

Carla Remulla

Brutlag

Genomics and Medicine

6 December 2012

Immunoglobulin Deficiencies and the Effects on One's Life

Immunoglobulins, also known as antibodies, are substances that attach to foreign bodies to mark them for destruction by the immune response. There are five major types of immunoglobulins that are specific to different types of foreign bodies. A deficiency in any of these types leads to increased chances of infection and the possibility of repeated infection throughout one's lifetime. A few weeks ago, my RA, Eric Dunn was bedridden with the flu for over a week. I later learned about his experience with an IgG subclass deficiency, which he has struggled with his entire life. Immunoglobulin deficiencies currently cannot be completely cured, but patients can be treated with antibiotics and immune serum.

The types of immunoglobulins and deficiency syndromes associated with them include IgA, IgM, IgE, IgD and IgG. IgA antibodies are found in areas most exposed to outside foreign bodies. For example, they are found in the saliva, tears, and blood and along the digestive tract. Next, IgM antibodies are the biggest antibodies, found in the blood and lymph fluid and are the first antibody made in the immune response. IgE antibodies are found in the lungs, skin and mucous membranes, and IgD antibodies are found in tissues that line the belly and chest. Lastly, IgG antibodies are the most common antibodies, found in all body fluids. Thus, a deficiency in this immunoglobulin causes highly increased susceptibility to infection. Constituting 75% to 80% of antibodies, IgG is an antibody one would not want to be deficient in.

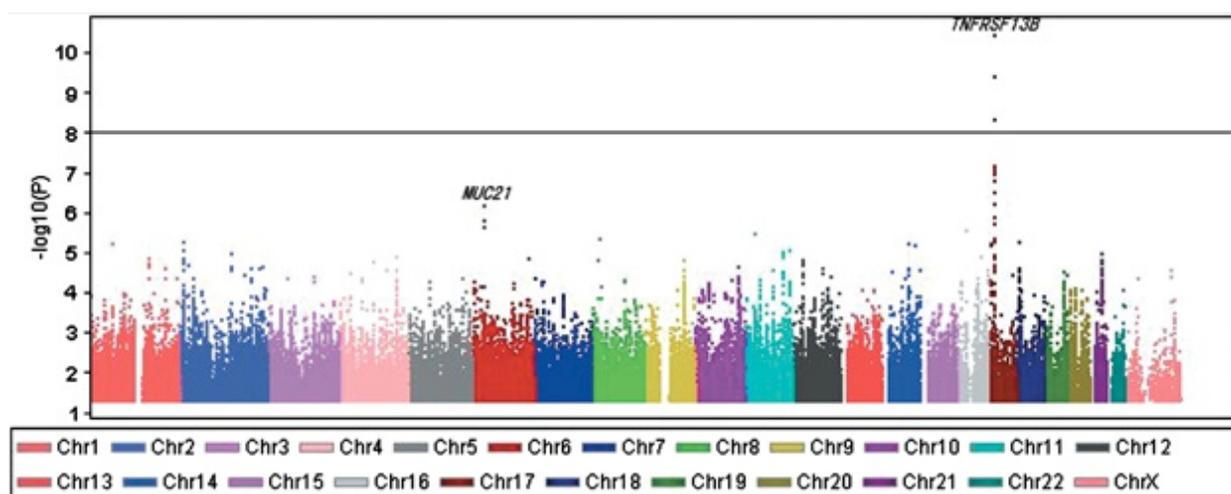
Furthermore, IgG has four subclasses, IgG1, IgG2, IgG3 and IgG4, arranged by decreasing concentration. Patients are said to have a selective IgG subclass deficiency if they lack one or two IgG subclasses, even if they have normal levels of other immunoglobulins (including total IgG). The course of the condition differs between patients. The deficiency occurs more often in children than in adults, suggesting that it is possible to “outgrow” it. For reference, “In a large Swedish study examining the serum IgG subclass levels of 6580 patients with increased susceptibility to infection, the normal ranges were derived from a group of 40 adults and 182 children stratified by age” (Oxelius et al, 1986). Studies have shown that some children can develop normal subclass levels as they grow older; others retain their deficiency, while some deficiencies can evolve into Common Variable Immunodeficiency.

