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Genomic insight into the passive transfer of immunity

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Abstract
The neonatal calf, which is born with little or no humoral immunity, is totally dependent upon absorption of colostrally derived immunoglobulins mainly IgG for its early disease resistance through the process of passive transfer. They represent a family of proteins with a range of protective bioactivities and classified into several classes as IgM, IgA, IgG, IgE and IgD. IgG, IgA and IgM are the major immunoglobulin classes in mammary secretions. In general, colostrum produced in large volumes will have lower Ig concentration than colostrum produced in smaller volumes. Increased neonatal morbidity and mortality from neonatal enteric, systemic, and respiratory diseases are well-accepted consequences of Failure of passive transfer (FPT). The conservation and bioavailability of IgG at all stages of mammalian life can be attributed to Fc receptor (FcRn). The β2 m acts as an integral component of FcRn heterodimer for its cell surface expression and in its absence, FcRn is retained in endoplasmic reticulum. Although β2 m gene is closely associated with MHC class I molecule (highly polymorphic), still it is minimally polymorphic within the species. So, genomic research for passive transfer of immunity will pave the way for development of immunotolerant animals in future

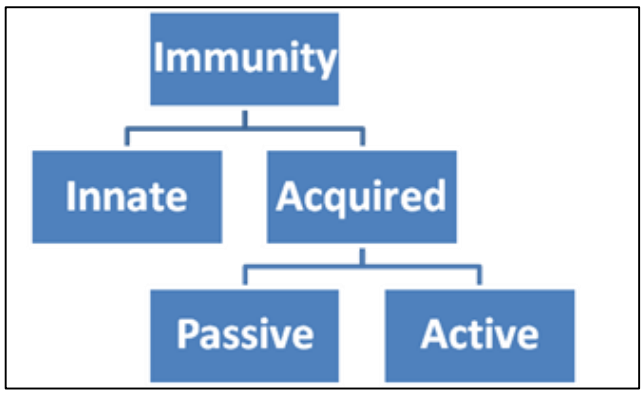
Keywords: β2 m gene, Colostrum, FPT, Immunoglobulin, Neonatal

Introduction
Dairy farming is an enterprise that requires proper feeding, management and health care of animals. For improving the reproduction efficiency higher calving rates, reduced still born and pre-weaned calf mortalities are prerequisite. Providing proper and timely nutrition and health care to new born calves can help increase the percentage of calves that are born alive and survive up to the age of weaning that will ultimately increase the number of replacement heifer calves. The neonatal calf, which is born with little or no humoral immunity, is totally dependent upon absorption of colostrally derived immunoglobulins for its early disease resistance [1,2].The protective effects of colostrum in relation to the incidence and severity of neonatal calf diseases are well established.
The cardinal feature of the immune response is the specific interaction of immune system with antigen. Immunology owes must to cattle since the first truly safe vaccine was produced by the English physician Edward Jenner in the year 1798 who identified that cowpox produced a harmless infection in man but rendered him immune to infection by the small pox agent [3]. In 1888, the exact nature of immunity was predicted by Roux and his colleague who found that specific resistance to diphtheria could be transferred with serum, a finding which led to widespread use of serotherapy with antitoxin prepared in horses [4]. The word antibody was coined to describe the active component of sera capable of imparting protection. In attempts to immunize against tuberculosis Koch in the 1890's recognized "bacterial allergy" or delayed hypersensitivity. These two phenomena, antitoxic immunity and delayed hypersensitivity represent two components of immune response, humoral and cellular immunity [5].

The Immune System
Lymphocytes are the basic components of the immune system. Primary organs having regulatory function include the thymus and bursa of fabricius in birds and the thymus and bone marrow in mammals [6]. Secondary lymphoid organs are those in which the actual effectors of immune response are produced. Antibody is the effector of humoral immunity and the sensitized small lymphocyte the mediator of cellular immunity. The spleen and lymph nodes are the principal secondary organs but individual lymphocytes or lymph follicles in any tissue can function in immune response. In general thymic derived or T lymphocytes function in cellular immune response and bursa or bone marrow dependent lymphocytes (B lymphocytes)

generate humoral immune response.

