A Silent Invasion: The Alpha-gal Syndrome Explosion in Southern Virginia

Benjamin G. Currin ‘25

Special note: This journal entry is dedicated to my grandfather, Ronald “Ronnie” Currin, who lived with alpha-gal syndrome for 2 ½ years before passing in October 2023 at 71.

Introduction

If you have resided in Virginia’s southern Piedmont region for the last several years, there is a good chance that you have either heard of alpha-gal syndrome or know someone who suffers from it. Alpha-gal syndrome, an allergy to red meat caused by a tick bite, has become an emerging concern in our area. This disease has quite literally come out of the woodwork and has many people scared even to step foot in the woods. An alarming July 2023 report from the CDC revealed that the highest prevalence of suspected alpha-gal cases in relation to population was found in Charlotte County, VA[1]. Overall, Virginia has one of the highest prevalences of suspected alpha-gal syndrome in relation to its population in the country. Charlotte County’s number of suspected alpha-gal cases is only about 1.2% of the population, but this is almost twice the value of the number of cases found in Muhlenberg Kentucky, which had the second highest number of suspected alpha-gal cases with respect to population[1]. With one of Prince Edward’s adjacent counties being Charlotte, this statistic goes to show that we are truly living in a hot zone.

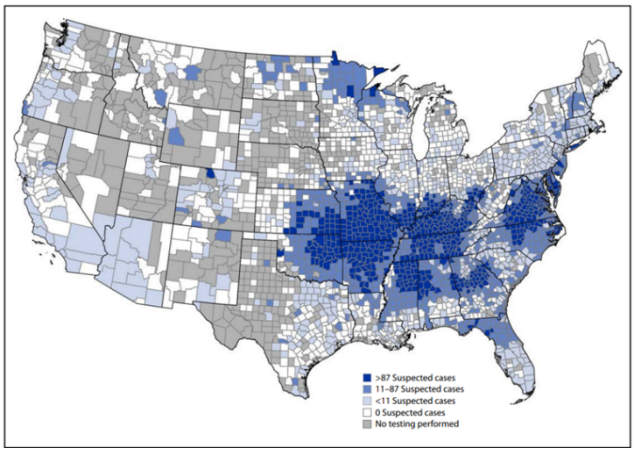

Figure 1: Geographic distribution of suspected alpha-gal syndrome cases per 1 million population per year in the United States, 2017-2022[1]

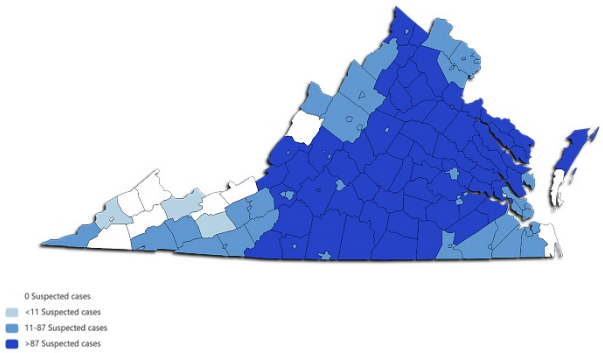

Figure 2: Geographic distribution of suspected alpha-gal syndrome cases per 1 million population per year in Virginia, 2017-2022[1]

Overview and Discovery

Alpha-gal syndrome is a hypersensitivity to a sugar called galactose-α-1,3-galactose, commonly known as alpha-gal. This carbohydrate is found in all mammals and their derivatives except for humans and primates. Alpha-gal syndrome was only recently discovered in the United States by Dr. Thomas Platts-Mills at the University of Virginia in 2007. It all began in 2004 with the drug cetuximab, a monoclonal antibody that was in clinical trials for the treatment of metastatic colorectal cancer. Early into the trials, it became evident that cetuximab was causing hypersensitivity reactions, but they were only occurring in participants in a group of southern US states. Cetuximab is estimated to have around 2040 micrograms of alpha-gal per gram. Dr. Thomas Platts-Mills and a group of researchers were asked to investigate these reactions. What they noticed was that there was an overlap in a group of southeastern states where cetuximab reactions and delayed reactions to red meat were occurring. During this investigation, three members of the group developed a red meat allergy and each one remembered being bitten by a tick weeks to months before symptoms developed. Serum from these individuals obtained prior to the tick bite had a significantly lower amount of immunoglobin E (IgE) to alpha-gal compared to serum collected after the tick bite. After consulting with patients involved in the clinical trials, it became

evident that most of the patients who had experienced hypersensitivity reactions had also experienced recent tick bites[2]. Geographic distribution maps of the Lone Star tick were shown to overlap with the regions where cetuximab reactions and delayed reactions to red meat were occurring. It was later determined that the Lone Star tick was the only vector in the United States that carried the antigen that produced the IgE response to alpha-gal[3].

