



DICER1-
pre-miRNA complex

Pre-miRNA

RNase III domains

miRNA
duplex

miRISC

DICER1
processing

Mature
miRNA

3' overhang

PAZ domain

Complementary
strand degradation

Regulation
of protein
expression

NUCLEUS

CYTOPLASM

Dicer1 Gene Mutation

**Giovanni Neri, Luigi Boccuto, Roger E.
Stevenson**



Dicer1 Gene Mutation

DICER1 Mutations Anne-Laure Chong, 2022 DICER1 syndrome is a pleiotropic tumour predisposition syndrome with patients harbouring heterozygous germline loss of function variants in the DICER1 gene. Over the years, various studies have expanded the DICER1 associated phenotypes, which now includes over 20 tumours or tumour-like conditions, including pleuropulmonary blastoma, Sertoli-Leydig cell tumour, cervical embryonal rhabdomyosarcoma, and multinodular goiter. The various tumours of DICER1 syndrome are rare and display morphologic overlaps with several other neoplasms, giving rise to diagnostic challenges. DICER1 associated tumours exhibit a distinctive mutation profile with nearly all tumours harbouring a germline DICER1 loss of function variant and somatic so-called hotspot mutations residing within exons encoding the RNase IIIb domain of DICER1. These hotspot mutations affect the metal ion binding residues that are necessary for processing microRNA precursor stem loops into mature single-stranded microRNAs by the Dicer1 enzyme. The DICER1 RNase IIIa and IIIb domains dimerize through hydrophobic interactions and are stabilized by two ball-and-socket junctions which bring together the negatively charged side chains needed to activate the Dicer1 enzyme. Previous *in vitro* cleavage experiments of a RNase IIIa socket residue p S1344L have been shown to behave more like a RNase IIIb mutation than a RNase IIIa mutation. In this work, we demonstrate the importance of characterizing DICER1 variants in three different contexts: 1) clinical determination, 2) exploration of novel associations, and 3) investigation of DICER1 function. The first part consisted in studying a series of possible DICER1 associated lesions of diagnostic uncertainty. DICER1 sequencing validated the diagnosis of five cases and led to re-diagnosis of 3, thereby providing critical information regarding clinical management, especially for suspected DICER1 syndrome patients. The second part involved the assessment of a series of tumours existing outside of the DICER1 syndrome spectrum, which harboured biallelic DICER1 mutations, followed by the investigation of DICER1 associated non-small cell lung cancer. Analysis of the DICER1 associated lung cancer cases revealed co-occurrence of DICER1 and CTNNB1 mutations, suggesting an interesting relationship between these two genes, as co-occurrence has been previously seen in other DICER1 associated lung tumours. The third part aimed to evaluate the effect of various mutations affecting ball-and-socket residues on DICER1 cleavage activity by *in vitro* cleavage experiments. DICER1 cleavage activity of the ball-and-socket mutants showed four different cleavage patterns: wild-type cleavage, delayed or reduced cleavage, no cleavage activity whatsoever, and trans-acting cleavage, proposing that DICER1 RNase III interdomain interactions are needed to drive synchronization of precursor miRNA processing. miRNA expression profiling of at least one mutant belonging to each of the cleavage pattern groups validated cleavage findings and also provided insights into pathogenicity of certain mutants. Findings for this thesis supported the hypothesis that the discovery of DICER1 variants not only serves a crucial role in proper assessment of possible DICER1 associated tumours with diagnostic uncertainty but also serves to identify new associations of DICER1 with neoplasms existing outside the classical DICER1 syndrome spectrum. Moreover, not only is the identification of DICER1 variants important for both clinical and investigative exploratory purposes, but the evaluation of various DICER1 mutations can help in getting a better understanding of DICER1 RNase III interactions in miRNA biogenesis.