IgG replacement therapy is often used for patients with the deficiency, in which patients are administered IgG intravenously, averaging around 100-200 mg/kg per week. Studies have reported improvement following the replacement therapy; however, it is generally only recommended for patients with recurrent infection and failure of specific antibody responses (Jefferis et al, p. 362). It is also common for patients with this deficiency to have recurring infections in the ears, sinuses, bronchi and lungs. Thus, it is common for patients to be prescribed antibiotics, for either treatment or prevention. On the other hand, vaccines can have a decreased effectiveness in individuals with the deficiency. To be more specific, “Subclass-deficient patients may require more than one dose of Hib-prp conjugate vaccines before they produce an adequate antibody response; this pattern of seroconversion is characteristic of young infants aged 6 months or less” (Granoff et al, 1989).

On a genetic level, there is no clear pattern of inheritance observed for the

deficiency, but a genome-wide association study has been performed by M Liao et al to determine specifically affected loci. In a two-stage GWAS of 1999 and 1496 participants, respectively, it was concluded that three single-nucleotide polymorphisms located in *TNFRSF13B* on 17p11.2 were significantly associated with IgG level: “rs4792800 in the intron (combined P -value= 1.45×10^{-12}), rs12603708 in the intron (combined P -value= 1.82×10^{-8}) and rs3751987 at ~65 kb downstream of the 5'-UTR region of *TNFRSF13B* (combined P -value= 3.67×10^{-9}).”

The Manhattan plot of the GWAS:



Evidently, the SNPs located in the *TNFRSF13B* region are most significant, followed by those in *MUC21*. After testing the SNPs through multiple regression analysis, five were selected to be further studied, three in *TNFRSF13B*, one in *MUC21* and one in the intergenic region. In the second stage, only the SNPs in the *TNFRSF13B* region were confirmed, while the other two were not, having P -values that were too high. The following table lists the SNPs associated with levels of serum IgG:

SNP	Chr	Position ^a	Function	Genes	Allele	First stage (N=1999)						Second stage (N=1496)						Combined	
						Allele(m)	Freq(m)	Mean			P-values ^b	Hwe	Freq (m)	Mean			P-values ^b	Hwe	P-values ^b
								mm	mM	MM				mm	mM	MM			
rs1634731	6	31063660	Intron	MUC21	A/G	G	0.18	13.93	13.37	12.92	2.13 × 10 ⁻⁶	0.88	0.19	12.04	12.49	12.19	1.56 × 10 ⁻¹	0.03	3.13 × 10 ⁻⁵
rs1260370	17	16787838	Intron	TNFRSF13B	A/G	G	0.25	12.43	12.83	13.32	5.61 × 10 ⁻⁷	0.08	0.24	11.55	12.21	12.44	6.96 × 10 ⁻⁴	0.22	1.82 × 10 ⁻⁸
rs3751987	17	16777150	Promotor	TNFRSF13B	A/G	G	0.49	12.73	13.01	13.56	1.57 × 10 ⁻⁷	0.42	0.49	11.94	12.29	12.60	6.74 × 10 ⁻⁴	0.84	3.67 × 10 ⁻⁹
rs4792800	17	16785892	Intron	TNFRSF13B	A/G	G	0.50	13.63	13.04	12.62	3.33 × 10 ⁻¹¹	0.72	0.52	12.59	12.34	11.82	6.32 × 10 ⁻⁵	0.57	1.45 × 10 ⁻¹²
rs2013111	21	33198616	Intergenic		T/C	T	0.45	13.56	13.07	12.79	9.77 × 10 ⁻⁶	0.44	0.46	12.37	12.28	12.24	6.16 × 10 ⁻¹	0.30	7.05 × 10 ⁻⁴

Also in the GWAS, smokers versus non-smokers were compared as well as alcohol drinkers versus non-drinkers. While no definite conclusion was made about alcohol use, it was observed that smokers have significantly lower levels of IgG.

The influence of smoking and alcohol drinking on IgG level:

Characteristic	First stage			Second stage			P-value ^b
	n	IgG level(g/l ⁻¹)	P-value ^b	n	IgG level(g/l ⁻¹)	P-value ^b	
Smoking			<0.001			<0.001	
Yes	1012	12.57±1.21		771	11.90±1.23		
No	983	13.62±1.21		712	12.71±1.24		
Alcohol drinking			<0.001			0.158	
Yes	1706	12.97±1.21		1233	12.24±1.24		
No	289	13.75±1.23		261	12.50±1.26		

^a Values are shown as mean±s.d.; IgG level was log-transformed and the values presented were back-transformed.

^b T-test was used to compare the means between the sub-groups of smoking or drinking.