The bovine immune system has two major components: the innate immunity and the acquired immunity. Innate immunity is a type of non-specific immune response system mediated by some chemical factors and some special type of cells. Acquired immunity is a specific immune response system that requires longer duration to develop. Acquired immunity may be passive or active. Passive immunity is due to antibodies that are transmitted naturally through the placenta to fetus, through colostrum to infant, or artificially by injection of antiserum for prophylaxis. Passive immunity is not permanent and does not last as long as active immunity. As far as neonatal calves are concerned, maternally derived passive immunity (antibody-mediated immunity from mother to fetus during pregnancy or post birth colostrums feeding) is the measure of sole protection against harmful pathgens. The ruminant neonates are entirely dependent on intestinal absorption of colostral immunoglobulins/antibodies in the first few hours of life for its immunity [1].



Colostrum

Colostrum the "first milk," is considered to be "liquid gold" as it contains maternal immunoglobulins that protect the neonates from invading pathogens [7]. Besides this, colostrum is also a rich source of proteins, vitamins and minerals. The immunoglobulins present in colostrums are absorbed through ruminant neonatal gut; provide passive immunity to young animals. However, both the concentration of immunoglobulin in colostrum and the permeability of the gut decrease rapidly and progressively over the first 48 h after birth [8,9]. Therefore, an adequate supply of colostrum, with abundant immunoglobulins, is essential during the initial period of life for the young to gain sufficient passive immunity to be able to survive until its own immune system is fully developed.

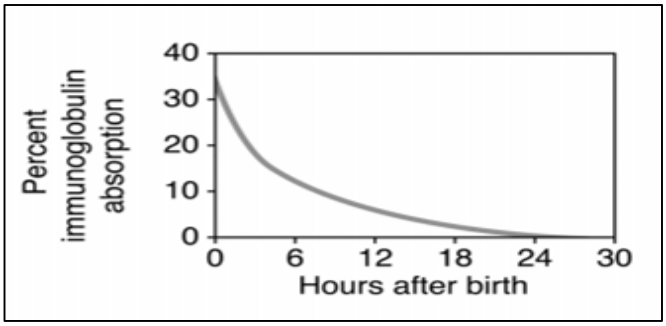


Fig 1: The ability of a calf to absorb immunoglobulins declines rapidly after birth

Colostrum contains many factors important in protection from microbial infection. Antimicrobial factors present in colostrum include immunoglobulins, lysozyme, lactoferin, lactoperoxidase and cytokines. Immunoglobulins are considered the most important defence factors present in colostrum, and are responsible for protection against both systemic and enteric diseases. Since immunoglobulins absorbed from colostrum circulate in the blood of the calf, they counteract any infection from spreading systemically. However, some of the immunoglobulins are "resecreted" from serum back into the intestine to provide local "enteric" immunity to prevent enteric diseases [10]. Most studies on the failure of passive transfer have concentrated on the level of immunoglobulins because they play such a crucial role in disease protection.

Immunoglobulins and passive immunity

The immunoglobulins present in colostrum or milk are the same as those found in the blood or mucosal secretions. They represent a family of proteins with a range of protective bioactivities and are classified into several classes including IgM, IgA, IgG, IgE and IgD [11]. IgG, IgA and IgM are the major immunoglobulin classes in mammary secretions. IgM appears initially when an organism is exposed to an antigen for the first time and has a low specificity in defeating the infection. IgA is the major immunoglobulin class found in mucosal secretions and prevents mucosal infections by agglutinating microbes. IgG is the primary immunoglobulin present in ruminant milk, in contrast to IgA being the key immunoglobulin present in human milk [12]. The bovine IgG is subdivided into IgG1 and IgG2. Out of them IgG1 predominates (80%) the total immunoglobulins absorbed by the neonatal calf [13]. Although the neonatal gut environment is primarily geared toward digestion of nutrients, the immunoglobulins remain sufficiently stable to provide protective benefits against pathogens.

Table 1: Immunoglobulin concentrations in bovine serum and mammary secretion

Immunoglobulin	Serum	Colostrum	Milk
IgG-total (mg/ml)	25	32-212	0.72
IgG1	14	20-200	0.6
IgG2	11	12	0.12

(Source- Larson[7])

Immunoglobulins in mammary secretions come from several sources and represent a history of the antigen exposure of the mother and the response of her immune system. They are transferred out of the mammary gland by milk ejection during suckling, enter the gastrointestinal tract of the neonate and are absorbed into the circulation of the neonatal calves by a process called micro-pinocytosis [14]. This will protect neonatal calves against high mortality and morbidity due to diarrhea, pneumonia and other diseases [15]. During the absorptive process, competition between microorganisms and immunoglobulins occurs for intestinal receptors for their transportation to the circulation. The immunoglobulins found in milk and the transfer of passive immunity from mother to neonate have been reviewed by many authors [12, 16, 17, 18].

