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Neurofibromatosis Type 1

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INTRODUCTION

In 1882, Friedrich von Recklinghausen described a clinical syndrome characterised by nerve-derived tumours called neurofibromas. This syndrome was subsequently termed von Recklinghausen neurofibromatosis, and is now referred to as neurofibromatosis type 1 (NF1) [1,2]. NF1 has been erroneously referred to as the "elephant man" disease from Sir Frederick Treves' description of Joseph Merrick, an Englishman afflicted with a disfiguring disease with features similar to NF1 [3]. While NF1 gained much publicity and notoriety through this misnomer, it is now widely accepted that Merrick instead had proteus syndrome, and the association of NF1 with the "elephant man" is being discouraged [4]. According to current interpretations of literature and ancient artworks, NF1 has been present throughout history [5] and is one of the most frequently occurring human autosomal dominant diseases (1/3500 individuals). This disease is inherited in an autosomal dominant fashion, is found across all ethnic groups and primarily affects tissues derived from the embryonic neural crest.

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CLINICAL FEATURES OF NF1

Reviews of clinical and pathological findings of NF1, which are briefly summarised below, can be found in various references [2,6–8]. (Biochemical and cell biological analyses of the disorder, mostly done prior to the cloning of the *NF1* gene, are not discussed here but are reviewed in several references [2,9,10]). A NIH consensus panel has established a set of NF1 diagnostic criteria [11], an important accomplishment since currently NF1 can only be diagnosed by clinical examination with there being no biochemical test, and direct DNA diagnosis is not routinely available. Patients are diagnosed with NF1 if they meet two or more of the criteria described below.

NF1 derives its name from one of its more prevalent features, neurofibromas. Most commonly, these benign tumours arise along peripheral nerves (cutaneous form). These tumours often appear in adolescence, and increase is size and number with age and/or hormonal fluctuations, such as pregnancy. The less common, but more serious form is the plexiform neurofibroma, which develops from a deeply placed nerve and may become quite large. While both types are histologically similar, containing primarily Schwann cells, fibroblasts and mast cells, plexiform tumours have an apparent propensity for progression to malignancy (to neurofibrosarcoma, in an estimated 6% or more of NF1 patients [2]). If present in childhood, plexiform neurofibromas may lead to severe disfigurement or functional impairment via overgrowth and local distortion. Two or more cutaneous neurofibromas and/or at least one plexiform type is one diagnostic criterion.

Another commonly-recognised feature is the café-au-lait spot, a lightly-pigmented symmetric area that does not otherwise grossly differ from normal skin and appears in 95% of NF1 patients by adulthood. While it is not unusual for an unaffected person to have one or two such spots, the finding of six or more of diameter $\geq$0.5 cm in a prepubertal child, or $\geq$1.5 cm in a postpubertal individual, is another NF1 criterion. Perhaps related to this, freckling in the axilla or groin is common in NF1 patients, yet is rarely seen in the general population; this finding also represents a diagnostic criterion.

Another useful diagnostic feature in NF1 is the presence of Lisch nodules, tiny hamartomata of melanocytic origin on the surface of the iris, detectable by slit lamp examination. These nodules are functionally benign, and are present in over 90% of adult NF1 patients. The presence of two or more Lisch nodules is an NF1 criterion. Other diagnostic criteria include bone dysplasia (such as absence of sphenoid bone), optic glioma and a first-degree relative (parent, sibling or child) with NF1.

The exact clinical expression of NF1 can vary dramatically (variable expressivity), and a number of less-common features can be found. These include macrocephaly, learning disabilities or outright mental retardation, short stature, scoliosis, seizures, hypertension, pruritus, headaches and malignancy (especially tumours of the central nervous system [2]). While approximately two-thirds of NF1 patients have fairly mild symptoms and are able to live relatively normal lives, the average lifespan in NF1 patients is somewhat reduced overall due to the increased occurrence of malignancy and other complications [2]. Malignancies which appear to have an increased incidence in NF1 patients include phaeochromocytomas, neuronal tumours (including neurofibrosarcoma, also known as malignant schwannoma), rhabdomyosarcomas, and leukaemias [12–17]. Diagnosis in many cases is difficult due to the clinical variability and the progression of symptoms over time (affected children may not officially meet diagnostic criteria until teens or later). In fact, mild cases may go undiagnosed, particularly if the individuals suffer no complications.

