



PRIMARY RESEARCH

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Genotype-phenotype associations in neurofibromatosis type 1 (NF1): an increased risk of tumor complications in patients with *NF1* splice-site mutations?

Adila Alkindy¹, Nadia Chuzhanova², Usha Kini³, David N Cooper⁴ and Meena Upadhyaya^{1*}

Abstract

Neurofibromatosis type 1 (NF1) is a complex neurocutaneous disorder with an increased susceptibility to develop both benign and malignant tumors but with a wide spectrum of inter and intrafamilial clinical variability. The establishment of genotype-phenotype associations in NF1 is potentially useful for targeted therapeutic intervention but has generally been unsuccessful, apart from small subsets of molecularly defined patients. The objective of this study was to evaluate the clinical phenotype associated with the specific types of *NF1* mutation in a retrospectively recorded clinical dataset comprising 149 *NF1* mutation-known individuals from unrelated families. Each patient was assessed for ten NF1-related clinical features, including the number of café-au-lait spots, cutaneous and subcutaneous neurofibromas and the presence/absence of intertriginous skin freckling, Lisch nodules, plexiform and spinal neurofibromas, optic gliomas, other neoplasms (in particular CNS gliomas, malignant peripheral nerve sheath tumors (MPNSTs), juvenile myelomonocytic leukemia, rhabdomyosarcoma, pheochromocytoma, gastrointestinal stromal tumors, juvenile xanthogranuloma, and lipoma) and evidence of learning difficulties. Gender and age at examination were also recorded. Patients were subcategorized according to their associated *NF1* germ line mutations: frame shift deletions (52), splice-site mutations (23), nonsense mutations (36), missense mutations (32) and other types of mutation (6). A significant association was apparent between possession of a splice-site mutation and the presence of brain gliomas and MPNSTs ($p = 0.006$). If confirmed, these findings are likely to be clinically important since up to a third of NF1 patients harbor splice-site mutations. A significant influence of gender was also observed on the number of subcutaneous neurofibromas (females, $p = 0.009$) and preschool learning difficulties (females, $p = 0.022$).

Keywords: Neurofibromatosis type 1, Genotype-phenotype correlation, Malignant peripheral nerve sheath tumors, Brain glioma, Increased cancer susceptibility, Splice-site mutations, *NF1* gene, Gender effect

Introduction

Neurofibromatosis type 1 (NF1) (MIM #162200) [1] is a common familial cancer syndrome with a prevalence of 1 in 2,500 [2] and an autosomal dominant inheritance pattern; it is fully penetrant by 5 years of age. NF1 is a complex disorder that affects many cell types and involves multiple body systems [3]. The clinical phenotypic expression in NF1 is characterized by marked intra

and interfamilial variability with many NF1 individuals only relatively mildly affected and their disease is limited to cutaneous involvement. Most NF1 patients also have mild learning difficulties. About a quarter of NF1 cases eventually develop one or more serious clinical multisystemic complications that lead to the significant morbidity and increased mortality characteristic of this disorder [4]. The many NF1-related clinical complications include neurological, cardiovascular, gastrointestinal, endocrine and orthopedic features. The overall risk of malignancy in NF1 is 5% to 15% higher than in the general population, the age of onset being earlier and with a poorer

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Neurofibromatosis Type I From Genotype To Phenotype

**Shirley V. Hodgson, William D.
Foulkes, Charis Eng, Eamonn R. Maher**



Neurofibromatosis Type I From Genotype To Phenotype:

Neurofibromatosis Type I Senior Lecturer in Medical Genetics David N Cooper, Dr, 1998-05 Neurofibromatosis type 1 NF1 is one of the most common dominantly inherited neurogenetic disorders Affecting 1 in 4000 individuals worldwide Symptoms include facial and body disfigurement mental retardation and abnormalities of the cardiovascular renal and endocrine systems This book is written for a broad readership ranging from students to professionals It provides the reader with a basic overview of the disease before discussing the most recent research and therapeutic developments in detail It is essential reading for medical geneticists molecular biologists dermatologists oncologists neurologists genetic counsellors general practitioners and research students The volume attempts to cover clinical aspects of the disease gene structure expression and mutation structural and functional aspects of the encoded protein neurofibromin the role of the NF1 gene as a tumour suppressor the emerging genotype phenotype relationship for NF1 animal models of the disease and future prospects for disease treatment and prevention **Neurocutaneous Disorders** Martino Ruggieri, Ignacio Pascual