Alpha-gal Syndrome Complications

Other than not being able to consume red meat, alpha-gal syndrome could cause more drawbacks. Many medications and vaccines contain gelatin derived from pigs that have caused anaphylaxis in patients. For example, heparin, which is used in high doses during cardiopulmonary bypass surgeries to prevent blood clots, is derived from bovine lungs and can have detectable levels of alpha-gal. A study by Hawkins *et al.* in 2021 showed that around 24% of patients sensitized to alpha-gal experienced anaphylaxis when given heparin during cardiac surgery[4]. Immune responses to alpha-gal are also believed to be a trigger for transplant rejection in humans when they are given animal organs. Recent studies have revealed further complications from the allergy specifically to the heart. In 2018, a study came out that linked alpha-gal syndrome to the buildup of plaque in the coronary arteries. While it has long been believed that high saturated fat levels in red meat contribute to heart disease, the study

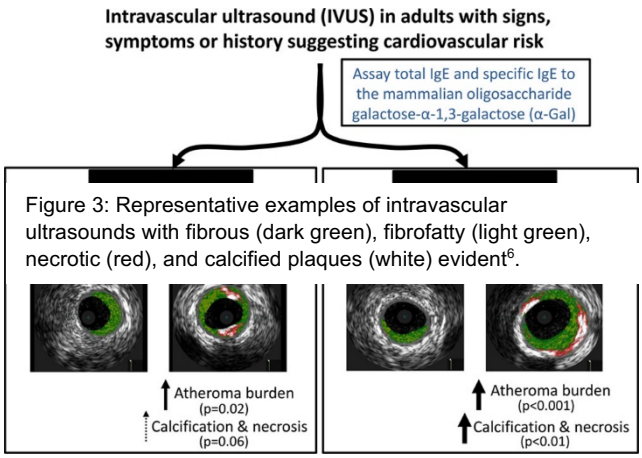

Figure 3: Representative examples of intravascular ultrasounds with fibrous (dark green), fibrofatty (light green), necrotic (red), and calcified plaques (white) evident[6].

counteracted that claim and showed that people affected by alpha-gal were at a higher risk. Intravascular ultrasounds of the coronary arteries in alpha-gal sensitized patients revealed a 30% higher quantity of plaque compared to non-sensitized patients[5]. In patients over the age of 65 who were alpha-gal sensitized, the atherosclerotic plaques had significantly more fibrofatty, necrotic, and calcified content but were less fibrous compared to non-sensitized patients over 65[6]. Plaque in the alpha-gal sensitized patients also tended to be more structurally unstable, meaning an increased likelihood of having a heart attack or stroke[5].

The Novel Lone Star tick

Amblyomma americanum, commonly known as the Lone Star tick, was first discovered in 1758 by Charles Linnaeus, the “father of modern taxonomy” who standardized binomial nomenclature. The tick is dispersed across the eastern, southeastern, and midwestern United States with concern that the tick is expanding its range more north and west. A Lone Star tick’s life cycle begins when a blood-engorged female tick deposits up to 5,000 eggs after falling from a host. After an incubation period that lasts anywhere from 31 to 60 days, the tick eggs transition into their larval stage where they are commonly referred to as seed ticks. This stage’s duration is dependent on the amount of time it takes for the larvae to find a suitable host[7]. The Lone Star Tick is very aggressive and will attack all mammals and even ground-dwelling birds. Larvae can survive for up to six months before finding a host to feed on. When the larvae find a host, they attach and feed on the host’s blood for 4 to 9 days before detaching and molting into the nymphal stage. Nymphs go through a similar process as the larvae and require another host to attach to so that it can develop and molt into an adult[7]. Mature females develop a white spot on the center of their back and adult males develop white streaks or spots along the outside of their body. Adult Lone Star ticks can survive for up to 2 years without feeding on a host. Mating occurs on the host and is stimulated by pheromones secreted by the female tick that encourage the male tick to detach from the host and locate the female. Males are capable of mating with multiple females before dying. Once a female Lone Star tick mates, she leaves the host and later dies after laying her eggs[7].

