both conventional and conditional models are beneficial in terms of studying the mechanism of human disease in mice. The new generation of humanized mice will remedy some of the concerns of current models used in research namely the genomic organizational difference between the two species. Mouse models have been able to elucidate the sufficiency of a single gene's potential in developing cancer as well as the predicted pleiotropic gene role in tumorigensis

The naked mole-rat is a mammal with very similar biology as humans that have attracted the cancer research community for many good reasons. The naked mole rat (*Heterocephalus glaber*) as a potential murine model for tumorigenesis studies because of their longer lifespan. These animals are indigenous to Africa, where they live in colonies. The features that would play a huge role in cancer research would be their longevity, with a life span of 28 years they would be good candidate for long term studies, specifically in cancer progression and metastasis. Life span is not the only feature of these animals that would make them a better model for cancer research; they have evolved similar anti-cancer defenses which consist of a tight cell cycle regulation, apoptosis and tumor suppressor genes. Furthermore, their cells show contact inhibition properties similar to human cells.¹ Future studies with genetic manipulation of *Heterocephalus glaber* will be important to study mechanisms related to long term development of germline cancers.

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Table 1

Familial Adenomatous Polyposis GEM models

Gene	Phenotype	Tumor Incidence	Multiplicity	References
<i>Apc</i> ^{min}	Adenoma, small intestine	High	58	5–7, 10
<i>Apc</i> ¹⁶³⁸	Adenoma/carcinoma; small intestine, colon	Low	4	7, 9–10
<i>Apc</i> ^{Δ716}	Adenoma; small intestine, colon	High	254	5–7, 10
<i>Double mutants</i>				
<i>Apc</i> ^{Δ716} ,Ptgs2 (COX-2)	Adenoma, small intestine	Low	98	9, 11
<i>Apc</i> ^{min} ,Ptgs1 (COX-1)	Adenoma, small intestine	Low	18	8
<i>Apc</i> ^{min} ,Ptgs2 (COX-2)	Adenoma, small intestine	Low	12	8

Table 2

Familial gastrointestinal cancer syndromes GEM Models

Gene	Tumor incidence	Tumor type/tumor site	Repair Defect (MSD)	DNA Damage response	References
MutS homologues					
<i>Msh2</i> ^{-/-}	High	Adenoma, carcinoma; small intestine, colon	High	Defective	16, 18–19
<i>Msh3</i> ^{-/-}	Low	Adenoma	Moderate	Normal	21, 25
<i>Msh6</i> ^{-/-}	High	Adenoma	None	Defective	22–23
<i>Msh3</i> ^{-/-} <i>Msh6</i> ^{-/-}	High	Adenoma, carcinoma; small intestine, colon			25
<i>Msh2</i> loxP; Vill-cre	High	Adenoma, colon	N/A	Normal	17
MutL homologues					
<i>Mlh1</i> ^{-/-}	High	Adenoma, carcinoma; stomach, small intestine, colon	High	Defective	19, 26–29
<i>Pms2</i> ^{-/-}	Low	Adenoma; brain	Low	Normal	29–32
<i>Mlh3</i> ^{-/-}	Low	Adenoma; small intestine	Moderate	Defective	32–34
<i>Pms1</i> ^{-/-}	None	None	Low	N/A	29
<i>Mlh3</i> ^{-/-} <i>Pms2</i> ^{-/-}	High	Adenoma, carcinoma; stomach, small intestine, colon	High	Defective	32–33
<i>Pms2 cre-lox</i>	Low	Adenoma	Low	Normal	35
Knock-in Models					
<i>Msh2</i> ^{G674A/G674A}	High	Adenoma; small intestine	High	Normal	37–38
<i>Msh6</i> ^{T1212D/T1212D}	High	Adenoma; small intestine	High	Normal	38
<i>Mlh1</i> ^{G67R/G67R}	High	Adenoma; small intestine	High	Normal	39
<i>Lkb1</i> ^{+/-}	N/A	Stomach, small intestine, liver, mammary	N/A	N/A	53
IBD/somatic inactivation					
<i>IL-2</i> ^{-/-}	No tumor/colitis	Colon	N/A	N/A	43
<i>IL-10</i> ^{-/-}	No tumor/Enterocolitis	Intestinal	N/A	N/A	42
<i>Muc2</i> ^{-/-}	No tumor/colitis	Colon	N/A	N/A	44–45
<i>Gia2</i> ^{-/-}	Low	Right side colon	High	N/A	46–47