Absorption of intact macromolecules across the intestinal epithelium into the neonatal circulation is possible for approximately 24 hours after the calf is born. The absorption of Ig occurs by an active process called pinocytosis. Maturation of the small intestine begins shortly after birth and the ability of the intestine to absorb macromolecules without digestion is lost by about 24 hours after birth. Traditionally,

determination of successful transfer of passive immunity has been by measuring the concentration of IgG in the serum of the calf at 24 to 48 hours after birth. If the serum IgG concentration exceeds some critical level, then the calf is thought to be relatively well protected against pathogens. The critical level for determining failure of passive transfer of immunity (FPT) is usually considered at 10 g/L, although some researchers have used other threshold serum IgG concentrations. There are many factors that influence the concentration of IgG in the blood of the calf at 24 to 48 hours. The amount of IgG in the bloodstream is, necessarily, affected by the size of the plasma or serum pool [19]. Intuitively, it is logical that calves with a larger blood volume will attain a lower IgG concentration than calves with smaller blood volume if they are fed the same mass of IgG. The amount of Ig in colostrum depends on a large number of factors, including the disease history of the cow. That is, cows tend to produce Ig in response to pathogens to which they have been exposed. Therefore, cows exposed to a greater number of pathogens tend to produce colostrum with greater Ig than cows exposed to fewer pathogens. This is often why older cows will produce colostrum containing more Ig than younger cows. Research has also indicated that the volume of colostrum produced will influence colostral Ig concentration. In general, colostrum produced in large volumes will have lower Ig concentration than colostrum produced in smaller volumes [8].

Failure of passive transfer (FPT)

Increased neonatal morbidity and mortality from neonatal enteric, systemic, and respiratory diseases are well-accepted consequences of FPT [19,20,21]. The consequences of FPT are not limited to the neonatal period, however. Effects on the incidence of disease and mortality are still seen at 2 months-of-age (Fig. 2), and diminished long-term performance is demonstrated by decreased weaning weights in beef calves [22] and decreased growth and milk production in dairy heifers [23,24].

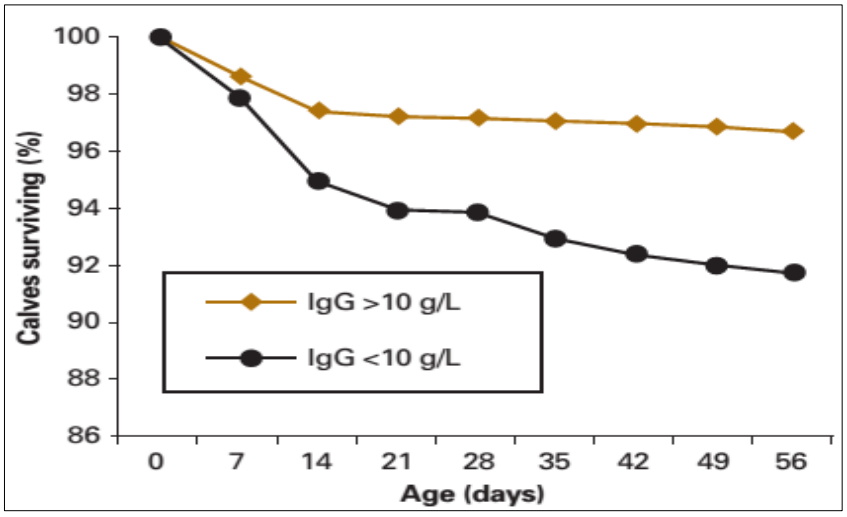


Fig 2: Relationship of Calves surviving upto 2 months with IgG

Measurement of FPT

The assessment of passive transfer has typically been done by the measurement of immunoglobulin concentration in the serum of calves, 24 to 48 hours after birth. The serum immunoglobulin concentration that is indicative of FPT is affected by the disease outcomes used to assess calf health, the management factors affecting calf health, and the method of immunoglobulin measurement. The calves with serum immunoglobulin levels in excess of 16 g/L had the lowest risk of disease, the greatest difference in risk occurred between groups of calves with serum immunoglobulin levels less than or greater than 8 g/L [25].