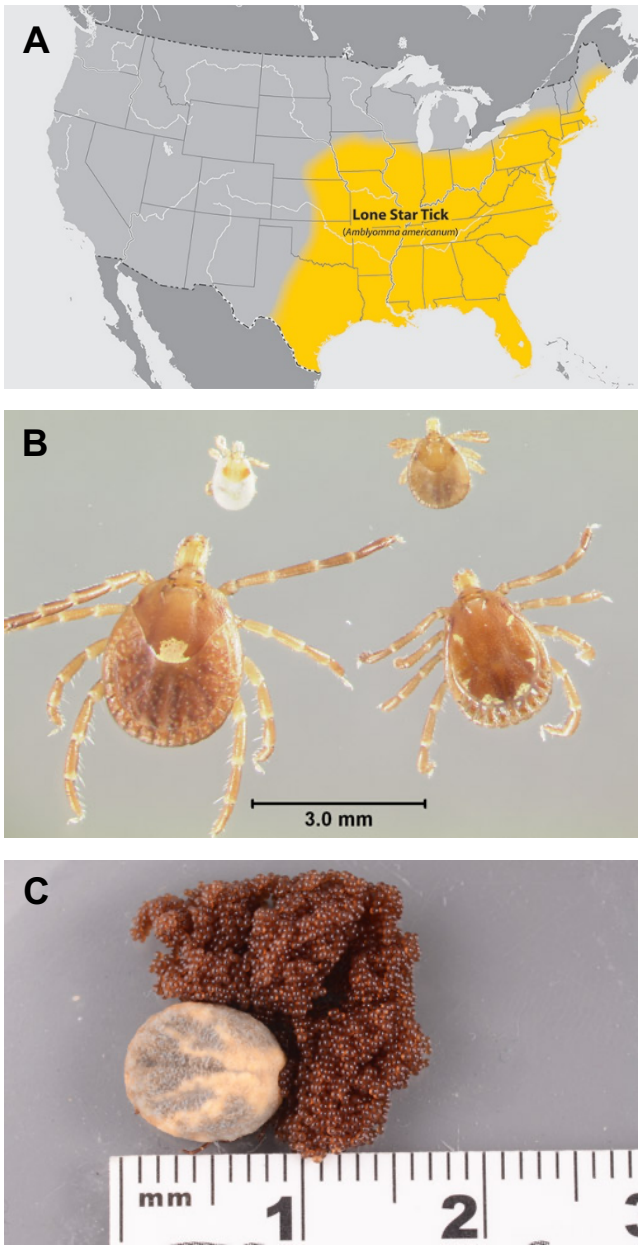

Figure 4: A) Geographic distribution of the Lone Star tick.[2] B) Life cycle of a Lone Star tick, from top left clockwise: larvae, nymph, adult male, adult female[7]. Photograph by Chris Holderman. C) Female Lone Star tick with egg mass[7].Photograph by Lyle Buss.

Before reaching the adult stage, the tick has already interacted with two different hosts, with one of the hosts most likely being a non-primate mammal. When the Lone Star tick bites the non-primate host, the tick brings in blood that can contain alpha-gal sugar molecules. Post-translational modifications of proteins found in the saliva result in the formation of glycoproteins that have alpha-gal sugars bound to the protein terminuses. Lipids also found in the saliva can have alpha-gal attached forming glycolipids[8]. Interestingly, tick saliva is very similar in composition to the venom of known venomous animals, producing an immune response similar to what is seen with envenomations[9]. Although carbohydrates have been regarded as poorly allergenic molecules, it has been recently shown that glycans such as alpha-gal can modulate innate and adaptive immune responses. Hypersensitivity to alpha-gal occurs after repeated tick bites. After repeated exposure to the tick saliva comprised of alpha-gal-containing glycoproteins and glycolipids, the body has a reserve of memory B cells expressing anti-alpha-gal B cell receptors as well as basophils and mast cells that are coated with anti-alpha-gal IgE antibodies[8]. Memory cells can survive for decades, which explains why some suffer from alpha-gal for the rest of their lives[10]. When red meat is digested in the body, it is broken down into smaller organic fragments that could potentially have the alpha-gal epitope present, stimulating an immune response. If basophils or mast cells coated in anti-alpha-gal IgE antibodies encounter alpha-gal in any form, the cells will degranulate leading to a systemic allergic reaction[8]. This could result in symptoms ranging from hives and stomach pain to anaphylaxis[11].

Habitat

The Lone Star tick is typically found in second-growth woodland habitats that have populations of white-tailed deer[7]. Secondary woodlands are forest areas that have been regenerated after human or naturally caused disturbances such as timber harvest, agriculture clearing, or forest fires. White-tailed deer and other native animals prefer the dense cover and foliage opportunities provided by secondary woodlands such as cutovers. It can take between 40 and 100 years for a secondary forest to resemble a mature or old-growth forest, although this timeline can vary depending on the forest type[12]. Land replanted in pine may take only around 30 years to reach maturity whereas a hardwood forest can take anywhere from 50 to 100 years to reach maturity. Recently, new cutovers have been planted in genetically improved pine trees that are supposed to be ready to cut again in as little as 15 years.

