Spinal Muscular Atrophy Genotype Probability Calculator: Usage Notes

Spinal Muscular Atrophy Genotype Probability Calculator (SMAGPC) (http://www.genecalcs.weebly.com/smagpc.html) is designed to calculate a subject's probability of having any one of 10 possible broad genotypes for the *SMN1* gene. These probabilities are calculated based on specifiable family history information and genetic testing results. It is particularly useful for the calculation of residual carrier risk following dosage testing for the *SMN1* gene. Information on the clinical status, *SMN1* dosage status, and genotype (whether unknown, partially known, or completely known) can be specified for the subject, his or her siblings, nieces, and nephews; parents; half siblings, nieces, and nephews; grandparents; and aunts, uncles, and cousins. Information can be specified for up to 10th degree relations. It is hoped that SMAGPC will account for the vast majority of scenarios encountered in a clinical genetics setting.

The assumptions box allows users to adjust the calculator parameters in accordance with the ethnicity of the subject. Users can edit the assumed population prevalence of SMA (thereby adjusting the overall mutation frequency), and the relative population proportions of the two types of normal (single:two copies) and mutant (deletion:point mutation) alleles. By default, these assumptions are set as a population prevalence of 1 in 10,000 individuals, with two *SMN1* copies accounting for 4% of normal alleles, and point mutations accounting for 2% of mutant alleles. Please note that SMAGPC currently assumes that both parents of the subject are of the same ethnicity (or at least of ethnicities with identical allele frequency profiles). Therefore, unless at least one parent has a fully, or near fully, characterised genotype (i.e. no '*?*' alleles reliant on population frequency), it is recommended that SMAGPC is not used in scenarios where the subject is of mixed ancestry.

In this calculator, alleles are denoted as follows: *1* = 1 normal *SMN1* copy, *2* = 2 normal *SMN1* copies, *0* = No *SMN1* copies (i.e. a deletion mutation), *pt* = *SMN1* point mutation, and *?* = any allele that is compatible with the stated clinical status and / or dosage status (i.e. allele unknown). The subject's and relations' clinical status' are specified as either '*unknown*', '*unaffected*', or '*affected*'. A clinical status of '*unknown*' means that the calculation will allow the relevant family member's possible genotypes to include affected genotypes (i.e. 0 / 0, 0 / pt, or pt / pt), as well as unaffected genotypes (i.e. carrier and non-carrier genotypes). For the most accurate calculation, intervening relatives' clinical status should be specified as '*unaffected*' where this is known to be true. This is in contrast to a common (but slightly less accurate) practice when undertaking calculations manually to assume that the chance of having inherited a mutation from a distant parent is 0.5^n, where *n* is the genealogical distance in degrees. This common practice assumes, often against knowledge, that intervening relatives *may* have been affected.

To input a specific relation, the calculator requires the genealogic distance in degrees to be specified relative to the subject. For example, a 'great grandparent' would be a genealogic distance of three degrees relative to the subject. For aunts, uncles, and cousins, and siblings, nieces and nephews, the genealogic distances to common parents relative to both the subject and the relation are required. For example, to specify a first cousin, the common parents are the grandparents of both the subject and the cousin, so genealogic distance relative to the subject is two degrees, and genealogic distance relative the relation (i.e. the cousin) is also two degrees. Refer to Appendix 1 for a hypothetical example of how a rather complex pedigree can be specified in the calculator.
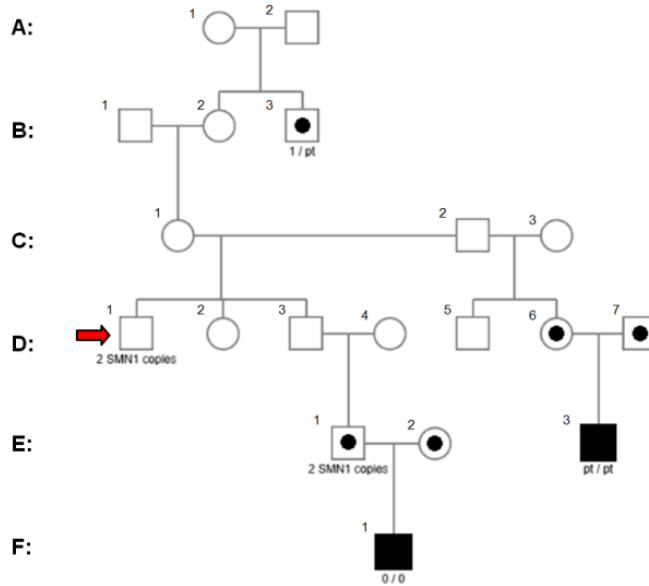
When specifying relevant family history, a good rule of thumb, where possible, is to specify the genealogically closest relative(s) for whom the full genotype is known. For example, if the subject has an affected niece or nephew, but the subject's sibling (the niece or nephew's parent) is known to have 1 *SMN1* copy, it is more informative to specify the sibling as a relation rather than the niece or nephew.