DICER1 Syndrome Mona Wu, 2019 DICER1 is an endoribonuclease central to the generation of microRNAs miRNAs small RNA molecules that are predicted to silence the expression of 30% of protein coding genes DICER1 utilizes its RNase IIIa and IIIb endonuclease domains to cleave pre miRNA stemloops to release the mature single strand miRNA coded within either the 5' or 3' arms DICER1 mutations have been identified in patients with pleiotropic tumour predisposition syndrome DICER1 syndrome Most DICER1 syndrome lesions tumours have one loss of function LOF DICER1 mutation and an in trans RNase IIIb 5p miRNA altering DICER1 mutation DICER1 syndrome usually manifests in childhood and includes multinodular goiter pleuropulmonary blastoma and cystic nephroma While biallelic DICER1 mutations LOF 5p miRNA altering are observed in the tumours lesions of DICER1 syndrome still other rare tumours could be DICER1 associated and it remains a mystery how these paired DICER1 mutations initiate tumourigenesis It is hypothesized that DICER1 syndrome and DICER1 associated tumours lesions originate from a multipotent cell whose miRNome transcriptome is altered due the presence of only an RNase IIIb mutated DICER1 that has acquired other genetic mutations An in vitro cleavage assay was developed to assess the ability of 38 different disease relevant DICER1 variants to cleave a pre miRNA The very rare anaplastic sarcoma of the kidney was often shown to have LOF 5p miRNA altering DICER1 mutations and are therefore DICER1 associated Mouse mesenchymal stromal stem cells MSCs lacking Dicer1 and rescued with various human variants of DICER1 were generated to model the cell of origin of DICER1 syndrome Analysis of these cell lines identified potential early disease biomarkers candidates for therapeutic intervention and genes potentially involved in tumour priming Introduction of ErbB2 and subsequent evaluation of transformation potential suggests that relative over abundance of 3p miRNAs may be key to transformation In vivo experiments suggest that MSCs may have chemo attractive potential The data for this thesis support the hypothesis that DICER1 syndrome DICER1 associated entities have LOF 5p miRNA altering mutations In addition many tools for the DICER1 syndrome research field have been generated including the in vitro cleavage assay and multiple cell isogenic cell lines with different DICER1 variants

DICER1 Syndrome - New Mutations, Novel Phenotypes and Unexpected Mechanisms Leanne de Kock, 2019 DICER1 syndrome is a rare tumour predisposition syndrome with an autosomal dominant inheritance pattern that is characterised by a unique spectrum of rare to very rare tumours and dysplastic lesions. The prototypic tumour of the syndrome is pleuropulmonary blastoma, a rare mixed pattern sarcoma of the lung. Other tumours prominently featured in the syndrome include ovarian Sertoli Leydig cell tumour, paediatric cystic nephroma, and embryonal rhabdomyosarcoma of the uterine cervix, but the syndrome also includes more well-known entities such as multinodular goitre (MNG). DICER1 syndrome predominantly affects young infants and children, but first phenotypic expression occasionally extends into adulthood. Loss of function variants in DICER1, a gene that encodes for a member of the microRNA biogenesis machinery, was identified as the underlying genetic cause of the syndrome in 2009. Later, so-called hotspot missense mutations within the RNase IIIb domain of DICER1 began to emerge as characteristic somatic events in syndrome-related tumours. Subsequent research efforts, including those that comprise this thesis, have focused on further defining the DICER1 syndrome phenotype, characterising the types and distributions of genetic alterations found within the DICER1 gene, determining the effect of identified mutations on microRNA processing, and elucidating the mechanisms that underpin DICER1-related tumorigenesis. The approaches used in this thesis investigation included investigative sequencing of DICER1 in various tumour types to assess their relation to the syndrome. This led to the addition of 6 entities to the syndrome phenotype that were not previously recognised to be part of the syndrome, including the exceptionally rare pituitary gland tumour, pituitary blastoma (PitB). The employment of deep sequencing and high sensitivity sequencing techniques allowed us to recognise that clonal distributions of hotspot mutations characterise the nodular architecture of MNG, and that rare mosaic distributions of RNase IIIb hotspot mutations predispose to development of an unusually high number of DICER1-related tumours at especially young ages in children. Thorough molecular profiling of the transcriptome and miRNome of PitB relative to normal adult and normal fetal pituitary revealed a drastic and distinct alteration in expression of miRNAs within the tumours. We observed not only a decrease in expression of miRNAs derived from the 5' arm of the miRNA hairpin precursors, but also a relative increase in the preponderance of those from the 3' arm. Furthermore, preliminary evidence suggests a possible oncofetal signature in PitBs, which may represent an oncogenic switch at the root of PitB tumorigenesis. Taken together, the results presented in this thesis represent significant contributions towards the clinical and molecular characterisation of the DICER1 syndrome.