Table 1: Timber production by county in the Southern Piedmont and their respective alpha-gal prevalence[13].

County	Volume of timber production in 2022 (MCF)	Volume of timber production in 2022 (green tons)	County rank	Volume of timber production since 2013 (MCF) *	Volume of timber production since 2013 (green tons) *	Southern Piedmont Rank	Alpha-gal syndrome prevalence (per 1 M PPY)
Amherst	2,849	102,732	50	34,461	2,038,573	16	>87
Appomattox	9,188	325,247	23	70,609	3,034,317	12	>87
Bedford	5,347	193,521	37	61,795	2,683,045	14	>87
Brunswick	34,371	1,203,731	1	249,289	8,530104	1	>87
Campbell	17,324	610,377	10	118,955	4,352,717	9	>87
Charlotte	28,316	1,026949	2	205,637	7,328,745	3	>87
Dinwiddie	18,966	664,927	7	136,970	4,763,138	6	>87
Franklin	11,975	441,045	16	83,651	3,190,162	11	>87
Greensville	15,404	540,084	11	110,937	3,961,730	10	>87
Halifax	24,185	860,781	3	226,302	7,432,242	2	>87
Henry	7,599	277,793	27	51,844	2,015,915	17	>87
Lunenburg	22,430	782,386	4	153,864	5,343,388	5	>87
Mecklenburg	18,319	648,369	8	137,370	4,753,949	7	>87
Nottoway	5,953	209,254	31	77,602	2,758,734	13	>87
Patrick	5,523	201,822	34	54,994	1,991,247	18	>87
Pittsylvania	17,500	618,535	9	170,109	5,571,569	4	>87
Prince Edward	9,557	349,164	22	60655	2,132463	15	>87
Sussex	19,728	696,783	6	141886	4,554,964	8	11-87
Total	274,561	9,753,284		2,146,940	76,436,999		

All data was collected from the USDA Forestry Service. https://www.fs.usda.gov/research/

*Timber production values were not collected by the USDA Forest Service in 2014 and 2016

Table 1: Summary of timber production in the Southern Piedmont region of Virginia

Virginia Timber Production

Comparing timber production in counties in the Southern Piedmont reveals a striking correlation between secondary woodland rates and alpha-gal syndrome prevalence. Of the 18 counties in the Southern Piedmont region of Virginia, only Amherst was outside the top 50% of timber-producing counties. In fact, 9 of the 10 highest timber-producing counties in Virginia came from the Southern Piedmont region. The Southern Piedmont region accounted for around 43.5% of the total timber production in Virginia. Lunenburg, Charlotte, and Prince Edward, often referred to as the tri-county, were responsible for around 10% of all timber production in the state[13]. Higher timber production rates mean more ideal locations for the Lone Star tick to thrive. After harvesting a tract of timber, landowners have 4 main options: 1) converting the land into fields, 2) replanting in pines, 3) replanting in hardwoods, or 4) allowing the land to regrow trees naturally. Nevertheless, three of the four situations lead to secondary woodland areas that are desirable conditions for the Lone Star tick. 17 of the 18 counties in the Southern Piedmont had a number of alpha-gal cases in their population that would be considered high. As a whole, Virginia's Piedmont region is one of the several alpha-gal hotspots in the southern United States and could only get worse as more secondary woodlands are created.

Although higher timber production values in the Southern Piedmont region may cause some to worry of an impending forestry crisis, this is not the case. Virginia can sustain this level of timber production every year; both hardwood and softwood's growth/drain ratios are between 2.0 and 2.5, indicating that forest volumes are growing at a faster rate than being removed[15]. However, as around 160 mills in Virginia process wood to make paper, biomass, telephone phones, pallets, and building materials, more and more secondary woodland areas are forming[13]. Both mature and secondary woodlands contribute to biodiversity and soil erosion control, but it is important to try and maintain the integrity of our old-growth Virginia forests. Currently, more than 60% of Virginia's forests are classified as large diameter (11 inches for hardwood/ 9 inches for softwood),

meaning most of our forests are least considered juvenile[16]. As it takes time for secondary woodlands to reach maturity and be cut again, the percentage of mature forests could dwindle as the timber industry keeps up with demand.