Castroviejo, Concezio Di Rocco, 2009-10-01 The book provides an authoritative source of knowledge about these problematic disorders It bridges the gap between clinical recognition and the new molecular medicine The editors distinguished clinicians and geneticists assembled an internationally renowned group of collaborators many of them the experts who first described a particular disorder or established its present accepted definition They have written a practical comprehensive guide to the recognition investigation and management of more than 60 recognised phakomatoses **The Molecular Biology of**

Neurofibromatosis Type 1 Meena Upadhyaya, 2014-02-01 Neurofibromatosis type 1 NF1 is a common autosomal dominantly inherited tumour predisposition syndrome affecting 1 3 000 4 000 individuals worldwide This inherited disorder results from the mutational inactivation of the NF1 gene on human chromosome 17 The NF1 gene contains 61 exons that give rise to 12kb mRNA encoding neurofibromin The 327kDa 2 818 amino acid neurofibromin protein is expressed in most tissues and has a number of alternative isoforms Neurofibromin is a tumour suppressor protein and down regulates cellular Ras Increased active Ras GTP levels also stimulate the important PI3K AKT mTOR signalling pathway that protects cells from apoptosis The major clinical features of NF1 include multiple café au lait macules skinfold freckles iris Lisch nodules and neurofibromas The diagnostic criteria for clinical diagnosis have been well established However there are a small number of cases in which the diagnosis is not certain The germline mutation rate for the NF1 gene is 10 fold higher than that observed for most other inherited diseases Using a combination of different techniques almost 95% of germline mutations can be detected To date only two firm genotype phenotype correlations have been reported NF1 phenotype exhibits large variations within a family evidence for modifying loci regulating the expression of an NF1 gene is beginning to emerge We also are gaining knowledge on the molecular mechanisms associated with the development of different types of tumours It is encouraging that the results of recent laboratory and clinical research are finally being translated into clinical trials With the

availability of high throughput technologies sophisticated animal models and multi centre clinical trials the future for NF1 sufferers is looking optimistic This book aims to provide an overview of the genetic and clinical aspects of NF1 and its role in both NF1 associated and sporadic tumour development It emphasizes the recent developments in this field and some of the promising on going clinical trials

Multidisciplinary Approach to Neurofibromatosis Type 1 Gianluca Tadini, Eric Legius, Hilde Brems, 2020-06-02 This volume offers an update of the clinical signs diagnostic criteria including molecular diagnosis and targeted therapies for a particular type of genodermatosis providing a handy and unique tool for early diagnosis In recent years our understanding of genodermatosis and neurocutaneous syndromes has increased but although Type 1 Neurofibromatosis NF1 is the most common neuroectodermal disorder and involves a large number of patients and medical disciplines this syndrome remains underestimated often misdiagnosed thus leading to inaccurate treatment The literature on the molecular and pathogenetic aspects is ample but current clinical approaches classification diagnostic criteria and treatment protocols are outdated creating difficulties in early diagnosis and treatment As such a chapter is devoted renewing current diagnostic criteria it includes clinical and molecular data to offer a sound updated discussion basis for a consensus conference NF1 is a time dependent disorder meaning that the onset of clinical signs are closely linked to patient age and the book discusses this particularly neglected aspect extensively as well as the latest molecular diagnosis techniques which are highly sensitive have not been included in the diagnostic criteria It also explains the role of the RAS MAPK pathway and genotype phenotype correlations In addition it explores new concepts concerning the pathogenesis of neurofibromas and other hamartomas and their relevance for a modern therapeutical approach with targeted molecular drugs as well as newly discovered aspects of NF1 in all internal organs together with their diagnostic counterparts A chapter on mosaic neurofibromatosis is also included There is a particular focus on differential diagnosis i e other diseases with café au lait macules and the recently described Legius syndrome will be presented directly by Prof Eric Legius All chapters are easy to understand up to date comprehensive and concise tools and are intended for a wide range of professionals involved with genetic disorders of the skin and neurocutaneous diseases dermatologists pediatricians neurologists oncologists and general practitioners