Please note that whilst every effort has been made to ensure this calculator is error-free, this cannot be 100% guaranteed. Therefore, results should always be verified by users own calculations. This is particularly important where the results are to be used in a clinical setting.

Please contact the author if you notice any errors, have any questions, or would like to query a result.

Appendix 1: Input of a Pedigree into SMAGPC: A Hypothetical Example

Details (including clinical status, MLPA result, and genotype) of the subject, his / her parents (i.e. Mother and Father), and any other class of relation are inputted into specific sections, as shown in the screenshot below. Please note that the green 'Maternal Family History' and 'Paternal Family History' sections should only be used for relatives that are specific to the mother *or* the father's side of the family; they should *not* be used for relatives that are genetically related to *both* the mother *and* the father. In other words, they should not be used for full siblings of the subject or any of their offspring / descendants (these should instead be inputted in the central grey 'Siblings / Nieces / Nephews' section).

A:

B:

1 / pt

C:

D:

2 SMN1 copies

E:

2 SMN1 copies   pt / pt

F:

0 / 0

Refers to C1 in pedigree.

Refers to D1 in pedigree.

Should include unaffected full siblings that have not been tested and for whom genotype is unknown. Refers to D2 and D3 in pedigree.

Refers to C2 in pedigree.

Refers to E1, as E1 has been tested and is closer to subject than F1.

Either this or the equivalent box under 'Mother' must be 'Yes' to input details of siblings, nieces, or nephews in middle grey section.

Either this or the equivalent box under 'Father' must be 'Yes' to input details of siblings, nieces, or nephews in middle grey section.

Should include unaffected, untested paternal half siblings with unknown genotype. Refers to D5 and D6 in pedigree. *(a)

The subject has no maternal half siblings.

Refers to C3 in pedigree.

Refers to E3 in pedigree. *(b)

Refers to B3 in pedigree.

Refers to A1 and A2 in pedigree.

Refers to C2 and C3 in pedigree. *(c)

Refers to A1, A2, B1, and B2 in pedigree.

Refers to D6 **and** D7 in pedigree (includes partners of intervening relatives). *(d)

Refers to D3 **and** D4 in pedigree (includes partners of intervening relatives).

These details can be edited as appropriate to the ethnicity of the family.

*Instead of inputting details for E3 in 'Paternal Family History', details for D6 could be entered and would be equally informative. To do this: set **(a)** to '1'; set **(b)** to 'Half Sibling / Niece / Nephew', 'Unaffected', 'Untested', and 'pt / ?'; and set **(c)** to '1' and '1'. No input would be required for **(d)**, as D7 is irrelevant. The result would be identical.

