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Neurofibromatosis Type 2 (NF2)

- Linked research
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1996 1997

Molecular Biology & Genetics

- Gene for NF2 localized to 22q12 (formal separation of NF1 and NF2). 1987
- *NF2* gene cloned; *NF2* gene product identified as Merlin/ Schwannomin. 1993
- Mutation rate for NF2 is ~6.5 x 10^{-6}. 1993
- Two major isoforms (splice variants) of *NF2* identified. 1994
- Correlations made between genotype and phenotype: •Parry et al. •Ruttledge et al. •Kluewe et al. 1996
- NF2 gene product shares similarity with the 4.1 family of cytoskeleton-associated proteins – specifically, the ERM (Ezrin Radixin Moesin) proteins. 1997

Cellular Biology

- Merlin is expressed in the nervous system, smooth muscle, Schwann cells, melanocytes, RBCs, endothelial cells, and neurons such as Purkinje cells and motor neurons, but not in glial cells. 1996
- Immunocytochemistry shows Merlin localized to the cell membrane (filopodia, ruffling membrane, and leading edge). 1996
- Truncated forms of Merlin are not detected in NF2 tumors, suggesting protein instability and degradation. 1997
- Merlin self-interaction (N- to C-terminal) is involved in growth suppression. 1997
- Merlin co-localized with CD44 and the actin cytoskeleton. 1997

Pathobiology

- NF2 mutations detected in ~50%-80% of NF2 tumors. 1992+
- Merlin (NF2 mutation) is implicated in breast cancers and colorectal cancers. 1994
- Merlin is lost in ~60% of sporadic meningiomas and ~80% of sporadic schwannomas. 1994
- Merlin (NF2 mutation) is implicated in mesotheliomas. 1995
- Germline mutations in NF2 found in at least two-thirds of all individuals with typical bilateral vestibular schwannoma. 1996

Technology/ Animal Models

- Drosophila NF2 mutations isolated and characterized. 1997
- Drosophila homologue of NF2 (Merlin) identified. 1997
- Inactivation of mouse NF2 gene results in embryonic lethality between day 6.5 and 7.0. 1997
- NF2 heterozygous (+/-) mice are developed; predisposed to cancer at advanced age, but do not develop the hallmark tumors of NF2. 1997

Imaging, Detection, & Diagnosis

- Type 2 neurofibromatosis first described by Dr. Wishart. 1820
- Type 1 neurofibromatosis first identified in the literature by Dr. Friedrich von Recklinghausen. 1882
- NF2 characterized by schwannomas of the 8th cranial nerve – can also involve schwannomas of other cranial nerves, meningiomas, ependymomas, and ocular manifestations. 1987
- Gadolinium-enhanced Magnetic Resonance Imaging (MRI) made available for imaging, detection, and diagnosis of vestibular schwannoma; lesions as small as 2 mm are detectable. 1988
- Diagnostic criteria for NF2 outlined:
  - Bilateral masses of the 8th cranial nerve; *or*
  - 1 or more 1st degree relative with NF2 + unilateral vestibular mass of 8th cranial nerve; *or*
  - 2 of the following: Neurofibroma, meningioma, glioma, schwannoma, juvenile posterior subcapsular lenticular opacities
  1990
- Two types of NF2 identified:
  (1) Gardner type – mild with late onset and few tumors other than vestibular schwannoma
  (2) Wishart type – severe, early onset with multiple tumors
  1992
- Mosaicism at NF2 locus is uncommon and probably under-recognized; unilateral vestibular schwannoma, ipsilateral intracranial tumors, schwannomatosis, and/or asymmetric involvement. 1996
- Schwannomatosis described as a separate clinical entity from other forms of NF: Multiple schwannomas without evidence of vestibular schwannoma. 1996
- Diagnostic criteria for NF2 outlined:
  - Bilateral vestibular schwannoma; *or*
  - 1 or more 1st degree relative with NF2 + unilateral vestibular schwannoma at <30 years; *or*
  - 2 of the following: Meningioma, glioma, schwannoma, juvenile posterior lenticular opacities
  1997

