

## What is Schwannomatosis?

Schwannomatosis is a recently recognized third form of neurofibromatosis, in addition to NF1 and NF2. Schwannomatosis shares many features with the better-known forms of neurofibromatosis, however, current evidence suggests that it is a distinct genetic disease, separate from *NF1* and *NF2*. Multiple schwannomas, or tumors of nerve sheaths, are seen in schwannomatosis, but *not* the characteristic vestibular (ear nerve) tumors seen in NF2.

Some have estimated the prevalence of schwannomatosis to be similar to NF2; about 1 in 40,000 births. Estimation is difficult, because many people may have been misdiagnosed with NF2 or other nerve tumor disorders.

Patients with schwannomatosis develop tumors on the sheaths, or coverings, of their nerves. They do not develop vestibular tumors, as patients with NF2 do. Once a person is found to have multiple schwannomas, NF2 must be ruled out as a diagnosis before the diagnosis of schwannomatosis may be established. In an older person with no hearing loss, NF2 is an unlikely diagnosis. In a younger person, a high quality MRI scan of the base of the skull must be done to exclude the vestibular tumors of NF2 [INSERT “small bvs arrows”, right image]. There is currently no blood test to rule in or rule out the diagnosis of schwannomatosis.

Patients affected by schwannomatosis usually have problems with pain related to their tumors, though they usually do not experience neurologic disability. As with NF1 and NF2, the severity of the disease varies greatly between individuals. Generally, patients experience their first symptoms of schwannomatosis as adults.

The tumors of schwannomatosis are relatively slow growing. In approximately one-third of patients, tumors are limited to a single part of the body such as an arm, leg, or segment of the spine. Neurofibromas and malignant peripheral nerve sheath tumors, which are seen in NF1, are not seen in schwannomatosis. Patients with schwannomatosis do not have learning disabilities related to the disease. There is no evidence that schwannomatosis decreases life span.

An International Concensus Conference in 2003 yielded standards for diagnosis and evaluation of schwannomatosis, which were revised and recommended as diagnostic criteria by MacCollin et al (2005).

The International Concensus Conference of 2003 recommends no set schedules of tests that all patients should undergo. Yearly complete physical and neurological evaluation is recommended, with special attention to symptoms of pain and its effect on daily life. The tumors of schwannomatosis need only to be imaged when symptoms change, or when a tumor which threatens the spinal cord has been identified and is being followed closely. Surgical removal of painful tumors is often quite effective, especially in the early course of the disease. Pain often subsides when a tumor is fully removed, though new, painful

tumors may form. When surgical intervention is not helpful, management by a multidisciplinary pain clinic is advised for best possible outcome. [INSERT tables on initial diagnosis and follow up.]

Studies of multiple schwannomas removed from patients with schwannomatosis have shown that these tumors are caused by *NF2* gene inactivation, but that each tumor has a DIFFERNT mutation: This is in contrast to multiple schwannomas removed from NF2 patients, which do share a common constitutional mutation. This is a remarkable pattern, which has never been seen in any other human disease, and has yet to be explained. Linkage analysis in families with schwannomatosis has placed the genetic location near the *NF2* gene, on chromosome 22q.

Schwannomatosis is a genetic condition, but for poorly understood reasons its occurrence does not follow the common inheritance patterns. In some families, a clear autosomal dominant inheritance pattern of transmission is seen, but most patients with schwannomatosis have no affected relatives. When the disease is inherited within a family, it is often not seen in every generation, unlike NF1 or NF2. The risk of transmission to offspring from a sporadic affected individual (with no family history) is approximately 15%, which is far less than the 50% risk seen in NF1 and NF2. Unfortunatel, at the current time neither molecular genetic testing nor prenatal diagnosis is available to diagnose the condition.

Reference:

MacCollin, M; Chiocca, E.A.; Evans, D.G.; Friedman, J.M.; Horvitz, R.; Jaramillo, D.; Lev, M.; Mautner, V.F.; Niimura, M.; Plotkin, S.R.; Sang, C.N.; Stemmer-Rechamimov, A.; Roach, E.S. (2005). Diagnostic criteria for schwannomatosis. *Neurology*, 64, 1838-1845).

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## **Proposed Diagnostic Criteria for Schwannomatosis**

### **DEFINITE**

Age over 30 years and no evidence of vestibular tumor on high quality MRI scan, no known constitutional NF2 mutation and two or more non-intradermal (within or between layers of the skin) schwannomas, at least 1 with histologic confirmation

*Or*

One pathologically confirmed non-vestibular schwannoma plus a first-degree relative who meets above criteria

### **POSSIBLE**

Age under 30 years and otherwise meeting criteria for definite schwannomatosis

*Or*

Age over 45 years and two or more non-intradermal schwannomas, at least one with histologic confirmation and no symptoms of 8<sup>th</sup> nerve dysfunction and no known constitutional NF2 mutation

*Or*

Radiographic evidence of a schwannoma and first degree relative meeting criteria for definite schwannomatosis

### **SEGMENTAL**

Meets criteria for either definite or possible schwannomatosis but limited to one limb or five or fewer contiguous segments of the spine.