Neurofibromatosis Type 1 Meena Upadhyaya, David N Cooper, 2013-01-29 Neurofibromatosis type 1 NF1 caused by mutational inactivation of the NF1 tumour suppressor gene is one of the most common dominantly inherited human disorders affecting 1 in 3000 individuals worldwide This book presents in concise fashion but as comprehensively as possible our current state of knowledge on the molecular genetics molecular biology and cellular biology of this tumour predisposition syndrome Written by internationally recognized experts in the field the 44 chapters that constitute this edited volume provide the reader with a broad overview of the clinical features of the disease the structure and expression of the NF1 gene its germ line and somatic mutational spectra and genotype phenotype relationships the structure and function of its protein product neurofibromin NF1 modifying loci the molecular pathology of NF1 associated tumours animal models of

the disease psycho social aspects and future prospects for therapeutic treatment **Rosenberg's Molecular and Genetic Basis of Neurological and Psychiatric Disease, Seventh Edition** Roger N. Rosenberg, Juan M. Pascual, 2024-10-07

Rosenberg's Molecular and Genetic Basis of Neurologic and Psychiatric Disease Seventh Edition provides a comprehensive introduction and reference to the foundations and practical aspects relevant to the majority of neurologic and psychiatric disease. This updated volume focuses on degenerative disorders, movement disorders, neuro-oncology, neurocutaneous disorders, epilepsy, white matter diseases, neuropathies and neuronopathies, muscle and neuromuscular junction disorders, stroke, psychiatric disease, and a neurologic gene map. This volume includes new chapters on Von Hippel Lindau disease, antisocial and violent behavior, and Autism. A favorite of over four generations of students, clinicians, and scholars, this new edition retains and expands on the informative, concise, and critical tone of the previous edition. This is an essential reference for general medical practitioners, neurologists, psychiatrists, geneticists, related professionals, and for the neuroscience and neurology research community at large. Both volumes combined provide a comprehensive coverage on the neurogenetic foundation of neurological and psychiatric disease. This volume presents detailed coverage of disease mechanisms and management for degenerative disorders, movement disorders, and muscle and neuromuscular junction disorders. Includes new chapters on the pharmacogenomics of Alzheimer's Disease and Epilepsy and the most recent updates in molecular genetics focusing on pain genetics and muscular dystrophy.

Rosenberg's Molecular and Genetic Basis of Neurological and Psychiatric Disease Roger N. Rosenberg, Juan M. Pascual, 2020-06-24

Rosenberg's Molecular and Genetic Basis of Neurologic and Psychiatric Disease Sixth Edition Volume Two provides a comprehensive introduction and reference to the foundations and practical aspects relevant to the majority of neurologic and psychiatric disease. This updated volume focuses on degenerative disorders, movement disorders, neuro-oncology, neurocutaneous disorders, epilepsy, white matter diseases, neuropathies and neuronopathies, muscle and neuromuscular junction disorders, stroke, psychiatric disease, and a neurologic gene map. A favorite of over three generations of students, clinicians, and scholars, this new edition retains and expands on the informative, concise, and critical tone of the first edition. This is an essential reference for general medical practitioners, neurologists, psychiatrists, geneticists, related professionals, and for the neuroscience and neurology research community at large. The content covers all aspects essential to the practice of neurogenetics to inform clinical diagnosis, treatment, and genetic counseling. Provides comprehensive coverage on the neurogenetic foundation of neurological and psychiatric disease. Presents detailed coverage of genomics, animal models, and diagnostic methods with new coverage on evaluating patients with biochemical abnormalities or gene mutations. Includes new chapters on the pharmacogenomics of epilepsy and the most recent updates in molecular genetics focusing on neurodegenerative and psychiatric diseases.