Spinal Muscular Atrophy Genotype Probability Calculator
Designed and created by Jesse BG Hayesmoore

Mother

Clinical Status:	Unaffected
MLPA Test Status:	Untested
Genotype:	? / ?
Consider Family History?	Yes

Maternal Family History

No. Unaffected Half Siblings:	0

Other Parent's:
Clinical Status:	
MLPA Test Status:	
Genotype:	
Other Relation to Subject:	Aunt / Uncle / Cousin
Clinical Status:	Unaffected
MLPA Test Status:	2 Copies
Genotype:	1 / pt
Closest Common Parent(s):	3
Intervening Relatives' Clinical Status:	Unaffected

Subject

Name / Initials:	Subject	Date of Birth:
Clinical Status:	Unaffected	Family No:
MLPA Test Status:	2 Copies	Sample ID:

Siblings / Nieces / Nephews

No. Unaffected Siblings:	2	
Consider Another Sibling / Niece / Nephew?		Yes
Genealogic Distance:	2 degree(s)	Clinical Status: Unaffected
MLPA Test Status:	2 Copies	Genotype: ? / 0
Intervening Relatives' Clinical Status:		Unaffected

Instructions

See results of calulations in mauve tables below. Results should always be verified by users' own calculations.

Assumptions

SMA Prevalence (1 in):	10,000			
Carrier Frequency:	0.0198	1	2	0	pt
Mutation Frequency:	0.01	0.96	0.04	0.98	0.02

Father

Clinical Status:	Unaffected
MLPA Test Status:	Untested
Genotype:	? / ?
Consider Family History?	Yes

Paternal Family History

No. Unaffected Half Siblings:	2

Other Parent's:
Clinical Status:	Unaffected
MLPA Test Status:	Untested
Genotype:	? / ?
Other Relation to Subject:	Half Sibling / Niece / Nephew
Clinical Status:	Affected
MLPA Test Status:	2 Copies
Genotype:	pt / pt
Closest Common Parent(s):	1 / 2
Intervening Relatives' Clinical Status:	Unaffected

Parental Genotype Combination Probabilities (Maternal)

1/1 1/1	1/1 1/2	...	...	...	...
0	0.31568	0.0192	0.16598	0	0.00707	0.12016
0.00065	0.01743	0	0	1.6E-05	0.00037
0.04798	5.2E-05	0.00298	0	0	0
0	0	0.00194	0	0	0

Parental Genotype Combination Probabilities (Paternal)

0	0	0	0.02383	0.00134	0.01605	0.20919
0.00742	1.4E-05	0.00046	0	0	0.00058
0.00225	0.0465	0	0	1.1E-06	0.00012
0	0	0	0	0	1

Genotype Probability Calculations for Subject

Genotype		Prior Probability	Clinical Status	MLPA Result	Joint Probability	Posterior Probability
Non-Carrier:	1 / 1	0.315240395	1	1	0.315240395	0.68307938
	1 / 2	0.323629097	1	0	0	0
	2 / 2	0.011917038	1	0	0	0
	Sum:	0.65078653	-	-	0.315240395	0.68307938
Carrier:	1 / 0	0.103564809	1	0	0	0
	1 / pt	0.141101005	1	1	0.141101005	0.30574504
	2 / 0	0.00515752	1	1	0.00515752	0.01117559
	2 / pt	0.073786076	1	0	0	0
	Sum:	0.323609411	-	-	0.146258525	0.31692062
Affected:	0 / 0	0.000159003	0	0	0	0
	0 / pt	0.013334805	0	0	0	0
	pt / pt	0.012110251	0	1	0	0
	Sum:	0.025604059	-	-	0	0
All:	Sum:	1	-	-	0.46149892	

Summary Genotype Probabilities for Subject

	Pre-MLPA	Post-MLPA
Non-Carrier:	~1 in 1.5	~1 in 1.5
	0.667887152	0.683079377
Carrier:	~1 in 3	~1 in 3.2
	0.332112848	0.316920623
Affected:	0	0
	0	0

The 'Parental Genotype Combination Probability' boxes display the probability of each possible genotype combination for the parents after all the inputted family history information has been taken into account. These probabilities are used to calculate the prior probability of each possible genotype for the subject, which are then adjusted for the subject's clinical status and MLPA result (as displayed in the lower left mauve table). The overall result (i.e. probability of being a non-carrier, carrier, or having an affected genotype) before and after MLPA testing is displayed in the lower right mauve table.