Epidemiology

- Birth incidence of NF2 is determined to be ~1:33,000-40,000. 1992
- Diagnostic prevalence of NF2 is ~1:200,000 because of late onset and early death. 1992
- Correlations made between genotype and phenotype:
  - Nonsense/frameshift mutations = severe phenotypes
  - Splice-site mutations = variable phenotype within/ between families
  - Very few non-truncating mutations detected
  - Mutations not detected by exon-scanning = mild phenotype
  1996

Experimental Therapeutics

- First auditory brainstem implant for treatment of hearing loss from NF2. 1979
- FDA granted an Investigational Clinical Trial of a multichannel Auditory Brainstem Implant for NF2. 1994
- Calpain inhibitors or calcium channel-blocking agents could prevent growth/relapse of tumors (in vitro); more studies required. 1995
- Aminoglycosides suppress expression of nonsense mutations of NF2 and modify the neoplastic phenotype of tumor cells in culture. 1996
- SU-101 tested in Phase II trial for patients with recurrent malignant gliomas. 1997

Symptom Management

- Recommended screening:
  - Routine eye exams
  - Enhanced MRI scanning should occur annually, beginning in the teens
  - Surveillance of at-risk but asymptomatic individuals
  1980s
- Total excision of vestibular schwannomas or radiation therapy. 1991
- Stereotactic radiosurgery (gamma-knife) available for vestibular schwannoma (typically results in loss of hearing). 1992
- Hearing preservation/ augmentation strategies: Hearing aids, cochlear implants, training in lip reading and/or sign language. 1992
- Partial excision of vestibular schwannoma in cases of large tumors. 1993

Important Meetings & Symposia

- Foundation of the National Neurofibromatosis Foundation (NNFF). 1978
- National Institutes of Health (NIH) Consensus Development Conference on Neurofibromatosis: Delineated NF1 from NF2 and diagnostic criteria for each. 1987
- Foundation of Neurofibromatosis, Inc. 1988
- NIH Consensus Development Conference on Acoustic Neuroma. 1991
- Department of Defense Neurofibromatosis Research Program (NFRP) established. 1996
- NNFF Clinical Care Advisory Board: Diagnostic Evaluation and Management of NF1 and NF2. 1997
- House Ear Institute and NNFF workshop on NF2: Reviewed current knowledge, made short-term and long-term goals. 1997