Neurofibromatosis: New Insights for the Healthcare Professional: 2013 Edition, 2013-07-22

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Neurofibromatoses Dieter Kaufmann,2008 The neurofibromatoses are autosomal dominant genetic disorders of the nervous system that primarily affect the development and growth of neural cell tissue These disorders cause tumors to grow on nerves and produce other abnormalities such as skin changes and bone deformities In recent years the genes and mutations causing neurofibromatoses have been identified The main types of neurofibromatoses type 1 NF1 and type 2 NF2 have been shown to be distinctive disorders both clinically and genetically More recently allelic and non allelic subtypes of NF1 have been defined as well as the NF2 related condition schwannomatosis Many of the complex molecular mechanisms leading to the neurofibromatoses have been elucidated resulting in a growing body of publications which are difficult to keep up with This volume provides an important overview of recent findings on the neurofibromatoses It focuses on the genetics and molecular biology underlying these diseases but also covers their clinical features diagnosis and treatment stressing the need for interdisciplinary medical care With contributions by the foremost investigators in the field this timely book will appeal to geneticists genetic counselors pediatricians neurologists and oncologists

Genomics and Models of Nerve Sheath Tumors Angela C. Hirbe,Christine A. Pratilas,Rebecca D. Dodd,2020-11-18 Nerve sheath tumors can be a significant cause of morbidity for many patients These include benign tumors such as schwannomas diffuse and plexiform neurofibromas and atypical neurofibromas as well as the aggressive soft tissue sarcoma known as the malignant peripheral nerve sheath tumor MPNST Nerve sheath tumors occur sporadically and in the context of the clinical neuro genetic tumor predisposition syndromes neurofibromatosis type 1 NF1 and type 2 NF2 Historically the mainstay of treatment for nerve sheath tumors has been surgery However for both benign and malignant nerve sheath tumors there is a high recurrence rate highlighting the pressing need for novel therapies As we have entered the genomic era the hope is that an improved understanding of the genetics and therefore the biology of these tumors will ultimately lead to therapies that result in better outcomes In this Special Issue we include both review articles and original research related to the genomic understanding and modeling of schwannomas plexiform and diffuse neurofibromas atypical neurofibromas and malignant peripheral nerve sheath tumors as well as genomic methods being developed and applied to advance our understanding of these tumors

Genetic Diseases of the Eye Elias I.

Traboulsi, Professor of Ophthalmology and Director Center for Genetic Eye Diseases Elias I Traboulsi, Med, Virginia Miraldi Utz, Department Chair Pediatric & Neuro-Ophthalmology Arif O Khan, 2025-08-22 Since the publication of the Human Genome Project in 2001 and the development of Genome Wide Association Studies GWAS there has been a major shift toward large scale international collaboration in genetic eye disease research Eye researchers involved in genetics have now joined forces with traditional epidemiologists to develop the field of genetic epidemiology Whilst ophthalmic geneticists had focused on rare pathogenic variants mutations with strong effects epidemiologists had focused on common gene variants with small but additive effects see Figure 1 These two areas have now merged identifying a spectrum of genetic variants that are rare intermediate or common with strong medium or mild pathogenicity *The RASopathies* Katherine A.

Rauen, 2024-11-29 This book presents comprehensive coverage of the RASopathies one of the largest known recognizable patterns of malformation syndromes affecting approximately 1 in 1 000 people These syndromes include neurofibromatosis type 1 Noonan syndrome Noonan syndrome with multiple lentigines Costello syndrome cardio facio cutaneous syndrome Legius syndrome capillary malformation arteriovenous malformation syndrome SYNGAP1 syndrome and central conducting lymphatic anomalies Noted physician and authority Katherine Rauen and an assembly of the top international experts present detailed discussions of both the science and clinical implications of these fascinating disorders The major topics covered in this book include the syndromes and genes the RAS pathway phenotypic features animal modeling and treatments The book will appeal to a wide audience including clinicians and basic scientists alike such as medical geneticists genetics counsellors oncologists neurologists cardiologists dermatologists behavioralists orthopedists ophthalmologists neuroscientists RAS biologists and signal transductionists This book is also intended for advocate leaders trainees and families with RASopathies

A Practical Guide to Human Cancer Genetics Shirley V. Hodgson, William D. Foulkes, Charis Eng, Eamonn R.

