

## Case report of pregnancy management and genetic evaluation after negative carrier screening for spinal muscular atrophy in an affected family

Heather M. Lucas<sup>\*</sup>, Mojirayo A. Sarumi

Department of Maternal Fetal Medicine, CHRISTUS Trinity Mother Frances, 620 S Fleishel Ave, Tyler, TX 75701, USA

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### ABSTRACT

**Background:** Screening for spinal muscular atrophy (SMA) is recommended for all pregnant women; however, interpreting the results of carrier screening in the context of family history can be challenging.

**Case:** We report the case of a 28-year-old woman (G4P3001) with two previous children affected with SMA and negative carrier screening via the Horizon 4 panel. *SMN1*/2 analysis was pursued to clarify risk for point mutations, carrier screening for her partner, and diagnostic testing for the fetus for SMA. Results of this testing confirmed her status as a silent carrier for SMA and the status of the fetus.

**Conclusion:** Carrier screening does not account for family history and can therefore generate results inconsistent with known inheritance patterns. In these situations, additional genetic testing and genetic counseling are indicated to clarify risk for SMA in pregnancy and guide prenatal and neonatal healthcare.

### 1. Introduction

Carrier screening is recommended by the American College of Obstetrics and Gynecologists for all couples in pregnancy or who are trying to get pregnant [1]. Currently, screening for spinal muscular atrophy (SMA), cystic fibrosis, and hemoglobinopathies is recommended for all women. This designation comes from the relatively high frequency of carriers in the population. For SMA, this frequency is estimated to be 1/50 across all ethnicities, with lower frequencies of 1/77 and 1/100 for Hispanic and African American populations, respectively [2].

SMA is inherited in an autosomal recessive manner, usually from carrier parents, though approximately 2% of cases are due to de novo events [3]. Unaffected individuals have between 1 and 4 copies of the gene *SMN1* carried between the two copies of chromosome 5. Carriers have either one working copy of *SMN1* or two copies carried in cis configuration. Individuals with SMA have no working copies of *SMN1*, which encodes survival motor neuron protein and is responsible for maintenance of motor neurons which facilitate communication between the central nervous system and skeletal muscle. Most often, *SMN1* is deleted in affected patients; however, about 4% of cases of SMA are due to point mutations which render the gene nonfunctional [4]. Standard carrier screening for SMA is dosage based and detects the number of copies of *SMN1*. Phase is estimated based on the presence of a single nucleotide polymorphism (SNP), g.27134 T > G, which is correlated to

cis configuration and increased risk of silent carrier status [5] (Fig. 1). Utilization of this SNP data in carrier screening can help clarify risk for silent carrier status. However, it is most accurate in Ashkenazi Jewish and Asian populations and not nearly as accurate in other ethnic populations [6]. Standard screening does not include sequencing of *SMN1* to detect point mutations.

Until recently, SMA was considered a lethal diagnosis with no effective treatment to halt disease progression. There are now three FDA-approved treatment options available. The first is Spinraza (nusinersen), which is given intrathecally with four initial loading doses and a maintenance dose every four months which increases production of useable protein from *SMN2*. This treatment is shown to be effective at halting disease progression and providing some improvement in patients of all ages with SMA [7]. The second treatment is Zolgensma (onasemnogene abeparvovec-xioi). This is a gene therapy administered as single infusion which replaces the faulty copy of *SMN1* and has been shown to halt progression and improve function in treated individuals. Zolgensma is only available to children under two years of age [8]. The third treatment is Evrysdi (risdiplam), which is an oral medication taken daily that can be given to individuals two months of age and older which modifies the splice site of *SMN2* to increase production of functional SMN protein [9].

Despite improved screening and therapies, due to the mechanism of SMA, it remains difficult for carrier screening to accurately predict risk,

<sup>\*</sup> Corresponding author.

E-mail address: [heather.lucas@christushealth.org](mailto:heather.lucas@christushealth.org) (H.M. Lucas).

