NF2-related Schwannomatosis: from epidemiology through genotype-phenotype to targeted treatment

Evans D Gareth MD FRCP

Department of Genomic Medicine, St Mary's Hospital, Manchester Academic Health Sciences Centre (MAHSC), Division of Evolution and Genomic Science, University of Manchester, Manchester, UK. Disclosures:

NF2-related schwannomatosis (NF2) was first described by Wishart in 1822, but because Harvey Cushing conflated the cardinal feature of NF2 (bilateral vestibular schwannoma) with von Recklinghausen disease (NF1) at the turn of the last century the two conditions were not formally separated until NIH consensus meeting in 1986. The condition is also characterized by schwannomas on other cranial, spinal and peripheral nerves as well as within the skin. Cranial and spinal meningiomas and ependymomas also occur and ophthalmic features such as juvenile cataracts, retinal hamartoma and epiretinal membranes are also helpful diagnostically. The Manchester criteria were devised in 1992 as an improvement to NIH criteria and have now been recently updated (Genet Med. 2022). An updated UK prevalence has been generated with an emphasis on the rate of *de novo* NF2 (50% rate is widely quoted). The UK National NF2 database identifies patients meeting updated NF2 criteria from a highly ascertained population cared through England's highly specialized commissioned 4-centre NF2 service. Diagnostic prevalence was assessed on 01/02/2023.

A total of 1082 living NF2 patients were identified on prevalence day (equivalent to 1 in 61,445 but 1 in 58,000 in England). The table details the rates of *de novo*, familial and mosaic NF2. The proportion with inherited NF2 from an affected parent was only 23% in England. If those without a confirmed molecular diagnosis or bilateral

	Popu-lation (millions)	NF2 patients living	Prevalence per 1000	1 in x	Hetero-zygotes	Familial	%familial of total living	*de novo*	Mosaic	%mosaic of *de novo*	Hetero-zygote, proven mosaic, or BVS	%familial
England	56.00	960	0.01714	58331	415	222	23.1	738	204	27.6	787	28.2
Wales	3.14	50	0.01594	62720	22	12	24.0	38	9	23.7	44	27.3
Scotland	5.45	51	0.00936	106863	21	6	11.8	37	14	37.8	43	14.0
N Ireland	1.90	21	0.01105	90476	14	5	23.8	16	3	18.8	21	23.8
Total	66.48	1082	0.01627	61445	472	245	22.6	831	230	27.7	895	27.4

vestibular schwannoma (BVS) are excluded, the rate of *de novo* NF2 remains high (72%). This work confirms a far higher rate of *de novo* NF2 than previously reported, and highlights the benefits of maintaining patient databases for accurate counselling.

Genotype-phenotype correlations can be seen from this recent update with truncating variants in exons 2-13 causing the most severe disease with reduced genetic fitness as evidenced by the low birth rates in affected people with these variants. Copy number and splicing variants that do not lead to a truncated protein are intermediate with missense variants causing the mildest disease.

Inception of England's highly specialized commissioned 4-centre NF2 service in 2010 has led to improved survival at least in part due to targeted treatment with the VEGF antibody bevacizumab.

Forde C,[1] Bowers NL[1] Roberts N,[1] Burghel G,[1] King AT,[2] Lloyd SKW,[3] Rutherford SA,[2] Hammerbeck-Ward C,[2] Pathmanaban ON [2], Freeman SR,[3] Lavin T[4] Laitt R,[2#] Thomas O,[2#] Halliday D,[5] Afridi S,[6] Taylor A[7], Duff C,[8] Smith MJ[1]