Germline DICER1 Mutations in Human Disease Amin Bahubeshi, 2011 The DICER1 gene, which codes for a protein of the same name, is vital to the production of microRNA. As small 20nt fragments of RNA, microRNAs alter gene expression post-transcriptionally by directly binding to mRNA and affecting translation. Current estimates suggest that expression of 30-70% of all protein-coding genes is modified by microRNA activity. Germline DICER1 mutations have recently been associated with cases of pleuropulmonary blastoma, a childhood lung tumor. We have discovered germline DICER1 mutations to be associated with other diseases by identifying mutations in nearly 60 individuals within 15 different families and across 7 different disease phenotypes. These include cases of pleuropulmonary blastoma, cystic nephroma, a benign kidney tumor, and Wilms tumor, the malignant version of cystic nephroma. Furthermore, we have identified DICER1 mutations in several families with Sertoli Leydig cell tumor (SLCT), a rare androgen-producing cancer of

Mutation Analysis of the DICER1 Gene in Pleuropulmonary Blastoma Yannic Saathoff, 2020

Overgrowth Syndromes Giovanni Neri, Luigi Boccutto, Roger E. Stevenson, 2019-02-15 Overgrowth Syndromes is a comprehensive clinical guide to the well defined genetic disorders and others that are less well defined for which somatic overgrowth is a major manifestation It details the unique characteristics and known causative genes for this class of disorders offering clinicians an expert resource for both clinical diagnosis and laboratory confirmation Assembled by the world s leading experts on overgrowth this volume maximizes clinical utility without sacrificing nuance or rigor It codifies the last decade s sweeping advances in understanding general and segmental overgrowth including the latter s mosaic nature and phenotypic variability It is an essential resource for clinicians navigating this set of conditions from clinical presentation all the way to counseling and anticipatory management

Thyroid Cytopathology Douglas P. Clark, William C. Faquin, 2010-06-17 Eighth volume to be published in the Essentials in Cytopathology book series More than 115 full color images 12 tables and a series of algorithms Designed to be concise and easy to use Fits in lab coat pocket Site specific Illustration oriented accompanied by text in outline format A must have for every pathologist cytopathologist cytotechnologist fellow and trainee

Diagnostic Pathology: Familial Cancer Syndromes Vania Nosé, 2020-02-14 This expert volume in the Diagnostic Pathology series is an excellent point of care resource for practitioners at all levels of experience and training Physicians should have the knowledge derived from morphological findings to identify the likelihood of a cancer patient having an additional underlying familial syndrome and to decide if that patient should undergo molecular genetic evaluation This volume is specifically designed to help pathologists oncologists and other physicians who diagnose and treat cancer to recognize syndromes and syndrome associated neoplasms and advise patients and their families on the possibility of a familial syndrome and their risk of developing other tumors Diagnostic Pathology Familial Cancer Syndromes second edition is an easy to use one stop reference for information on hereditary cancer syndromes including differential diagnosis and management that offers a templated highly formatted design concise bulleted text and superior color images throughout Contains all the information necessary to determine whether a neoplasm typically encountered in daily practice is sporadic or related to a familial cancer syndrome Features a revised structure to keep you up to date Part I includes more than 80 detailed chapters describing diagnoses associated with familial cancer syndromes Part II contains more than 70 chapters with detailed descriptions of major syndromes cross referenced with diagnoses and Part III features a molecular factors index that includes a complete description of each known gene associated with a familial cancer syndrome Contains updated chapters with newly classified GI neurology multiple organ eye endocrine GYN and kidney tumors as well as more than 20 entirely new chapters covering recently recognized syndromes Incorporates up to date molecular findings and their significance for familial cancer syndromes new techniques and technologies being used to discover gene mutations and other alterations and details on personalized medicine targeted to specific genes Features more than 2 200 images throughout including clinical and radiological images algorithms graphics gross pathology histology and a wide range of special and immunohistochemical stains all carefully annotated to highlight the most diagnostically significant factors Features time saving bulleted text key facts in each chapter an extensive index and numerous tables for quick reference and thorough understanding

Central Nervous System Tumours Thomas James Deeley, Thomas J. Deeley, 1974

MicroRNAs in Cancer Cesar Lopez-Camarillo, Laurence A. Marchat, 2013-02-22 MicroRNA miRNA biology is a cutting edge topic in basic as well as biomedical research This is a specialized book focusing on the current understanding of the role of miRNAs in the development progression invasion and metastasis of diverse types of cancer It also reviews their potential for applications in cancer diagnosis prognosis and th