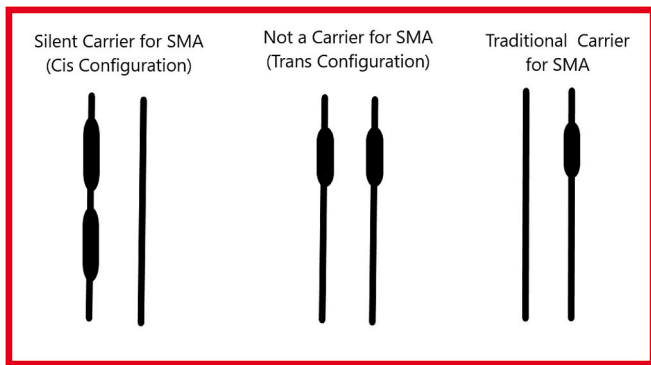


Fig. 1. Phase configurations of SMN1 copies.

particularly for individuals who are not of Ashkenazi or Asian descent. This ethnic gap and the limitations of standard screening leave many families at significant residual risk to have a child affected with SMA and unprepared to navigate effective diagnosis and treatment.

2. Case

We present the case of a 28-year-old Hispanic female who had two previous children with spinal muscular atrophy (SMA). Her first child had a more severe presentation and died within the first four months of life. He did not receive treatment due to the rapid progression of the disease, which outpaced diagnosis. The second affected child had milder symptoms and was diagnosed more quickly due to the known family history of SMA. He had been receiving Spinraza treatments and doing well, per mother, prior to his death due to an accident. In addition, she has one unaffected child.

The patient presented at 18 weeks and one day of gestation. This pregnancy was conceived with a different reproductive partner from her previous children. As part of her prenatal workup, she had undergone carrier screening with the Horizon 4 panel and had received a negative result for SMA based on having two copies of SMN1 and no SNP detected. The patient was referred to genetic counseling to discuss the negative result and possibility for another affected child. The patient came to genetic counseling with the intention to pursue prenatal diagnosis for SMA to enroll an affected child in the Zolgensma protocol.

In reviewing her results, the negative screening result set the likelihood of her being a silent carrier at 1/1762 or 0.05%. This result was based on the presence of two copies of SMN1 and the absence of the

g.27134 T > G SNP variant. At the time genetic testing, records were not available for her children and it was determined that it would be beneficial to confirm that she did not carry a point mutation that could lead to SMA. SMN1/2 dosage analysis and sequencing were performed. This did not reveal a point mutation and confirmed the presence of two copies of SMN1. Of note, this testing did not assess phase. Based on the family history of two affected children, the patient was an obligate carrier, and it was concluded that she was a silent carrier for SMA with both of her copies of SMN1 in cis configuration, despite the low predicted risk. Concurrently, carrier screening for her new partner was ordered via the Horizon 4 panel and revealed the same risk assessment for him based on the presence of two copies of SMN1 and a 1/1762 chance to be a silent carrier based on SNP analysis (Fig. 2).

While these results for her partner were reassuring statistically, because the patient herself had received the same result and was still presumed to be a carrier, and because the parents wished to know the status of the baby in order to facilitate early treatment if the child were affected, they elected to pursue diagnostic testing for the fetus. Amniocentesis was performed and sample was sent for SMN1/2 analysis and chromosomal microarray (CMA).

CMA was normal and SMN1/2 analysis revealed the fetus had 3 copies of SMN1 and was unaffected. It should be noted that these results corroborate that one parent is a silent carrier and contributed 2 copies of SMN1, while the other is not a silent carrier and contributed 1 copy. This confirms the theory that this patient was in fact a silent carrier, despite the low odds cited by the laboratory based on SNP analysis. This also indicates that the father of this fetus is not a carrier and that their future children are not at increased risk for SMA, though future children do have a 50% chance to be carriers of the condition.

3. Discussion

This case highlights important considerations when interpreting test results from carrier screening, including family history data and recognition of limitations of the testing itself. While this patient and her new partner had received identical carrier screening results, their respective family histories clearly led to a change in the way they were interpreted and highlight the need for follow-up testing that was more comprehensive to determine fetal risk.