NF2

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	1998	1999	2000	2001
Molecular Biology & Genetics	Merlin lacks the conventional C-terminal actin-binding site, but has other actin-binding sites within its FERM (4.1 ERM) domain. 1998 Correlations made between genotype and phenotype: • Evans et al. 1998			High resolution microarray-CGH detected an overall 20.7% detection rate out of 116 NF2 patients with differing severity; found a high frequency of large chromosome 22 deletions. 2001
Cellular Biology	Merlin indirectly associates with the actin cytoskeleton through an interaction with βII-Spectrin. 1998 Merlin interacts with hNHE-RF, which localizes to actin-rich structures. 1998 Merlin binds Paxillin, which facilitates binding to the cell membrane. 1998 Merlin co-localizes with F-actin filaments along the membrane. 1998 Merlin constitutively degraded by the calpain system in intact cells; N-terminal 35 kD fragment results. 1998 Merlin interacts with β-integrin in differentiating Schwann cells. 1998	Method developed for establishing short-term primary schwannoma cells in culture. 1999	Merlin interacts with schwannomin – interacting protein-1 (SCHIP-1), a novel protein that interacts specifically with spliced forms of Merlin. 2000 Hepatocyte growth factor –regulated tyrosine kinase substrate (HRS) interacts with Merlin both in vivo and in vitro. 2000	Activation of Rac1 or Cdc42 promotes Merlin phosphorylation (inactivation). 2001 Five multi-allelic complementation groups (including scribbler/ brakeless, blistered, and net) identified that alter the subcellular localization of Merlin. 2001 Syntenin specifically interacts with Merlin isoform 1 – links active Merlin to membrane protein signaling through the actin cytoskeleton. 2001 HRS interacts with the C-terminus of Merlin in its open form. 2001 Regulated overexpression of cells has HGS (HRS) in rat schwannoma the same effect as Merlin overexpression. 2001
Pathobiology	Naturally occurring mutant NF2 proteins demonstrate altered localizations; C-terminal deletions = cell membrane, N-terminal deletions = perinuclear/cytoplasmic region. 1998 NF2 schwannoma-derived cells have abnormal actin cytoskeletal architecture and proliferation defects. 1998			
Technology/ Animal Models	Somatic cell mosaic analysis reveals Drosophila Merlin acts as a tumor suppressor. 1998	Transgenic mice expressing the first 314 amino acids of Merlin are normal. 1999 Transgenic mice expressing a mutant NF2 that lacks exon 2-3 develop peripheral nerve sheath tumors and Schwann cell hyperplasia. 1999	Conditional NF2 knockout mice developed (NF2 disrupted specifically in myelin P0-expressing cells); these develop schwannomas in association with peripheral nerves. 2000	Drosophila Merlin mutants show defects in nuclear migration and mRNA localization in the oocyte. 2001
Imaging, Detection, & Diagnosis			Pre-symptomatic diagnosis available for ~66% of all classically affected NF2 patients. 2000	
Epidemiology	Families with splice-site or missense mutations or large deletions of the NF2 gene tend to have fewer tumors and later onset. 1998 Preliminary work done on growth rate of vestibular schwannomas. 1998			
Experimental Therapeutics		Phase I trial of SU-101 in children. 1999	FDA approval of Nucleus 24-Multichannel Auditory Brainstem Implant. 2000	
Symptom Management	MRI annually to screen tumor growth and other intracranial risks + annual audiometric studies to monitor hearing (surgery required when hearing is no longer useful or tumor grows enough to endanger patient). 1998 Middle fossa internal auditory canal bony decompression – useful when a change in hearing is documented (for long-term hearing stabilization). 1998 Translabyrinthine total tumor removal with auditory brainstem implant – used for patients with non-useful hearing or large tumors with brainstem compression. 1998 Suboccipital approach total tumor removal – used for smaller, medially based tumors (hearing preservation is unlikely and risk of tumor recurrence is high). 1998 Strategic radiation therapy (gamma knife) – used in elderly patients with documented tumor growth (low chance of hearing preservation). 1998			
Important Meetings & Symposia			National Institute of Neurological Disorders and Stroke (NINDS) Workshop: Defining the Future of Neurofibromatosis Research. 2000	

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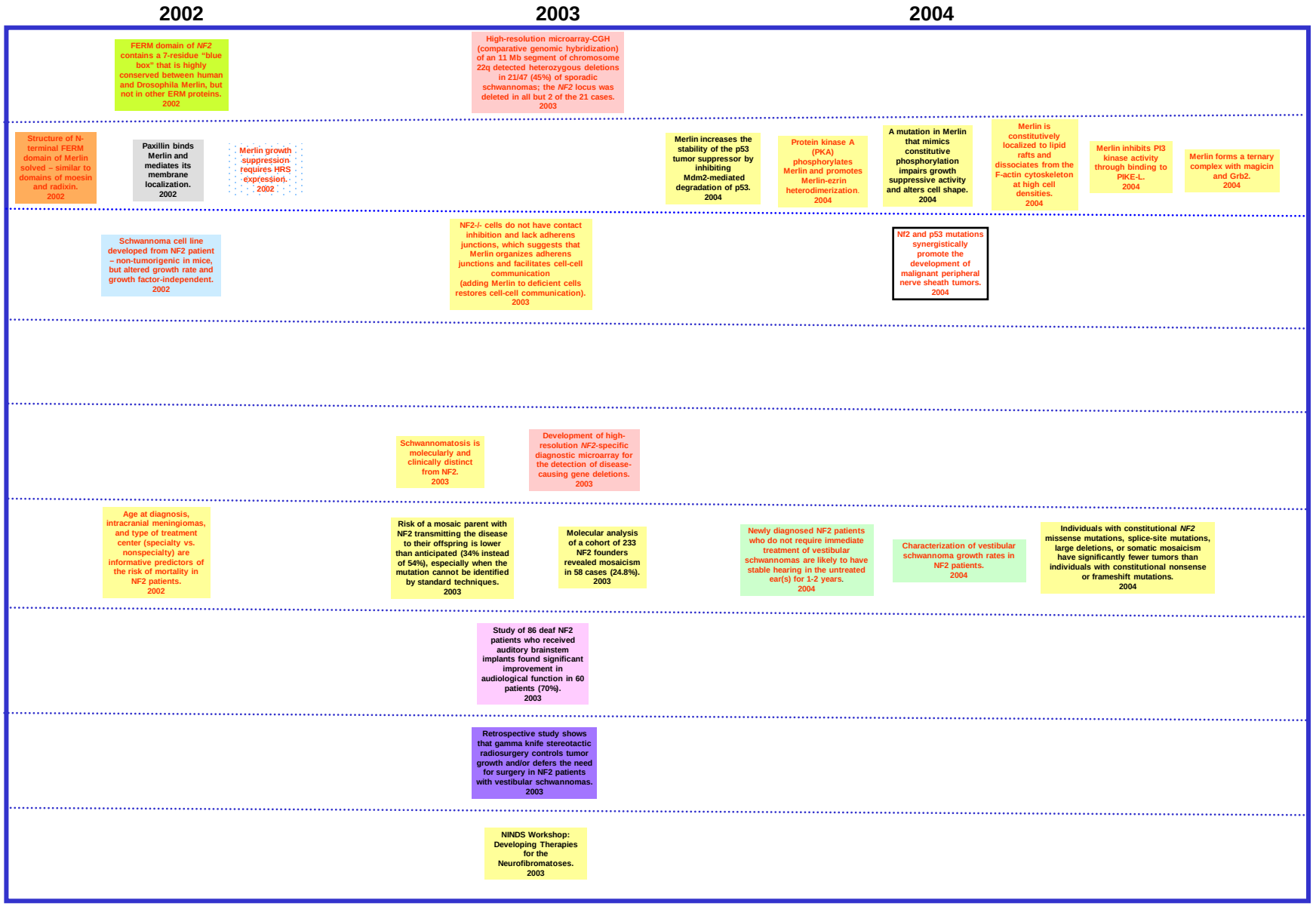