Evidence based practice in Neuro-oncology Supriya Mallick, Prashanth Giridhar, Goura K. Rath, 2021-07-24 This book provides evidence based management in neuro oncology covering all aspects such as pathology radiology surgery radiation and chemotherapy The field of neuro oncology is rapidly evolving and new evidence is coming out every day towards the optimal management of brain tumors This necessitates a requirement of a complete guide that shall provide an evidence based and personalized approach towards dealing with patients This book also covers recent advances in personalized treatment formed through the relevant basis of anatomy imaging radiology surgical radiation and systemic treatment of brain and spinal tumors In addition it also covers the practical aspects of the planning of the Gamma knife and other radio surgical aspects The book shall provide valuable assistance to practicing neuro oncologists to practice better evidence based personalized medicine

The Hereditary Basis of Childhood Cancer David Malkin, 2021-09-07 This volume elaborates on the research and clinical implications of the hereditary and molecular basis of childhood cancers The focus of the disease related chapters of the book is to integrate what is known about the molecular basis of that particular clinical entity or group of related entities with the clinical manifestations to relate the relationship of the molecular oncologic pathways with relevant developmental or non human species biology in order to better understand the complexity of these systems The resulting clinical implications of understanding this biology are elaborated on Chapters 13 16 discuss the broader psychosocial ethical and genetic counseling issues that arise and that are so critical to translating the knowledge gained from advances in molecular genetics into the clinic Chapter 12 in particular provides a unique perspective of the application of this knowledge in less developed nations where modern technologies may not be readily available but where the clinical manifestations of these disorders are prevalent

Renal Tumors of Childhood Kathy Pritchard-Jones, Jeffrey S. Dome, 2016-10-06 This book provides a comprehensive overview of the biological basis of renal tumors in childhood and the clinical approaches to their treatment Recent advances in our understanding of the molecular genetics of Wilms and other renal tumors are placed in their clinical context including the differing treatment approaches of immediate surgery or pre operative chemotherapy The challenges in applying this knowledge to improve risk stratification and to incorporate biologically targeted agents into front line therapy are discussed All of the authors are experts from Europe and North America and the book has been written specifically as an easy reference for the practising clinician and the research scientist It lays the basis for understanding the future direction of clinical and translational research to improve outcomes in patients with childhood renal tumors and will prove indispensable for those treating or researching into these diseases

Recent Advances in Pediatric Cancer Predisposition Syndromes Angela Mastronuzzi, Luigi Boccutto, Riccardo Masetti, 2021-05-03 We would like to acknowledge Dr Giada Del Baldo and Dr Mariachiara Lodi from IRCCS Bambino Gesù Children's Hospital have acted as coordinator and have contributed to the preparation of the proposal for this Research Topic

Fetal and Neonatal Lung Development Alan H. Jobe, Jeffrey A. Whitsett, Steven H. Abman, 2016-04-18 Lung disease affects more than 600 million people worldwide While some of these lung diseases have an obvious developmental component there is growing appreciation that processes and pathways critical for normal lung development are also important for postnatal tissue homeostasis and are dysregulated in lung disease This book provides an authoritative review of fetal and neonatal lung development and is designed to provide a diverse group of scientists spanning the basic to clinical research spectrum with the latest developments on the cellular and molecular mechanisms of normal lung development and injury repair processes and how they are dysregulated in disease The book covers genetics omics and systems biology as well as new imaging techniques that are transforming studies of lung development The reader will learn where the field of lung development has been where it is presently and where it is going in order to improve outcomes for patients with common and rare lung diseases

WHO Classification of Tumours of Endocrine Organs Ricardo V. Lloyd, Robert Y. Osamura, Günter Klöppel, Juan Rosai, 2017 The WHO Classification of Tumours of Endocrine Organs is the 10th volume in the 4th Edition of the WHO series on histological and genetic typing of human tumours This authoritative concise reference provides an international standard for oncologists and pathologists and will serve as an indispensable guide for use in the design of studies evaluating response to therapy and clinical outcome Diagnostic criteria pathological features and associated genetic alterations are described in a disease oriented manner Sections on all recognized neoplasms and their variants include new ICD O codes epidemiology clinical features pathology genetics prognosis and predictive factors The book prepared by 166 authors from 25 countries contains more than 700 color images and tables and more than 3100 references

