



Platelet Receptor Deficiency on the gene P2Y12

The Current Research

Occasional bleeding issues have been noted in the Greater Swiss Mountain Dog breed for years, but despite significant research the cause of this has not yet been determined. Some of the bleeding issues have been post-surgical, some have been after illness/injury and some have been spontaneous. There have been a few reports of multiple affected dogs in a litter. A case study report was published by researchers at Auburn University in 2011 which seemed to point to a platelet receptor deficiency on the gene P2Y12. This article will explain an overview of blood clotting as well as an update from the research our club supported through Cornell University.

Blood clotting, or hemostasis is vital to life because the body needs to be able to respond to injuries. Primary phase hemostasis involves platelets (small blood particles) adhering to the injured blood vessel, aggregating together, and releasing substances that constrict the blood vessel and activate the platelets further to form a plug. That fragile plug is then reinforced by activation of the clotting cascade and proteins in the body that form a fibrin plug.

The clotting process is broken down into multiple steps and is affected by many different protein factors. This means that there are many different places where things can go wrong. There are two different pathways of factors (clotting cascade) that trigger each other and both of those must also come together into one path. For instance, blood thinner medications like warfarin (and rat poison) bind vitamin K which affects factor VII in the extrinsic pathway, but that is needed to trigger the rest of the cascade so even though the other factors are still functioning, the blood cannot clot, and the animal can bleed to death.

Over clotting is not as much of an issue in dogs as humans but occasionally the body does not break down the fibrin properly after the clotting process is activated which can lead to blood clots forming in the body.

Issues with primary hemostasis (platelets) usually show up as tiny bruises on the skin or gums, bleeding into the stool (black bowel movements) or urine and sometimes nose bleeds. Issues with secondary hemostasis usually show up as sudden severe bleeding into the chest, abdomen, or from a body orifice. Sometimes dogs with inherited deficits have issues from minor trauma at a young age but many times these issues do not show up until a patient has surgery for some reason. This is how hemophilia typically shows up, although it is a deficiency of one of the clotting factors.

Inherited platelet issues are not uncommon, von Willebrand's disease being the most common. This causes a deficiency in a protein needed to link platelets together and is present in multiple dog breeds with an easy DNA test available. P2RY12 is a gene that is responsible for platelet aggregation receptors, so the thought was that since the dog in the case study had the affected type, this was the



cause of her bleeding. The gene is present as wild type (normal) AA, carrier Aa and homozygous (though to be affected/abnormal) aa.

Cornell University research was supported by GSMDCA as well as many of you who submitted dog blood samples to the study- a total of 44 GSMD were tested, 6 of which were clinically affected by bleeding episodes. Unfortunately there was no link to bleeding dogs and P2RY12- there were 2 clinically affected dogs out of the 21 that tested normal (AA) for the gene, 3 out of the 16 that tested carrier Aa and 2 out of the 7 that tested aa. That means that there were 5 clinically unaffected dogs that tested "abnormal" for this gene. Although these dogs had slightly longer platelet reactivity index values (and the carrier dogs having intermediate), it did not seem to cause an elevation in any of the normal clotting blood tests or cause clinical symptoms. This study did develop an effective way of evaluating platelet response factors and proteins and may help lay the groundwork for further research. There are also DNA samples banked from 45 affected dogs. But the important take home message is that P2Y12 gene abnormality does not predict bleeding events. It is probably not in the best interest of the GSMD breed to continue to test for this.

If you are concerned your dog may have a clotting issue (they have any unexplained bleeding event, or they act suddenly weak or have pale gums), they should be evaluated by a veterinarian ASAP. Make sure that the vet clinic has clotting tests and blood products available if needed (you may need to go to an emergency or specialty practice.) There are several common tests that can be done on blood samples such as platelet count, PT and PTT to determine the likely cause of the bleeding issue. Tests such as setting a blood tube on the counter to see how long it takes to clot are not accurate and although mucosal bleeding tests have their place, they should probably not be used in the initial phases.

It is important to note the most common cause of clotting issues especially in older Swissies is internal bleeding from a splenic tumor. If the spleen tumor ruptures and the dog starts bleeding internally, the platelets and the clotting factors can quickly get used up and the dog continues to bleed. They can go into a state called disseminated intravascular coagulation or DIC. The clotting factors start acting errantly and small clots form in the blood stream as well as bleeding out of many small blood vessels. This quickly leads to death, many times even if it is treated aggressively. For example, this is what happens as a result of heat stroke as well as more severe cases of bloat and other illnesses and is why many recently deceased animals have blood in their abdomen and lungs.

Other common blood clotting issues are from rat poison (less common as the types have changed recently), tick borne diseases, autoimmune issues affecting platelets, and cancers.

Blood clotting issues are often treated with a transfusion of fresh frozen plasma. While this does not contain platelets, it contains all the clotting factors and proteins. If the blood clotting issue is caused by a lack of platelets, some dogs can get platelet transfusions, but these are often not as effective as we would like. If the clotting factors are still present and the underlying disease can be



treated most dogs will not bleed to death even with hardly any platelets. Dogs that have lost significant amounts of blood may also need red blood cell transfusions.

Dogs do have blood types, and although all Swissies tested so far have been DEA 1.1 Positive, getting a negative transfusion should not be a problem.

I would encourage breeders to have puppy homes notice and notify them of any bleeding events and have their vet be cautious before spay/neuter surgery. Unfortunately by waiting until our dogs are mature to do alteration surgery, we make the surgery much more difficult in these giant dogs. Veterinary surgeons need to be prepared for that. Swissies have giant blood vessels corresponding to their giant size and if these are not perfectly tied off and all bleeding is stopped they can continue to bleed as the dog wakes up and their blood pressure improves. A small skin bleeder from a neuter incision in a tiny dog is likely to stop while in a giant dog it may continue to get worse. It is important to note that spays are major surgeries, especially if puppies have been allowed to get fat. A vet clinic that has access to blood products and nighttime care if needed is ideal. It is likely that some of the unexplained bleeding events in young Swissies after surgery could have been prevented with better techniques.

There are also many medications including NSAIDs like Carprofen, aspirin, and even fish oil that can cause prolonged clotting times and you should notify your vet of medications used. There are certain times when blood thinner and platelet aggregation prevention medications should be used to prevent clots in dogs with auto immune, kidney and some other illnesses.

All in all, while the P2Y12 research may not have indicated the cause of the bleeding issues, it is important research, and we know more than we did before. Thank you for your participation and please continue to support the health initiatives to make our breed as healthy as possible.