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2005 2006 2007 →

Molecular Biology & Genetics

Cellular Biology

Erbin links Merlin to both adherens junction protein complexes and the MAP kinase signaling pathway.
2005

Merlin is targeted to the nucleus in glioma and osteosarcoma cells in a cell cycle-dependent manner.
2005

Merlin inhibits N-WASP-mediated actin assembly.
2005

Merlin regulates abnormal cell proliferation via its interaction with Grb2.
2005

Merlin facilitates ubiquitination and degradation of the oncogenic protein TRBP.
2005

Merlin functions as a tumor suppressor by inhibiting RalGDS-mediated oncogenic signals.
2005

Merlin and Expanded act through Hippo to regulate cell proliferation and apoptosis.
2006

MLK3 is a component of the BRaf/Raf-1 complex that is negatively regulated by merlin.
2006

HEI10, a cell cycle regulator, identified as a novel merlin binding partner.
2006

Protein 4.1B/DAL-1 functions as a growth suppressor in meningioma cells through the activation of Rac-1-dependent JNK signaling.
2006

Merlin inhibits tumor growth, in part, by negatively regulating CD44 function.
2007

A novel GTP-binding protein, NGB, is a tumor suppressor that regulates and requires merlin to suppress cell proliferation.
2007

Merlin suppresses growth by inhibiting activation of Rac and Ras.
2007

Pathobiology

Array-CGH identify a higher frequency of biallelic NF2 inactivation in fibroblastic (52%) vs. meningiothelial (18%) tumors.
2007

Technology/ Animal Models

- Small animal MRI protocol using gadolinium enhancement delineates time-course of meningiothelial proliferation and meningioma development in mice.
- Loss of Ink4a enhances the incidence of meningioma formation in NF2 homozygous conditional knockout mice.

