CORRESPONDENCE

Update on the Manchester Scoring System for *BRCA1* and *BRCA2* testing

We recently published a new scoring system to estimate the chance of identifying mutations in the *BRCA1* and *BRCA2* genes (table 1).[1] A potential criticism of the original paper was that not all cases were fully screened for mutations in both *BRCA1* and *BRCA2*. We have now extended our analyses to address this. In total, we have screened 921 samples from familial breast cancer pedigrees from the Manchester region through the whole coding sequence and intron/exons boundaries of both genes. In addition, 200 cases, with all cases with a Manchester combined score for *BRCA1* and *BRCA2* of 40 or above, were screened for exonic deletions/duplications by multiplex ligation dependent probe amplification (MLPA). These analyses resulted in the identification of 206 (22.5%) intragenic mutations and nine (4.5%) exonic deletions or duplications (tables 2 and 3).

Table 2 shows that the 10 point Manchester score for a 10% threshold for each gene holds up well. The results for *BRCA1* are presented with and without *BRCA2* positive families with male breast cancer. Similarly, the results for *BRCA2* are presented with and without *BRCA1* positive families with ovarian cancer. These data allow one to estimate the likelihood of identifying a mutation in the gene screened second. For example, a breast/ovarian cancer family with a score of 28 for *BRCA1* and 22 for *BRCA2* has a 58% chance (column 3, table 2) of harbouring a *BRCA1* mutation. If *BRCA1* screening in the family is negative, the chance of identifying a *BRCA2* mutation is 57% (column 5, table 2). The overall chance of a *BRCA2* mutation in such a family prior to testing *BRCA1* is therefore 24% (57% of 42%, the remainder of 100%–58%). The overall chance of a mutation in either gene is 82% (58%+24%). A similar process could be undertaken for families with male breast cancer.

As can be seen from table 3, a combined Manchester score of 15 is the cut off for a 10% threshold for *BRCA1/2* testing. The cut off for a 20% threshold is less clear. Families with scores >20 would definitely qualify and those with scores of 17 points or above could reasonably be tested. It can be assumed that virtually all families with scores of 40 or above are due to either *BRCA1* or *BRCA2*, although not all will have identifiable *BRCA1/2* abnormalities as the sensitivity of gene testing is not 100% even with full gene screening and MLPA.[2] Moreover, the pathogenicity of unclassified variants (which were not included in our analyses) remains unclear.

Table 1 Manchester scoring system

	BRCA1	*BRCA2*
FBC <30	6	5
FBC 30–39	4	4
FBC 40–49	3	3
FBC 50–59	2	2
FBC >59	1	1
MBC <60	5 (if *BRCA2* tested)	8
MBC >59	5 (if *BRCA2* tested)	5
Ovarian cancer <60	8	5 (if *BRCA1* tested)
Ovarian cancer >59	5	5 (if *BRCA1* tested)
Pancreatic cancer	0	1
Prostate cancer <60	0	2
Prostate cancer >59	0	1

Scores are added for each cancer in a direct lineage. FBC, female breast cancer; MBC, male breast cancer.

Table 2 Proportion of families with pathogenic mutations for each Manchester score range

	BRCA1	*BRCA1**	*BRCA2*	*BRCA2*†
30+	15/19 (79%)	15/18 (83%)	3/9 (33%)	3/3 (100%)
25–29	7/14 (50%)	7/12 (58%)	5/11 (45%)	5/6 (83%)
20–24	19/45 (42%)	19/42 (45%)	8/28 (30%)	8/14 (57%)
15–19	28/80 (35%)	28/75 (37%)	21/74 (28%)	21/57 (37%)
12–14	19/120 (16%)	19/118 (16%)	20/120 (17%)	20/103 (20%)
10–11	12/119 (10%)	12/117 (10%)	21/140 (15%)	21/125 (17%)
8–9	4/163 (2.5%)	4/163 (2.5%)	14/180 (8%)	14/175 (8%)
<8	3/360 (0.9%)	3/360 (0.9%)	7/359 (2%)	7/359 (2%)
Total	107/921 (11.5%)	107/906 (11.8%)	99/921 (10.5%)	99/842 (11.7%)

*Excluding male breast cancer families with *BRCA2* mutations (n = 15); †excluding ovarian cancer families with *BRCA1* mutations (n = 79).

Table 3 Proportion with mutations using the combined *BRCA1/2* score

	BRCA1	*BRCA2*	Combined
40+	34 (63%)	12 (23%)	46/54 (85%)
35–39	10 (31%)	9 (28%)	19/32 (59%)
30–34	12 (27%)	13 (29%)	25/45 (56%)
25–29	20 (21%)	16 (17%)	36/95 (38%)
20–24	19 (13%)	20 (14%)	39/143 (27%)
15–19	9 (5%)	24 (12%)	33/199 (17%)
19	4	2	6/24 (25%)
18	4	6	10/67 (15%)
17	0	7	7/27 (26%)
16	1	7	8/63 (12.5%)
14	0 (0%)	3 (3.5%)	3/85 (3.5%)
12	2 (2.5%)	1 (1%)	3/80 (3.5%)
0–14	2 (0.5%)	6 (1.5%)	8/353 (2%)
Total	107/921 (11.5%)	99/921 (11%)	204/921 (22.5%)

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References

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2 **Evans DGR**, Bulman M, Young K, Gokhale D, Lalloo F. Sensitivity of *BRCA1/2* mutation testing in 466 breast/ovarian cancer families. *J Med Genet* 2003;**40**(9):e107.