Mount Sinai Genetic Testing Laboratory

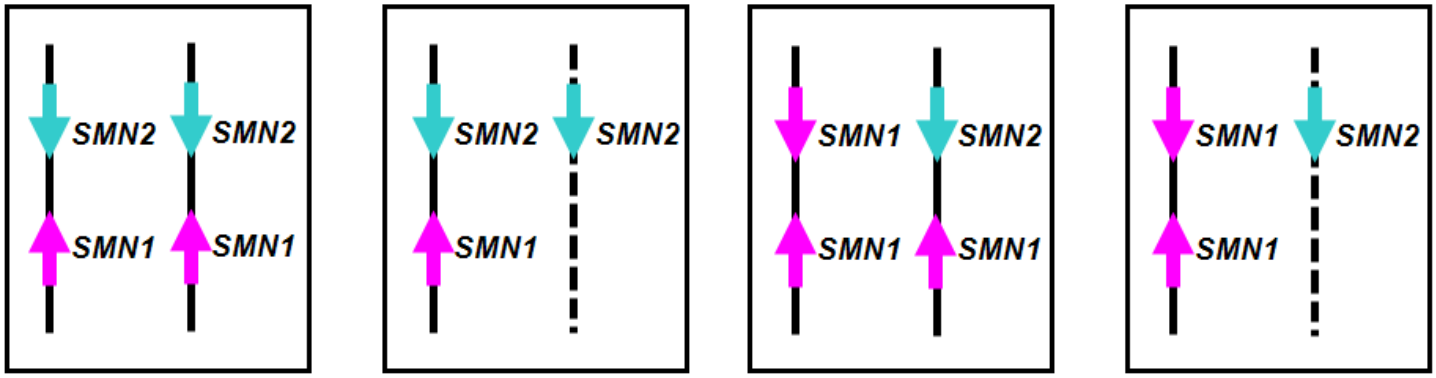
Enhanced Carrier Testing for Spinal Muscular Atrophy

Detection of SMA (2+0) Silent Carriers and Improved Residual Risk Estimates

Background information:

Spinal muscular atrophy (SMA) is one of the most common autosomal recessive diseases with an incidence of about 1 in 10,000 livebirths and a carrier frequency of 1 in 35 to 1 in 117, depending on ethnicity[1]. The disease is characterized by the progressive degeneration and loss of anterior horn cells in the spinal cord and brain stem nuclei causing symmetric muscle weakness and atrophy[2]. SMA is caused by mutations in the *SMN1* gene generally involving its deletion or gene conversion with the highly homologous, tightly linked *SMN2* gene. SMA carrier screening employs dosage sensitive methods that determine *SMN1* copy number; however, these methods are limited by their inability to identify silent (2+0) carriers, with two copies (duplication) of *SMN1* on one chromosome 5 and deletion on the other. Consequently, carrier detection rates currently range from 71 - 94% depending on ethnicity[1,3]. The Mount Sinai Genetic Testing Laboratory has identified an *SMN1* specific haplotype that delineates duplication alleles, which significantly improves detection rates and/or residual risk estimates for SMA carrier screening in all populations examined [4].

Schematic of *SMN1* and *SMN2* gene configuration:



Wild-type: 2 copies of *SMN1*

Carrier: 1 copy of *SMN1*

Duplication: 3 copies of *SMN1*

Silent Carrier: 2 copies *SMN1*

Testing methods, detection rates, turnaround time, and residual risk estimates:

Enhanced SMA carrier screening developed at Mount Sinai involves testing for a single polymorphism in intron 7 of *SMN1*, g.27134T>G, which is part of a haplotype specific for *SMN1* duplication alleles in the Ashkenazi Jewish and Asian populations and is significantly enriched in individuals with *SMN1* duplications in the African American, Hispanic and Caucasian populations. Importantly, the detection rate in the Ashkenazi Jewish population increases from 90 to 94% by testing for the g.27134T>G polymorphism as part of the carrier screen. For African Americans, testing negative for g.27134T>G decreases the residual risk of being a carrier in an individual with two copies of *SMN1* from 1 in 121 to 1 in 396. Conversely, African Americans with two copies of *SMN1* that test positive for g.27134T>G have a residual risk that is increased to 1 in 34.

Testing is performed in parallel with general carrier screening for SMA by dosage sensitive methods and the results are reported together with final residual risk estimates calculated based on the presence or absence of g.27134T>G (see table below. This testing strategy keeps the overall turnaround time of SMA screening within the usual 7-12 day period.

Ethnicity	Carrier Frequency	Current Detection Rate	Residual risk after negative result*	Enhanced detection rate with g.27134T>G	Residual risk g.27134T>G* negative	Residual risk g.27134T>G* positive
Ashkenazi Jewish	1 in 41[4]	90%[1,4]	1 in 345[4]	94%	1 in 580[4]	^Likely Carrier[4]
Asian	1 in 53[1]	92.6%[1]	1 in 628[1]	93.3%	1 in 702[4]	^Likely Carrier[4]
African American	1 in 66[1]	71.1%[1]	1 in 121[1]		1 in 396[4]	1 in 34[4]
Hispanic	1 in 117[1]	90.6%[1]	1 in 1061[1]		1 in 1762[4]	1 in 140[4]
Caucasian	1 in 35[1]	94.9%[1]	1 in 632[1]		1 in 769[4]	1 in 29[3]

* Residual risk with two copies *SMN1* detected using dosage sensitive methods
^ Parental follow-up will be requested for confirmation

Specimen & Shipping requirements:
Two lavender-top (EDTA) 5-10 ml tubes of blood shipped refrigerated or at room temperature (do NOT freeze).

References:

1. Hendrickson BC et al. Differences in SMN1 allele frequencies among ethnic groups within North America. J Med Genet. 2009;46:641–644.
2. Ogino S et al. Genetic risk assessment in carrier testing for spinal muscular atrophy. Am J Med Genet. 2002 Jul 15;110:301-7.
3. Prior TW et al. Technical standards and guidelines for spinal muscular atrophy testing. Genet in Med. 2011; 13:686-694.
4. Luo M et al. An Ashkenazi Jewish SMN1 haplotype specific to duplication alleles improves pan-ethnic carrier screening for spinal muscular atrophy. Genet Med. 2013 [Epub ahead of print].