GENETICS OF NF1

The hereditary nature of NF1 was not fully recognised until key studies by Borberg [18] and Crowe and associates [19] determined that its mode of inheritance is autosomal dominant. Since there have been a few reports of families in which NF1 has appeared to "skip" generations [20], it has not been entirely clear whether NF1 is fully penetrant. While there are no thoroughly documented cases of non-penetrance in adults, this may reflect the quality of diagnostic evaluation and the adherence to the recently-established diagnostic criteria. The frequency of new mutations also makes it difficult to determine empirically whether the disorder is fully penetrant. Thus, NF1 is generally considered completely penetrant, although the definitive proof will come from molecular studies of the gene itself in suspected non-penetrant families [2,21,22].

NF1 has a very high mutation rate, estimated at 1 per 10 000 alleles per generation, approximately 10-fold higher than most genes [19,23]. The frequency of this disorder, one of the highest among genetic diseases, is probably due to this high mutation rate. In fact, the disease is the result of a new mutation in approximately half of all patients (based on epidemiological studies [2]). One previous hypothesis for this unusually elevated mutation rate was that multiple genes were involved in NF1. However, careful linkage studies in families from all over the world have implicated one specific region at 17q11.2 [24], which was later confirmed by the cloning of a single gene in that region directly related to NF1 [25–27]. An alternate theory is that the mutation rate is due to the large size of the *NF1* gene (see below); this would be in accordance with the Duchenne muscular dystrophy (*DMD*) gene (dystrophin), which is similarly very large with a high mutation rate [28]. Similar to observations in *DMD* and retinoblastoma, linkage studies indicate that the majority of *NF1* mutations arise in the paternal germline [29,30], although this is not apparently related to paternal age.

THE *NF1* GENE AND NEUROFIBROMIN

The *NF1* gene, at 17q11.2, spans about 350 kb of genomic DNA, has 57 known exons, and produces two apparent transcripts (11 and 13 kb, presumably due to different lengths of the 3' untranslated region [31,32]). There are three small genes (whose functions are unclear) embedded within intron 27b, encoded on the opposite strand [33]. Two of these are predominantly lymphoid-specific genes, and the other is evidently involved in myelination. It is unknown whether these genes have any involvement in the NF1 phenotype. The *NF1* mRNA encodes a 2818-amino acid 250-kD hydrophilic protein (neurofibromin), which appears to associate with microtubules [34] and is enriched in the endoplasmic reticulum of neurons [35]. Neurofibromin is apparently present in virtually all tissues, however antibody studies have shown that it is present in greatest abundance in neurons, Schwann cells and oligodendrocytes [36–38].

The middle eighth of the molecule (encoded by exons 21–27b) shows strong homology to GTPase-activating proteins (GAPs) [39,40]. These include the mammalian $p120^{gap}$ protein and the homologous yeast proteins ira*1* and ira*2*. GAPs are at least partly responsible for keeping ras proteins, which play a crucial role in cell proliferation, in a GDP-bound, inactive state [41]. Several groups have shown that the homologous region of neurofibromin can function as a GAP both *in vitro* and *in vivo* [42–44], but it is

clearly not the only GAP-like protein regulating ras [45]. Studies showing that NF1 neurofibrosarcoma cells lack functional neurofibromin support the idea that neurofibromin may be a negative regulator of ras in neural-crest-derived tissues [46,47]. However, another study has shown normal GAP activity in melanoma and neuroblastoma cell lines (presumably due to the $p120^{gap}$), in spite of a lack of neurofibromin, suggesting that regulation of ras is not the only function for neurofibromin [48]. Neurofibromin's exact regulatory role in this signal transduction pathway is probably quite complex, as indicated by studies which have shown that when neurofibromin is bound to tubulin (in keeping with the microtubule association above), it has diminished GAP activity [49] and that alternatively spliced isoforms appear to have somewhat different distributions, levels and GAP activities (see below). The function of other regions of neurofibromin are probably significant because the overall gene structure and segments of the protein sequence have been highly conserved [50,51].