Family history is critical to interpretation of carrier screening results. Because SMA has a 2% de novo rate, a parent with only one affected child may not be a carrier for the condition. In fact, Bayesian analysis places a parent of Hispanic descent of a single affected child at a 39.2% chance to be a carrier. In this case, if parents have not previously had

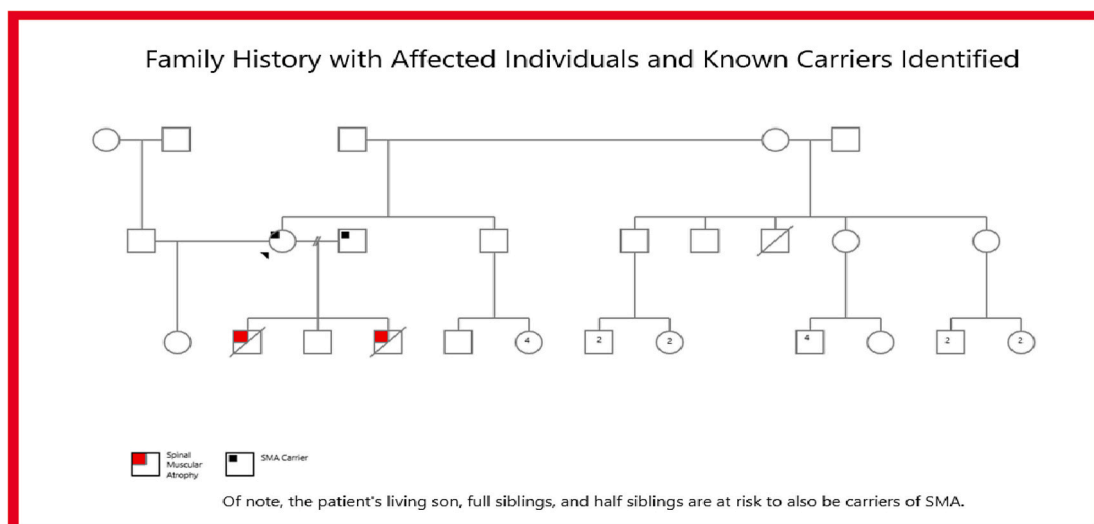


Fig. 2. Pedigree showing affected family members and carriers of SMA.

carrier testing, they should be screened to determine if the child's condition arose due to familial variants or a de novo event. However, as in this case, when an individual of Hispanic descent has two affected children the likelihood that they are a carrier increases to 96.9% on Bayesian analysis. This significant increase in likelihood with more than one affected child holds up across all ethnicities and therefore, clinically, a parent of multiple children with SMA should be considered an obligate carrier.

The variance in risk between the analysis of the genetic counselor and that of the lab arises due to the laboratory methodology not being designed to incorporate family history. Carrier screening performed by the lab is designed to look for dosage of the gene *SMN1* first. If the individual is found to have one copy of the gene, they are determined to be a carrier. If two copies are found, then the lab performs SNP analysis to help calculate risk the copies are in cis configuration and the patient is a silent carrier. A patient found to carry the SNP will be reported as being at "increased risk to be a carrier"; however, true silent carrier status cannot be known without linkage studies. Additionally, the ability of the SNP to predict phase of the copies of *SMN1* is significantly decreased for most ethnic groups. This variance should be communicated to patients as part of pretest counseling when possible or addressed as part of the results disclosure. Ultimately, the responsibility to interpret the laboratory results in the context of the patient's history and presentation falls to their provider.

In this case, the genetic counselor identified this increased risk based on family history above the reported carrier screen risk. This identification led to more comprehensive testing of the patient and her partner to clarify carrier status and mutation type. When she was not found to harbor a point mutation, this corroborated the theory that she was in fact a silent carrier. This was later proven by results from fetal testing, which revealed three copies of *SMN1*, one inherited from the father, and two from the carrier mother.

Providers are critical in interpreting results in the context of the patient's full history and guiding appropriate genetic testing to meet the patient's goals for their pregnancy. This role is especially important when patients are carriers for complex conditions like SMA which are difficult to screen for, but where care of an individual drastically changes when they are found to be affected. It is appropriate to refer patients with discordant clinical histories and genetic testing to a genetics provider to help clarify best steps for prenatal diagnosis.

For this patient, testing was driven by her desire to access treatment for her child if they were affected. While traditionally SMA work-ups are completed after children begin to display symptoms of SMA, couples who are known carriers for the condition are now able to pursue prenatal diagnosis, which can drastically shorten the time to treatment and improve long-term outcomes for their children. These at-risk couples should be offered prenatal diagnosis and have the opportunity to discuss treatment options prior to delivery as this information can impact pregnancy management.