Maher, 2013-11-22 This is a comprehensive and up to date guide to the diagnosis clinical features and management of inherited disorders conferring cancer susceptibility It is fully updated with much molecular screening and management information It covers risk analysis and genetic counselling for individuals with a family history of cancer It also discusses predictive testing and the organisation of the cancer genetics service There is information about the genes causing Mendelian cancer predisposing conditions and their mechanism of action It aims to provide such details in a practical format for geneticists and clinicians in all disciplines Genetics and Precision Medicine, An issue of Medical Clinics of North America

Howard P. Levy, 2019-10-08 This issue of Medical Clinics of North America guest edited by Dr Howard P Levy is devoted to Genetics and Precision Medicine Articles in this important issue include Family History in Genetics and Precision Medicine Genetic Testing Who What When and Why Test Result Disclosure and When to Consult a Geneticist or Genetic Counselor Patient Engagement to Inform a Large scale Population Sequencing Program Pharmacogenetics Prescribing Precisely DNA Testing for Early Cancer Diagnosis Breast Cancer BRCA and Beyond Colon Cancer and Other GI Cancers

Neurofibromatosis and Related Disorders Marfan Loeys Dietz and Other Syndromes Causing Arterial Fragility Ehlers Danlos Syndromes and Related Disorders of Connective Tissue Parkinson Alzheimer and Other Neuropsychiatric Diseases Genetic Neurologic and Neuromuscular Disorders and Polycystic Kidney Disease and Other Genetic Kidney Disorders A CME program is also available for this title *Peripheral Nerve Sheath Tumors* Ignazio Gaspare Vetrano,Vittoria Nazzi,2024-12-31 This book offers an update about peripheral nerve sheath tumors PNST both in their benign and malignant forms MPNST Starting from the most innovative preclinical studies about genetic and omics characterization it then explores the traditional and advanced imaging modalities ultrasound DTI etc and the electrophysiological assessment Another relevant part is reserved to the description of the most recent surgical techniques fluorescent dye for intraoperative surgical guidance neurophysiological monitoring endoscopic view Finally new oral treatment for PNST related to neurocutaneous diseases as selumetinib in plexiform neurofibromas is described Written by worldwide experts in each specific field it offers a multidisciplinary vision to PNST approaching the topic in a translational way from preclinical studies to the current medical practice The ideal readers are all health operators involved in the treatment of these tumors from neurosurgeons to radiologists neurologists geneticists biologists etc as well as medical students in these disciplines *Neurofibromatoses in Clinical Practice* Rosalie E Ferner,Susan Huson,D. Gareth R. Evans,2011-09-05 Neurofibromatoses in Clinical Practice provides a succinct accessible guide to the neurofibromatoses including diagnosis management protocols and indications for referral to specialist centers Neurocutaneous diseases are complex to diagnose and treat and many patients require specialist multidisciplinary management and surveillance Due to multiple disease manifestations patients can present to different clinicians without specialist expertise general practitioners pediatricians neurologists geneticists surgeons and ophthalmologists The clinically focused format will enable rapid consultation during clinics facilitate disease pattern recognition and indicate care pathways The clinical quiz highlights common pitfalls in diagnosis and management and a glossary and reference section provide details for access to specialist NF clinics throughout the UK and internationally Written by experts in the field Neurofibromatoses in Clinical Practice is a succinct and practical guide for consultants in training and practice general practitioners and specialist nurses **Scott-Brown's Otorhinolaryngology and Head and Neck Surgery** John Watkinson,Ray Clarke,2018-06-12 This second volume in the Scott Brown Otorhinolaryngology Head and Neck Surgery 8e three volume work is available either as an individual volume covering the sub specialties of Paediatrics The Ear and Skull Base Surgery or as part of the classic three volume set With over 100 chapters and numerous illustrations this specialist volume contains authoritative and cutting edge information from some of the world's outstanding clinicians It will be a constant companion through the specialty training years and beyond **Copy Number Variation in Rare Disorders** Judit Bene,Katalin Komlosi,Attila Gyenesi,2022-04-28 *Insights in Pediatric Cardiology: 2021* Ruth Heying,Antonio Francesco Corno,2023-01-06 **Schachner and Hansen's Textbook of Pediatric Dermatology** Antonio