Two alternatively spliced products are known; in one case the alternative exon, 23a, near the middle of the gene in the GAP-related domain, encodes a 21-amino acid sequence that is perfectly conserved across many species [52]. Tissue specificities or functions for neurofibromin containing this peptide are not entirely clear, but both forms seem to be present in most adult tissues; there are a number of studies pursuing its involvement in development and tumorigenesis [52–55]. The inclusion of this small peptide slightly decreases the GAP activity of the molecule, although this form has higher affinity for ras-GTP [31,56]. Another alternatively spliced exon, 48a, encodes 18 amino acids very near the carboxyl end of the molecule [26]. One study suggests that this version of neurofibromin may be involved in muscle cell development [57].

It is feasible that segments of neurofibromin may have different roles in different tissues, based on the observed variable expression, alternative splicing, and lack of abnormal phenotype in some tissues. Neurofibromin may also have different expression levels and roles in various developmental stages [36,58]. Gutmann and associates [36] also suggested that, given the ubiquitous expression of the *NF1* message, defects in only certain tissues of NF1 patients could be explained by one or more of several possibilities. Neurofibromin may, (1) normally be required at significantly higher levels and have a more crucial role in affected tissues (i.e. dosage effect), (2) be post-translationally modified in a tissue-specific manner and/or (3) associate with other signal transduction molecules that are expressed specifically in these tissues.

NF1 GERMLINE MUTATIONS

A number of groups have been analysing NF1 patient constitutional DNA and RNA for *NF1* gene mutations. This search has proven difficult due to several factors: (1) the large size of the gene, (2) the presence of the normal allele, (3) the high mutation rate and subsequent different mutations in most families, (4) wide variation in the size and type of mutations (from complete deletion of the locus to missense point changes), which require a number of detection methods and (5) several known homologous loci on other chromosomes which can interfere with Southern blot and PCR analyses [59]. In addition, each abnormality must be characterised to exclude functionally normal polymorphisms/variants.

Reported germline *NF1* mutations, numbering approximately 45, include single base substitutions, deletions of all sizes including the entire locus, insertions, splicing errors, and two translocations [26, 27, 60–84]. All of the mutations, except four encoding amino acid substitutions [26, 71, 80] and one 6 bp in-frame deletion [60], are predicted to result in premature translational truncation, and are thus clearly disease-related. It is not obvious whether there is a functional effect from three of the four amino acid changes, thus these could be rare normal variants. The other amino acid change lies at the conserved Lys 1423 residue in the GAP-related domain (exon 24). One constitutional missense mutation was found at this codon, with the resulting neurofibromin molecule shown to have reduced GAP activity [71] and thus it is likely to be a disease-related mutation.

As more mutations are characterised, questions regarding the presence of mutational hot spots and the possible correlation of characterised mutations with specific phenotypes (which may suggest heretofore unknown functions for the *NF1* gene product) can be addressed. No *NF1* mutational hot spots have yet been discerned, although the occurrence of an identical nonsense mutation in several unrelated individuals has been reported [26, 61, 64, 66]. All of these patients have a C→T transition at the same nucleotide in exon 31, changing an arginine codon to a stop codon. This observation suggests that this site, which is part of a CpG dinucleotide, may represent a mutational hot spot, however, mutations at this locus occur relatively infrequently, and no genotype–phenotype correlations have been inferred. One might expect that C→T transitions at CpG dinucleotides would be more common in mutations of paternal origin, due to methylation differences during gametogenesis [85], but it remains to be seen if this holds true for NF1. The involvement of the *NF1* gene in other genetic disorders that phenotypically overlap NF1 is also under study (including the NF-Noonan syndrome [86]) and an *NF1* deletion has recently been discovered in a Watson syndrome patient, indicating that this disorder is allelic to NF1 [80]. Overall, because of the difficulty of mutation analysis, direct DNA analysis of NF1 is not currently used diagnostically. However, due to development of a number of polymorphisms within the gene, linkage analysis for DNA diagnosis in families with a history of NF1 is quite feasible and accurate.