Lone Star Tick Management

By creating more young forests, we are inadvertently contributing to the spread of alpha-gal in places where the Lone Star tick has a presence as well as the expansion of the Lone Star tick across the United States. Desirable white-tailed deer habitats formed by human or natural interference provide the Lone Star tick with a host to reach maturity and reproduce. To slow the inevitable rise of alpha-gal cases, actions needed to be taken by the citizens of Virginia and potentially the state government. One simple precaution is to wear protective clothing and use tick repellants when outdoors. Knowing that Lone Star ticks prefer the dense undergrowth associated with secondary woodlands, it is best to avoid areas with high grasses and thick brush. After extended periods outside, inspecting your entire body for ticks or taking a shower to wash off any unattached ticks is always best[17]. Finding ticks before or shortly after they latch on will help prevent the body from producing an immune response to the tick's saliva.

Effective White-tailed Deer Regulation

Another necessary component of Lone Star tick management is quality deer management. Current estimates of deer population in Virginia show a pre-hunt population estimate between 850,000-1,000,000[18]. During the 2023-2024 deer hunting season, 206,586 deer were harvested in Virginia[19]. As the deer number naturally replenishes in the spring, marked by the birth of fawns, our deer population values remain around the same range. Unfortunately, Virginia has seen a decrease in the number of licensed deer hunters since the late 80s when the number of licensed numbers peaked. If the current decline in licensed deer hunters, we could see as much as a 32% decrease in deer hunting participation by 2030 and a 57% decrease by 2040[20]. These values are not unique to Virginia; other states are experiencing similar issues with deer hunter numbers. Besides a lack of deer hunters in Virginia, these decreasing values affect other wildlife conservation programs, with deer license sales providing nearly a third of wildlife agency funding on average[20]. Education and outreach, especially to younger generations, are crucial if we wish to disrupt the current trend. Finally, the state government could implement a Lone Star tick management program to ensure that tick population levels do not get out of hand. The government could devote funds to the management of tick populations in each county to help develop plans to regulate the population. For instance, yards and secondary woodlands could be treated in high-risk areas to reduce the number of alpha-gal cases. These ticks cannot be allowed to propagate as they normally would if we want to decrease the number of new alpha-gal cases. Elimination of the Lone Star tick is not the solution, but effective oversight is necessary.

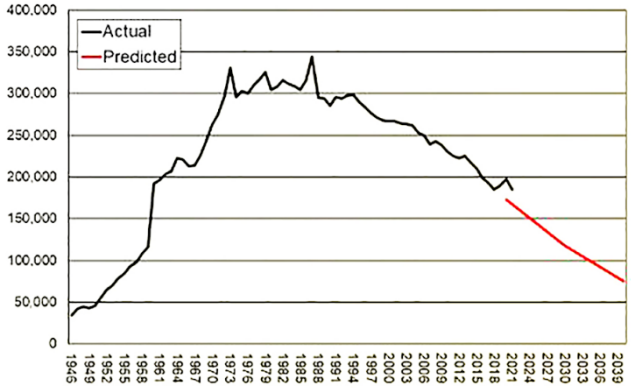

Figure 5: Virginia licensed deer hunter values from 1946 to 2021 as well as future predictions[20]. Note this does not include deer hunters exempt from purchasing a license such as landowners.

Future of Alpha-gal Syndrome

As the country adjusts to the lasting presence of alpha-gal syndrome, advancements have been made to improve the lives of people with the disease. In 2020, the FDA approved the first intentional genome alteration for food or therapeutic use in a line of pigs referred to as GalSafe pigs. These pigs have been altered in a way that the alpha-gal sugar is eliminated. This prevents a patient with alpha-gal syndrome from suffering from an allergic reaction. Medical products that use animal-based byproducts such as heparin can be created using GalSafe pigs. Because the alpha-gal sugar is believed to be the reason why tissues and organs from xenotransplantation are rejected by the body, this new line of pigs could open the door for the future of organ transplants[21]. All domesticated non-primates could have a cell line created that does not contain alpha-gal to accommodate affected people across the United States. Recently, acupuncture has gained ground as a potential low-risk treatment for

alpha-gal syndrome and has shown promise. Soliman Articular Allergy Treatment (SAAT) is a version of acupuncture that helps relieve allergy symptoms and involves the insertion of a hairlike needle in the ear. The SAAT method has shown effectiveness in a majority of patients[22]. With more research dedicated to alpha-gal syndrome, additional treatments will likely arise that could combat the disease. As alpha-gal syndrome gains recognition among the public, it is important that we actively take steps to prevent the escalation of this emerging health concern.

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