On a personal level, an IgG subclass deficiency provides for a unique experience growing up. My RA, Eric is the sixth of six siblings, with no family history of immunoglobulin deficiency (as, according to studies, it is not inherited). He reported that he was diagnosed when he was an infant through a series of blood tests. Moreover, he was tested for his antibody response to immunizations. He did not produce the associated antibodies, which was a cause for concern. From infancy, he frequented the ICU and continued to be in and out of the hospital throughout childhood.

Growing up, he was sick all the time. At infancy, he was sick more often than he was healthy. His mother was a nurse, so he was able to have monitoring equipment in his bedroom at home. From ages four through seven he would be sick approximately

once a month, and got a shot every month, as well as intravenous IgG. Finally, at age ten, he was the most sick he ever was, when he got mycoplasma pneumonia, a bacterial infection of the lungs, which lead to meningitis, the inflammation of the tissue that surrounds the brain and spinal cord, and encephalitis, an inflammation of the brain at the same time.

Since then, he has not had to have as many shots, and has been relatively healthy, although getting swine flu, mononucleosis (twice), and meningitis again, and having occasional problems with asthma. Now, he says, on the occasion that he does get sick, he gets sick for a long period of time (as he did a few weeks ago). Aside from these periods, and his use of anti-seizure medication and his inhaler, he lives a relatively healthy life.

His health aside, the situations this condition put him in shaped various aspects of his life. For example, in his family he received a lot of attention, especially from his nurse mom, that he wouldn't expect to have, being one of six children. This was exemplified by how he was given a toy at least once a month, whenever he would have to get a shot. Moreover, since he was so sickly as a child, he started school a whole year late; and when he did, he attended a school that met for only half the time a regular school met, leaving lots of time to go to Disneyland with his mother whenever he was healthy. Furthermore, Eric believes he grew up to be a very picky eater because when he was little, his mother would have such difficulty getting her sick child to eat that variety was not as important as making sure he had food in his system.

Before he was ten years old, he was advised to always stay inside rather than play outside as to not exhaust himself and make himself sick. Thus, after age ten when he no longer felt the heaviness of the condition, he got very involved in sports: he played baseball and continued playing all throughout high school. Lastly, as vaccines are not as

effective on him, he does not get the flu shot every year, and he says that he would be very cautious if he were ever to go Africa. Albeit a unique life, Eric says overall that he does not think his life was changed for the worse.

In conclusion, immunoglobulin deficiency syndromes are caused by the lack of different types of immunoglobulins, substances that are vital to the immune system. IgG is the most abundant immunoglobulin, and a deficiency of this type, caused by a genetic variant, causes increased susceptibility to infection. From one person's personal experience, it has been suggested that the condition vastly shapes one's life, but due to probability of "outgrowing" the condition as one grows older, it is possible that this shaping is not for the worst.

Works Cited

Dunn, Eric. Personal Interview. 2 Dec. 2012.

Dunn, Mrs. "Medical info." Message to Eric Dunn. 3 Dec. 2012. E-mail.

"IgG Subclass Deficiency." *ImmuneDisease.com*. Web.

<<http://www.immunedisease.com/about-pi/types-of-pi/igg-subclass-deficiency.html>>

"Immunoglobulins." *WebMD*, 29 July 2012. Web. <<http://www.webmd.com/a-to-z-guides/immunoglobulins>>

Jefferis, R et al. "Selective IgG subclass deficiency: quantification and clinical relevance," 14 May 1990. Web.

This paper referenced the following:

GRANOFF, D.M., CHACKO. A., LOTTENBACH, K. R. & SHEETZ, E. (1989)

Immunogenicity of Haemophilus influenzae type b polysaccharide outer membrane protein conjugate vaccine in patients who acquired Haemophilus disease previous vaccination with type b polysaccharide vaccine. *J. Pediatr.* 114, 925.

OXELIUS, V.A., HANSON, L.A., BJORKANDER, J., HAMMARSTROM, L. &

SJOHOLM, A. (1986) IgG3 deficiency: common in obstructive lung disease. In *Immunoglobulin Subclass Deficiencies* (ed. by L. A. Hanson, T. Soderstrom & V. A. Oxelius) p. 106 Karger, Basel.

Liao, M et al. "Genome-wide association study identifies common variants

at *TNFRSF13B* associated with IgG level in a healthy Chinese male population," 30 Aug. 2012. Web.

Schwartz, Robert A., MD, MPH. "Immunoglobulin G Deficiency." *Medscape*, 1 May

2012. Web. <<http://emedicine.medscape.com/article/136897-overview>>