THE *NF1* GENE AND NEUROFIBROMIN IN BENIGN AND MALIGNANT TUMOURS

Tumour suppressor hypothesis

Virtually all reported *NF1* mutations are predicted to disrupt or inactivate neurofibromin. Because its inactivation is associated with excessive proliferation of certain cell types (part of the NF1 phenotype) and part of its function is involved with regulation of the ras pathway, the *NF1* gene has been hypothesised to be a tumour suppressor gene [88]. Tumour suppressor genes encode proteins that participate in the negative regulation of growth-promoting genes/proteins, and their mutation or "knock-out" is associated with cancer [89]. It has been hypothesised that both alleles of tumour suppressor genes are inactivated in tissues where neoplasms arise [90,91]. The suggestion is that one allele is constitutionally inactivated since it is an inherited mutation from a parent, and the other allele is subsequently inactivated (a second hit) via mutation at the somatic level. This has been demonstrated for other inherited cancer syndromes, such as retinoblastoma [92] and familial adenomatous polyposis [93]. In theory, since neurofibromin presumably acts to downregulate cell growth, lack of this protein due to knockout would result in an increased rate of cell division. It is unclear, however, whether the symptoms of NF1 (benign and/or malignant) are due to such

a second mutation, or whether heterozygous cells can overproliferate under certain circumstances in the presence of (1) a reduced amount of functional neurofibromin (dosage effect) or (2) abnormal activity specific to a mutant molecule (dominant negative effect). The clinical variability within families could be explained by either a complex genetic/environmental process or random somatic mutation controlling the progression and severity of the disease. Discussed below are the major lines of evidence supporting the tumour suppressor role of the *NF1* gene.

NF1 *Mutations/loss of heterozygosity in malignant tumours*

Loss of heterozygosity (LOH) is the detected loss of one allele in the tumour DNA as compared to blood or other control tissue DNA of a patient who is constitutionally heterozygous at the locus being examined. This phenomenon is commonly seen at tumour suppressor loci or occasionally for entire chromosomes in tumour DNA. LOH has been observed in the *NF1* gene region in a number of tumours in NF1 patients, but is not a universal phenomenon. Menon and associates [94] found LOH in five of six neurofibrosarcomas, however, the common deleted region was 17p, not 17q. Glover and colleagues [95] found LOH for most or all of chromosome 17 in two of nine malignant NF1 tumours, including the *NF1* region, with 17p loss only in an NF1 glioblastoma. Three of the other tumours apparently did not lose the *NF1* region with the others uninformative. A later study revealed a 200-kb deletion involving a 3' half of the *NF1* gene in one of those tumours that had lost the other chromosome 17 homologue, supporting the tumour suppressor hypothesis [96]. Lothe and colleagues [97] also reported loss of a chromosome homologue in an NF1 malignant schwannoma. In a series of seven NF1 phaeochromocytomas, all showed LOH with markers flanking the *NF1* gene (and in some cases, losses on other parts of chromosome 17), and the authors showed that in three out of three of these tumours, the lost allele was the normal allele (did not contain the inherited *NF1* mutation)[98]. Western blot anlaysis later showed that all of those tumours, as well as several other adrenal gland tumours, lacked neurofibromin [99]. Knockout of the *NF1* gene has been seen in some neuroblastomas [100], but ras-GTP levels are not greatly increased in these cell lines, and GAP activity is normal in at least some such lines with *NF1* knockouts [48], suggesting that neurofibromin must have additional functions related to cell cycle control. Two of eight melanoma cell lines studied by Andersen and associaties [101] showed loss of *NF1* (one by homozygous deletion, the other by RNA and protein assays); the other six lines showed little or no decrease in *NF1* message or protein. In a series of six children with NF1 and malignant myeloid disorders, five showed LOH of the normal *NF1* allele in their bone marrow (tumour cells); losses did not include 17p [102]. This last point is important in that LOH is sometimes indicative of the loss of an entire chromosome 17 homologue (which would include the loss of other potent tumour suppressor genes such as *TP53* on 17p [103] and *BRCA1* on 17q [104]. Thus, while observation of *NF1* LOH is supportive of the two-hit hypothesis, one cannot discount the possibility that LOH at the *NF1* gene is a secondary or coincidental event if large segments of the rest of the chromosome are missing. Similarly, the failure to find LOH does not rule out inactivation of the *NF1* gene by other genetic means.