Gigantism and Acromegaly Constantine A. Stratakis, 2021-06-01 Gigantism and Acromegaly brings together pituitary experts taking readers from bench research to genetic analysis clinical analysis and new therapeutic approaches This book serves as a reference for growth hormone over secretion and its diagnosis and treatment for endocrinologists pediatricians internists and neurosurgeons and for geneticists Pharmaceutical companies may use it as a reference for drug development and research Students residents and fellows in medicine and endocrinology and genetics will also find it valuable as it provides a single up to date review of the molecular biology of gigantism and acromegaly as well as recommended approaches to evaluation and management Acromegaly is a rare pituitary disorder that slowly changes its adult victim s appearance over time larger hands and feet bigger jaw forehead nose and lips Generally a benign pituitary tumor is the cause and symptoms of acromegaly can vary from patient to patient making a diagnosis difficult and prolonging suffering for years Early detection is key in the management of acromegaly as the pathologic effects of increased growth hormone GH production are progressive and can be life threatening as the result of associated cardiovascular cerebrovascular and respiratory disorders and malignancies Accessible up to date overview of the characteristics state of the art diagnostic procedures and management of acromegaly and gigantism Provides a unique compendium of endocrinology genetics clinical diagnosis and therapeutics Contains contributions from internationally known experts who have treated patients with acromegaly and gigantism

Intraocular Tumors: An Atlas and Textbook Jerry A. Shields, Carol L. Shields, 2015-08-10 For outstanding visual clarity in ocular diagnosis nothing else comes close In this updated and revised third edition world renowned authorities at the Wills Eye Hospital provide outstanding guidance on recognition evaluation and treatment of ocular tumors highlighted by more than 2 500 stunning photographs and surgical drawings This unsurpassed ocular oncology resource is a comprehensive guide to the clinical features diagnosis management and pathology of intraocular tumors and pseudotumors depicting clinical variations treatment and histopathologic characteristics of the many varied benign and malignant lesions that affect the uveal tract retina and other intraocular structures Now brought thoroughly up to date with recent clinical and scientific innovations this unique volume has been greatly expanded with over 25% new material and offers more high quality images than any other text atlas in the field Presents each entity in an easy to follow format a concise description with references on the left hand page and six illustrations on the right hand page Depicts in precise photographic detail the gross and microscopic features that distinguish each condition while professional drawings and intraoperative photographs demonstrate key surgical principles and procedures Features numerous new references regarding diagnosis and treatment as well as new scientific tables containing key information for your clinical practice Features 25% new images including panoramic images surgical images diagnostic testing images from multiple modalities and updated OCT images with numerous enhanced depth imaging OCT EDI OCT Covers new information on evolving conditions such as the management of choroidal nevus and melanoma with guidance for early detection using risk factors information on the newest treatment for retinoblastoma with intra arterial and intravenous chemotherapy management of intraocular tumors with photodynamic therapy Important new information on genetics of uveal melanoma the implications of genetics and treatment outcomes is described

The Genetic Basis of Sleep and Sleep Disorders Paul Shaw, Mehdi Tafti, Michael J. Thorpy, 2013-10-24 The first comprehensive book on the subject The Genetic Basis of Sleep and Sleep Disorders covers detailed reviews of the general principles of genetics and genetic techniques in the study of sleep and sleep disorders The book contains sections on the genetics of circadian rhythms of normal sleep and wake states and of sleep homeostasis There are also sections discussing the role of genetics in the understanding of insomnias hypersomnias including narcolepsy parasomnias and sleep related movement disorders The final chapter highlights the use of gene therapy in sleep disorders Written by genetic experts and sleep specialists from around the world the book is up to date and geared specifically to the needs of both researchers and clinicians with an interest in sleep medicine This book will be an invaluable resource for sleep specialists neurologists geneticists psychiatrists and psychologists

RNAi Gregory J. Hannon, 2003 In the past three years the use of double stranded RNA to silence gene activity has become widely and rapidly adopted RNA interference is highly specific and remarkably potent and it acts on cells and tissues far removed from the site of introduction The principles behind RNAi are just being uncovered but this laboratory technique has been applied effectively in a wide variety of animal and plant species Variations on RNAi are revolutionizing many approaches to experimental biology complementing traditional genetic technologies with a quicker and less expensive way of mimicking the effects of mutations both in cell cultures and in living animals Recent advances in the use of RNAi to engineer heritable silencing in mammals to alter stem cells for organ reconstitution and to alter the course of disease in model systems indicate that RNAi may have a future in disease therapy Written by pioneers in this new field and edited by Gregory Hannon one of its leading figures RNAi A Guide to Gene Silencing presents the principles of RNAi and reliable protocols for its laboratory use in *Caenorhabditis elegans* *Drosophila* plants avian embryos mammalian cells mouse oocytes and more This important and unique book is an essential laboratory resource for scientists studying gene regulation and for all experimental biologists interested in the emerging practical applications of RNAi

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