In conclusion, carrier screening results are not diagnostic and only estimate risk for carrier status. Because of the complexity of SMA and the limitations of screening, patient results must be reviewed through the lens of family and medical history to be fully understood. For this reason, referral to a genetic counselor or genetics specialist should be considered when a history is suggestive of carrier status inconsistent with genetic screening. When there is concern for a fetus to have SMA, diagnostic testing and analysis for *SMN1/2* is a reasonable option and should be offered as part of a discussion of SMA and treatment.

## Contributors

Heather M. Lucas drafted and revised the manuscript.

Mojirayo A. Sarumi revised the manuscript for intellectual content.

Both authors were involved in the care of this patient and both approved the final version of the case report.

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## Patient consent

Obtained.

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## Conflict of interest statement

The authors declare that they have no conflict of interest regarding the publication of this case report.

## References

- [1] ACOG Position Statement Number 691, American College of Obstetrics and Gynecology, 2020. Reaffirmed.
- [2] I.E.C. Verhaart, A. Robertson, I.J. Wilson, A. Aartsma-Rus, S. Cameron, C.C. Jones, S. F. Cook, H. Lochmüller, Prevalence, incidence and carrier frequency of 5q-linked spinal muscular atrophy - a literature review, *Orphanet J. Rare Dis.* 12 (2017) 124.
- [3] B. Wirth, T. Schmidt, E. Hahnen, S. Rudnik-Schöneborn, M. Krawczak, B. Müller-Myhök, J. Schonling, K. Zerres, De novo rearrangements found in 2% of index patients with spinal muscular atrophy: mutational mechanisms, parental origin, mutation rate, and implications for genetic counseling, *Am. J. Hum. Genet.* 61 (1997) 1102-1111.
- [4] M.R. Lunn, C.H. Wang, Spinal muscular atrophy, *Lancet.* 371 (9630) (2008 Jun 21) 2120-2133, [https://doi.org/10.1016/S0140-6736\(08\)60921-6](https://doi.org/10.1016/S0140-6736(08)60921-6). 18572081.
- [5] M. Luo, L. Liu, I. Peter, J. Zhu, S.A. Scott, G. Zhao, C. Eversley, R. Kornreich, R. J. Desnick, L. Edelmann, An Ashkenazi Jewish *SMN1* haplotype specific to duplication alleles improves pan-ethnic carrier screening for spinal muscular atrophy, *Genet. Med.* 16 (2) (2014 Feb) 149-156, <https://doi.org/10.1038/gim.2013.84>. Epub 2013 Jun 20, 23788250.
- [6] E.A. Sugarman, N. Nagan, H. Zhu, V.R. Akmaev, Z. Zhou, E.M. Rohlf, K. Flynn, B. C. Hendrickson, T. Scholl, D.A. Sirko-Osadsa, B.A. Allitto, Pan-ethnic carrier screening and prenatal diagnosis for spinal muscular atrophy: clinical laboratory analysis of >72,400 specimens, *Eur. J. Hum. Genet.* 20 (1) (2012 Jan) 27-32, <https://doi.org/10.1038/ejhg.2011.134>. Epub 2011 Aug 3, 21811307. PMC3234503.
- [7] D.M. Paton, Nusinersen: antisense oligonucleotide to increase SMN protein production in spinal muscular atrophy, *Drugs Today (Barc).* 53 (6) (2017 Jun) 327-337, <https://doi.org/10.1358/dot.2017.53.6.2652413>. 28799578.
- [8] D. Stevens, M.K. Claborn, B.L. Gildon, T.L. Kessler, C. Walker, Onasemnogene abeparvovec-xioi: gene therapy for spinal muscular atrophy, *Ann. Pharmacother.* 54 (10) (2020 Oct) 1001-1009, <https://doi.org/10.1177/1060028020914274>. Epub 2020 Mar 23, 32204605.
- [9] R.N. Singh, E.W. Ottesen, N.N. Singh, The first orally deliverable small molecule for the treatment of spinal muscular atrophy, *Neurosci. Insights* 15 (2020 Nov 23), <https://doi.org/10.1177/2633105520973985>, 2633105520973985, 33283185. PMC7691903.