The studies mentioned above support the likely involvement of the *NF1* gene in cancer progression in both NF1 and non-NF1 patients, but do not fully address the tumour suppressor hypothesis as an explanation for the benign NF1 features. In NF1, one can hypothesise that losses of neurofibromin in neural crest-derived cells (e.g. Schwann cells, nerves, cartilage, melanocytes) could result in the symptoms. While one hypothesis is that neurofibrosarcomas in NF1 patients arise from progression of plexiform neurofibromas, there is no report of malignant transformation of cutaneous neurofibromas, café-au-lait spots, or Lisch nodules. Thus, it is possible that only malignancies are associated with a second mutation at the *NF1* locus and that other events cause the benign features. In contrast, it is possible that second *NF1* mutations are responsible for the benign features and that further genetic events cause full transformation. Investigation into the question of the two-hit hypothesis in neurofibromas, the most common NF1 tumours, is therefore important since it addresses not only the basic mechanism behind the genesis of neurofibromas, but may also elucidate a mechanism common to many or all NF1 features. Neurofibromas apparently do not arise due to gross genetic changes, as these tumours are cytogenetically normal or fail to show chromosomal abnormalities consistent in multiple tumours [95,105]. A recent study of primary tissue suggested that neurofibromas are monoclonal in origin, and can be studied at the genetic level in spite of minor contamination from normal cells in the preparation [106]. Previous LOH studies in neurofibromas failed to indicate loss in the general *NF1* region, however, those studies used flanking linked markers and did not include polymorphisms within the *NF1* gene [106,107]. Our laboratory has preliminary LOH data indicating somatic deletions in just the *NF1* gene region of the maternal allele in several cutaneous neurofibromas from a single NF1 patient, supporting the notion that inactivation of the *NF1* gene alone may be sufficient to promote neurofibroma formation (Colman and Wallace, unpublished data). Further to this hypothesis, one would expect each tumour to have an independent second mutational event, which may or may not be a large deletion (thus not necessarily evidence in LOH studies). In fact, some of the tumours from this patient do not appear to show LOH, although interpretations must also take into consideration the quantity of contaminating normal tissue.

Neurofibromin expression in malignant tumours

Recent reports implicate abnormal neurofibromin levels or GAP activity in malignancies in patients with or without NF1. A study by Li and colleagues [71] described two missense mutations in three different tumour types in the Lys 1423 codon of a highly conserved *NF1* exon (exon 24) crucial to GAP function (the status of the other *NF1* allele was unknown in each case). One such missense mutation, found in a non-NF1 astrocytoma, was shown to impair *in vitro* GAP activity of the resulting neurofibromin. In that study, the *NF1* gene was implicated in three of 60 malignancies (colon cancer and a myelodysplasia, in addition to the astrocytoma) in which this single exon was screened. Two other studies also showed decreased neurofibromin levels and abnormal ras regulation (decreased GAP activity) in NF1 neurofibrosarcomas [46,108]. Another NF1 neurofibrosarcoma line that is missing an entire chromosome 17 homologue showed a dramatically decreased level of *NF1* mRNA, suggesting that the remaining allele contains an *NF1* mutation (presumably the constitutional mutation)[109]. Several groups are also studying the involvement of the alternatively-spliced GAP-related domain isoforms of neurofibromin in tumour development; Suzuki and colleagues [110] detected apparent preferential expression of neurofibromin type II (contains the 21 amino acid insertion) in non-NF1