Familial breast cancer syndromes GEM models

Table 3

Gene	p53 co-mutation	Cre-transgene	Tumor Type	Mean tumor latency	References
<i>Brca1</i> ^{fl/r}	No		Mammary, Lymphoma		10, 58, 75
<i>Brca1</i> ⁵⁻⁶	No		Lymphoma		10, 58
<i>Brca1</i> ^{Δ11 loxp/loxp}	No	<i>MMTV-cre</i>	Mammary	>13	59, 68
<i>Brca1</i> ^{Δ11 loxp/loxp}	<i>p53</i> ^{Null}	<i>MMTV-cre</i> or <i>WAP-cre</i>	Mammary	8	59, 67
<i>Brca1</i> ^{Δ11 loxp/loxp}	<i>p53</i> ^{Δ5-6}	<i>WAP-cre</i>	Mammary	7	59, 84
<i>Brca1</i> ^{Δ22-24 loxp/loxp}	<i>p53</i> ^{Null}	<i>BLG-cre</i>	Mammary, Lymphoma	7	59, 72
<i>Brca1</i> ^{Δ5-13 loxp/loxp}	<i>p53</i> ^{Δ20-10}	<i>K14-cre</i>	Mammary	7	59, 71
<i>Brca1</i> ^{Δ1 loxp/loxp}	No	<i>WAP-cre</i>	Mammary	18	59, 61
<i>Brca2</i> ^{Δ27/27}			Lymphoma, sarcoma, carcinoma		10, 74
<i>Brca2</i> ^{Tr2014}			Lymphoma		10, 58
<i>Brca2</i> ^{loxp/loxp}		<i>WAP-cre</i>	Mammary		10, 75
<i>Pten</i> ^{+/-}	No		Mammary tumors		10, 20, 87, 88, 91
<i>Pten</i> ^{loxp/loxp}	No	<i>Gfap-cre</i>	Non-neoplastic brain lesions		10, 89, 90
<i>Pten</i> ^{loxp/loxp}		<i>MMTV-cre</i>	Mammary tumors		91

Table 4

Familial endocrine and neural cancers GEM models

Gene	Phenotype	Other conditions	References
<i>Rb1</i> ^{+/-}	Thyroid, pituitary, adrenal		9, 106
<i>Men1</i> ^{+/-}	Pancreatic islets, thyroid, pituitary, adrenal, accessory sex glands	Hyperparathyroidism	9, 102
<i>Men1</i> ^{ΔN/ΔN} ;RIP-cre	Pancreatic islets, pituitary		9, 102, 103
<i>Nf1</i> ^{+/-}	Phenochromocytoma, leukemia, lymphoma		9, 93, 99
<i>Nf1</i> ^{fllox/-} ;Krox20-cre	Neurofibroma		9, 99–100
<i>Nf1</i> ^{-/-} Chimera	Plexiform neurofibromas, myelodysplasia, neuromotor defects		95
<i>Nf1</i> ^{+/-} ;p53 ^{+/-}	Malignant peripheral nerve sheath tumors, malignant astrocytomas		95, 101
<i>Nf2</i> ^{+/-}	Osteogenic tumors, fibrosarcoma		9, 102–103
<i>Nf2</i> ^{fllox/fllox} ; P0-cre	Schwann cell hyperplasia, schwann cell tumors		92, 104
<i>Sdh</i> ^{+/-}	No tumor		112
<i>Prkar1a</i> ^{Δ2/+}	Schwannomas, bone tumors, and thyroid neoplasms		89
<i>TEC3</i> ;Prkar1a ^{loxP/loxP}	Facial tumors		89

Table 5

Familial hematopoietic tumor syndromes GM models

Gene	Phenotype	Other conditions	References
<i>Trp53</i> ^{-/-} (20% lethality)	Lymphoma, sarcoma, mammary		10, 115–116
<i>Atm</i> ^{-/-}	Lymphoma		10, 119–120
<i>Atm</i> ^{ΔSRI+/-}	Lymphoma	Neurological	10, 120–121
<i>Atm</i> ^{ΔSRI-/-}	Sarcoma		10, 120–121
<i>Blm</i> ^{m3/m3}	Lymphoma, carcinoma		10, 122–124
<i>Fanca</i> ^{-/-}	No tumors	Germ cell defect	10, 125

Table 6

Familial Kidney tumor syndromes GEM models

Gene	Phenotype	Other conditions	References
<i>Vhl</i> ^{+/-}	Hemangioma, hemanioscarcoma	Angiectasis	10, 127–128
<i>Vhl</i> ^{fl/d} /Cre	Hepatic vascular tumors		10, 128–129
<i>c-Met</i> Knock-in	Multiple tumors		10, 131–132
<i>Bhd</i> ^{+/-}	Kidney tumor		133–134

Table 7

Familial skin cancer syndromes GEM models

Gene	Phenotype	Other conditions	References
<i>Wtn</i> ^{-/-}	Various tumors	Myocardial fibrosis	10, 135–136
<i>Xpa</i> ^{-/-}	No tumor		10, 137–140
<i>Ptch</i> ^{+/-}	Medulloblastoma		10, 141–144
<i>Ptch</i> ^{neo67}	Rhabdomyosarcoma		10, 142
<i>Pl6</i> ^{Ink4a-/-}	Lymphoma, sarcoma		10, 145–147