2007

Imaging, Detection, & Diagnosis

Development of PCR method to detect deletions and duplications of the NF2 gene.
2005

Chromogenic in situ hybridization (CISH) validated as a reliable method for assessing NF2 gene deletions in sporadic schwannomas, meningiomas, and ependynomas.
2007

Epidemiology

Vestibular schwannoma growth rates are highly variable but tend to decrease with increasing age.
2005

Protein truncating mutations are associated with an increased prevalence of spinal tumors in NF2 patients.
2005

Individuals with Splice mutations in exons 1-5 of Nf2 had more severe disease than those with splice mutations in exons 11-15.
2005

The percentage of individuals with NF2 initially presenting with unilateral sporadic vestibular schwannoma is extremely small (~7.5%).
2007

Experimental Therapeutics

FK228, an anti-PAK1 drug, completely blocks the growth of NF2-deficient cancer cells in vitro.
2005

Development of an oncolytic recombinant herpes simplex virus (HSV) vector that reduced volume of schwannoma tumors in mouse model of NF2.
2006

Oncolytic recombinant HSV vector causes complete regression of schwannomas in a xenograft mouse model.
2007

Symptom Management

- Hearing bilaterally preserved in 75% of children with NF2 undergoing bilateral middle fossa surgery.
- Preoperative facial nerve grade preserved in 77% of middle fossa surgeries.

2007

Important Meetings & Symposia

NF Clinical Trials Consortium established.
2006

NF2

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2007 2008 →

Molecular Biology & Genetics

- SMARCB1 (SW1/SNF-related, matrix-associated, actin-dependent regulator of chromatin B1) mutations occur in tumors with and without somatic NF2 gene changes. SMARCB1 is a tumor suppressor for schwannomas in the context of familial disease. 2008
- Immunohistochemical analysis identifies a role for INI1/SMARCB1 in hereditary forms of schwannomas, but not in solitary, sporadic schwannomas. 2008

Cellular Biology

- Merlin negatively regulates epidermal growth factor receptor (EGFR) by sequestering EGFR to membrane compartment and blocking internalization and subsequent signaling. 2007
- Merlin directly binds to tubulin and regulates microtubule organization in vivo and in vitro. 2007
- AKT directly binds to and phosphorylates Merlin on residues Thr-230 and Ser-315
- AKT-mediated phosphorylation of Merlin leads to ubiquitination and degradation by the proteasome pathway
2007
- Merlin inhibits the interaction between hyaluronan and CD44. 2007
- The N-terminal 17 amino acids of Merlin are required for localization to the insoluble membrane compartment and the cortical actin network. 2008
- Schwannomin play important role in the control of Schwann cell number and necessary for the correct organization and regulation of axoglial heterotypic and glio-glial autotypic contacts. 2008
- Merlin regulates meningioma cell growth by suppressing Yes-associated protein (YAP). 2008
- The transcriptional coactivator activity of YAP1 is functionally inhibited by merlin through the induction of YAP1 phosphorylation at serine 127 and increased cytoplasmic retention of YAP1. 2008
- PKA dysregulation triggered by loss of Prkar1a causes Schwann cell tumorigenesis and loss of NF1/2 protein expression, through pathways that overlap, but are distinct from, those that cause NF1 and NF2. 2008
- PKA phosphorylates merlin on serine 10. Dephosphorylation of this site leads to defects in cellular migration. 2008

Pathobiology

- Merlin required for assembly (but not maintenance) of the junctional complex (adherens junctions and tight junctions) during tissue fusion. 2007
- Less than 10% of small mutations in NF2 clinical samples are nontruncating and are clustered in exons 2 and 3. 2007
- Pak1 is hyperactive in primary schwannomas isolated from NF2 patients, and suppression of Paks 1-3 via shRNAs reduces the ability of NF2 mutant cells to grow in vitro and form tumors in a xenograft model of NF2. Long-term Pak1 inhibition via shRNA is restored through a methylation-dependent mechanism. 2008

Technology/ Animal Models

Imaging, Detection, & Diagnosis

Epidemiology

- Risk of transmitting NF2 to offspring in individuals presenting with unilateral vestibular schwannoma is ~1 in 12.
- Risk of transmitting NF2 to offspring for individuals presenting with bilateral vestibular schwannoma and no identifiable NF2 mutation in blood is ~1 in 8. 2007

Experimental Therapeutics

- Oncolytic, replication-conditional herpes simplex virus vector G47Δ induced tumor regression when injected into subcutaneous schwannomas in mice. 2007
- Sorafenib decreases ERK1/2 and AKT activity and cell proliferation in human schwannoma cells. 2008

Symptom Management

- Clinical trial of auditory midbrain implant for hearing restoration in NF2. 2007

Important Meetings & Symposia

NF2

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2009 → 2009