brain tumours, while Uchida and colleagues [111] report no differential expression between the isoforms in non-NF1 gastric cancers (although type II predominated in normal stomach mucosa). Thus, abnormal distribution of the isoforms may affect one or more of neurofibromin's function(s) and contribute to tumorigenesis. Two groups have also analysed the effect of overexpression of neurofibromin by transfection studies in NIH 3T3 cells. One laboratory found that overexpression in oncogenic-ras-transformed cells virtually eliminated the ability of the cells to form soft agar colonies (reversal of a property of malignant cells), and they suggested that results obtained from deletion mutants indicated that a 91-residue stretch (amino acids 1441–1531) is the crucial region for ras binding, although by itself this region had a much weaker GAP activity [112]. Similarly, Johnson and associates [113] found that: (1) NIH 3T3 cells overexpressing neurofibromin grew significantly more slowly although the level of GTP-bound ras did not change, (2) ras transformation was drastically inhibited in NIH 3T3 cells overexpressing neurofibromin, and (3) introduction of neurofibromin expression in melanoma cell lines (deficient in neurofibromin) inhibited their growth and induced differentiation. These and the studies mentioned above together provide a convincing argument that *NF1* is a tumour suppressor gene whose protein product has ras-regulating ability and can also inhibit cell growth by an independent mechanism(s).

Based on the finding of the Lys 1423 point mutations (at least one of which had abnormal GAP function) in several tumours [71], several groups have studied this and other neurofibromin GAP-related domain residues by mutagenesis. A Lys-to-Met mutation at 1423 appeared to reduce the thermal stability of the GAP-related domain, thereby imparting a variable effect on its activity in the assays [114]. Nakafuku and colleagues [115] created two *NF1* GAP-related domain variants (Phe to Leu at residue 1434; Lys to Arg at residue 1436) whose resulting proteins not only maintained ability to inactivate normal ras, but were also able to suppress the phenotype from oncogenic versions of ras in yeast, an ability not held by normal neurofibromin. These variants were able to induce the morphological reversion of ras-transformed NIH 3T3 cells, further supporting the potential role of neurofibromin in cell cycle control. Poullet and colleagues [116] tested the effect of a number of other amino acids at Lys 1423 via GAP and yeast IRA-deficient complementation assays; they found that only the original Lys produced functional neurofibromin, while the other mutants had a much lower GTP-ras affinity. They also verified that the 1434 residue is important, as substitutions at that site were able to compensate for the Lys 1423 mutations and suppress oncogenic ras activity. A further study tested various GAP-related domain substitutions (including one at 1423) and found that some conferred reduced abilities to negatively regulate ras in yeast, while others had no effect or intermediate effect [117]. Together, these studies suggest that multiple amino acids in neurofibromin participate in its GAP activity, and that these residues affect complex interactions in the ras and perhaps other regulatory pathways.