Torrelo,2022-03-30 This two volume set is a complete guide to the diagnosis and treatment of paediatric skin conditions With its first edition having published more than 33 years ago this reference is renowned amongst clinicians practising in the field of paediatric dermatology The fifth edition has been thoroughly revised and updated to provide all the latest techniques and therapeutic advances for daily practice More than 2000 clinical and histologic pictures the majority new to this edition illustrate all the skin conditions described in the comprehensive text covering 2500 pages across the two volumes Detailed references offer suggestions for further reading Divided into 22 sections the book begins with an introduction to basic science and discussion on diagnosis in paediatric dermatology The following chapters cover a multitude of conditions from genetic diseases eczema and pigmentary disorders to vascular anomalies tumours and cysts skin infections and many more The book concludes with a section on the principles of treatment A complete section is dedicated to neonatal disorders The book is edited by Madrid based Antonio Torrelo with contributions from numerous other experts in the field The previous edition 9780723435402 published in 2010

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Table of Contents Neurofibromatosis Type I From Genotype To Phenotype

1. Understanding the eBook Neurofibromatosis Type I From Genotype To Phenotype
 - The Rise of Digital Reading Neurofibromatosis Type I From Genotype To Phenotype
 - Advantages of eBooks Over Traditional Books
2. Identifying Neurofibromatosis Type I From Genotype To Phenotype
 - Exploring Different Genres
 - Considering Fiction vs. Non-Fiction
 - Determining Your Reading Goals
3. Choosing the Right eBook Platform
 - Popular eBook Platforms
 - Features to Look for in an Neurofibromatosis Type I From Genotype To Phenotype
 - User-Friendly Interface
4. Exploring eBook Recommendations from Neurofibromatosis Type I From Genotype To Phenotype
 - Personalized Recommendations
 - Neurofibromatosis Type I From Genotype To Phenotype User Reviews and Ratings
 - Neurofibromatosis Type I From Genotype To Phenotype and Bestseller Lists
5. Accessing Neurofibromatosis Type I From Genotype To Phenotype Free and Paid eBooks
 - Neurofibromatosis Type I From Genotype To Phenotype Public Domain eBooks
 - Neurofibromatosis Type I From Genotype To Phenotype eBook Subscription Services
 - Neurofibromatosis Type I From Genotype To Phenotype Budget-Friendly Options
6. Navigating Neurofibromatosis Type I From Genotype To Phenotype eBook Formats

- ePub, PDF, MOBI, and More
 - Neurofibromatosis Type I From Genotype To Phenotype Compatibility with Devices
 - Neurofibromatosis Type I From Genotype To Phenotype Enhanced eBook Features
7. Enhancing Your Reading Experience
 - Adjustable Fonts and Text Sizes of Neurofibromatosis Type I From Genotype To Phenotype
 - Highlighting and Note-Taking Neurofibromatosis Type I From Genotype To Phenotype
 - Interactive Elements Neurofibromatosis Type I From Genotype To Phenotype
 8. Staying Engaged with Neurofibromatosis Type I From Genotype To Phenotype
 - Joining Online Reading Communities
 - Participating in Virtual Book Clubs
 - Following Authors and Publishers Neurofibromatosis Type I From Genotype To Phenotype
 9. Balancing eBooks and Physical Books Neurofibromatosis Type I From Genotype To Phenotype
 - Benefits of a Digital Library
 - Creating a Diverse Reading Collection Neurofibromatosis Type I From Genotype To Phenotype
 10. Overcoming Reading Challenges
 - Dealing with Digital Eye Strain
 - Minimizing Distractions
 - Managing Screen Time
 11. Cultivating a Reading Routine Neurofibromatosis Type I From Genotype To Phenotype
 - Setting Reading Goals Neurofibromatosis Type I From Genotype To Phenotype
 - Carving Out Dedicated Reading Time
 12. Sourcing Reliable Information of Neurofibromatosis Type I From Genotype To Phenotype
 - Fact-Checking eBook Content of Neurofibromatosis Type I From Genotype To Phenotype
 - Distinguishing Credible Sources
 13. Promoting Lifelong Learning
 - Utilizing eBooks for Skill Development
 - Exploring Educational eBooks
 14. Embracing eBook Trends
 - Integration of Multimedia Elements
 - Interactive and Gamified eBooks

Neurofibromatosis Type I From Genotype To Phenotype Introduction

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