CONCLUSIONS

Much still remains to be discovered about the structure, interactions, regulation and functions of full-length neurofibromin. Since the cloning of the *NF1* gene in 1990, a great deal has been learned about the genetics and biology of this disorder, although the current data only scratch the surface of what remains to be learned. The gene structure is still not completely determined; new exons are still being discovered and the structure/extent of the 3' untranslated region has yet to be reported. There may be additional alternative splices or internal promoters which could add to the variety of forms of neurofibromin (as has been recently discovered for dystrophin), and which might subsequently reveal developmental- or tissue-specific regulation and functions. Direct mutation analysis in NF1 is among the most difficult for any genetic disorder, with most laboratories currently having only a 10–15% success rate in detection after relatively detailed searching. Yet, the accumulation of mutational data could reveal functional domains, correlations between clinical features and DNA alterations, differences (if any) between NF1 arising maternally versus paternally, and involvement of the *NF1* gene in other genetic disorders. Any indication of mutational hot-spots or mechanisms will have immediate application in direct DNA diagnosis. Accumulated data may also resolve the issue of complete penetrance, and will help fully prove the tumour suppressor hypothesis for NF1. Clearly, the data from the last several years provide very strong evidence that neurofibromin is a tumour suppressor, and is probably involved in multiple tumour types. Many resources, including genomic and cDNA probes, polymorphism information and antibodies are now available to answer remaining questions in NF1 research. Investigators in numerous fields are now studying the *NF1* gene and protein, particularly with regard to cancer. Perhaps most importantly, advances in this field will ultimately result in the development of diagnostic tests and therapies for NF1, which may have application in general cancer therapy.

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Neurofibromatosis Type 2

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INTRODUCTION

TEN NEW cases of vestibular schwannomas per million inhabitants are being diagnosed each year [1, 2]. Because of its development in proximity of the cochlear branch of the eighth pair of cranial nerves, this tumour, which remains constantly benign, is a major cause of hearing loss. Close to 95% of patients with vestibular schwannomas will develop only a single schwannoma during their life time. However, for about 5% of affected patients, tumours will develop bilaterally. This bilateral development is the consequence of a genetic disease called neurofibromatosis type 2. Epidemiological studies stuggest that one person in 35 000 might be affected [3]. Here we summarise our present knowledge of this disease.

CLINICAL MANIFESTATIONS

The neurofibromatoses are autosomal dominant diseases, characterised by a predisposition to the development of nervous system tumours. They were long regarded as a single disease which could manifest with a large variety of symptoms. Currently, however, two forms of neurofibromatoses have been established. Neurofibromatosis type 1 (NF1) occurs with an incidence of 1/3000 and predisposes mainly to the development of peripheral neurofibromas, pheochromocytomas and optic nerve gliomas [4]. Alterations in a single gene localised on chromosome 17 have been shown to be causative in this disease [5] and its genetics are reviewed by Colman and Wallace in this issue. Neurofibromatosis type 2 (NF2), previously called central neurofibromatosis or bilateral acoustic neurofibromatosis (BANF), is approximately 10 times less frequent [3], and its main manifestations are clearly distinct from those of NF1.

Vestibular schwannoma is the major manifestation of the NF2 disease, being found bilaterally in 85% of gene carriers at disease onset [3, 6]. Most commonly it develops in close contact with the vestibular branch in proximity to the cochlear branch of the 8th pair of cranial nerves. The danger of this tumour arises from its development in the intracanalicular space, and subsequently in the posterior fossa; volumes that are strictly confined by bone structures. Therefore, increase in tumour volume causes progressive compression of the 8th pair of cranial nerves causing loss of hearing and tinnitus, and may later lead to compression of vital structures of the central nervous system. Less frequently, schwannomas develop in other locations, in particular in contact with the 9th cranial nerve or with spinal nerves. They may also develop from peripheral nerves and, when superficially located, can manifest as small, subcutaneous, well circumscribed tumours. The most frequent dermatological manifestations, however, are discrete hairy macules which are observed in 50%, of patients. Neurofibromas are also observed in a quarter of the patients. In contrast to NF1 patients, NF2 patients do not develop plexiform neurofibromata. Other nervous system tumours predisposed by NF2 are meningiomas, which develop in half the patients and, less frequently, ependymomas. The only non-tumoural manifestations of the NF2 disease are restricted to the eye. Indeed, the presence of opacities located centrally in

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