Immunoglobulin absorption and neonatal Fc receptor (FcRn)

Immunoglobulins that are vital to the host immunity are absorbed through specific receptors (called as Fc receptors) present on intestinal cell surface. The neonatal Fc receptor (FcRn) plays important role in multiple functions: FcRn transports maternal (colostrum derived) IgG to the circulation of the neonate from the gut lumen, regulates transfer of IgG into milk, transfer of maternal IgG across the placenta directly into the bloodstream of the fetus during pregnancy. FcRn is also expressed in tissues such as liver, mammary gland, intestine, kidney and lung indicating its role in IgG transport at these sites [26]. Additionally, FcRn is also expressed by vascular endothelial cells, which protects circulating IgG from degradation and significantly elongates its half-life. So it may be hypothesized that the conservation and bioavailability of IgG at all stages of mammalian life can be attributed to FcRn [26, 27].

The heavy chain of FcRn, also referred to as Fcgrt, is evolutionally distinct from all other Fc receptors [28] and is a novel member of the MHC class I protein family [29]. Fcgrt is comprised of 3 extracellular immunoglobulin superfamily domains (α_{1-3}) and forms an obligate heterodimer with the β2 microglobulin (β2 m) light chain [30]. Structurally, the FcRn heterodimer varies only subtly from conventional class I proteins by occlusion of the opposing α-helices that normally presents peptides to T cells and natural killer cells and most significantly, by the presence of localized glutamic and aspartic acid residues in the α_{2-3} domain junction [31]. These residues create an anionic pocket that allows easily protonated histidine residues unique to the hinge region of the CH_2-CH_3 IgG-Fc to engage in binding. However, binding only occurs in an acidic environment (pH~6-6.5) and shows a steep drop of affinity at neutral pH [32]. The C-terminus of Fcgrt carries an endosomal targeting motif that directs FcRn to its steady state location in the early acidic endosomes [33,34]. The FcRn is thought to gain access to extracellular IgG mainly as the result

of non-specific uptake of soluble extracellular material by fluid phase endocytosis (Fig. 3). Fusion of the endocytic vesicles with the early endosomes exposes the cargo to the acidic environment, which permits the binding of FcRn to IgG [35, 36]. This complex is then sequestered as microvesicles that exclude other proteins and is transported back to the cell membrane, whereupon fusion with the plasma membrane leads to exposure to a neutral pH and the release IgG to the extracellular environment [37].

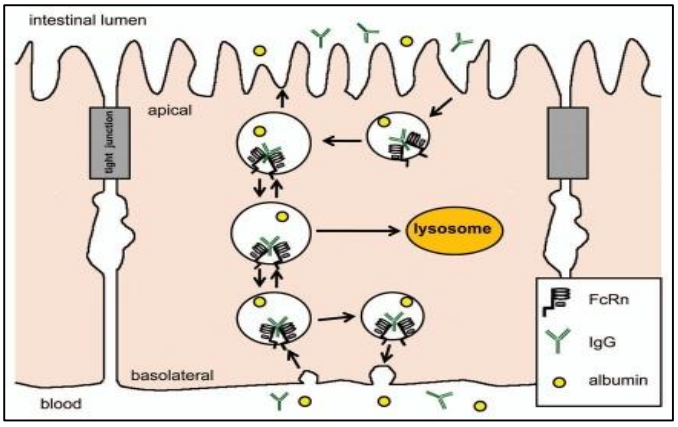


Fig 3: FcRn mediates bidirectional transport and membrane recycling of IgG in epithelial cells. IgG is believed to enter the cell by fluid phase pintocytosis and does not bind to FcRn until the endosome is acidified. However, in the duodenum, the acidic luminal environment may allow IgG to bind to FcRn.

Genetic variation of FcRn and its possible associations

Given the key role for FcRn in IgG and albumin homeostasis and transcytosis, it is reasonable to consider the possibility that there are naturally occurring allelic variants of FcRn that have functional consequence. The bovine FCGRT comprises 7 exons spanning approximately 6.5 kb DNA and present on its 18th autosome (Fig. 4). The first and second exons code for the UTR and signal polypeptide respectively. The third, fourth and fifth exons code for the three α polypeptides. The sixth and seventh exons code for the transmembrane domain and UTR region respectively [38]. The association study between bovine Fcgrt polymorphism and IgG concentration incolostrums revealed 4 SNP and 5 haplotypes. Out of them fifth haplotype was found to be significantly associated with a high IgG level. Significant association was also observed between bFcgrt haplotypes with serum IgG concentration in newborn calves [39]. The transgenic mice that over-express the bovine FcRn (bFcRn) in their lactating mammary glands showed increased IgG levels in the sera and milk.

The 5'-flanking region of the bFcRn alpha gene does not have a TATA box, but contains a potential Sp1 site close to the transcription start site that may stimulate constitutive promoter activity [40] similar to rat. Similar to its human counterpart, the bovine promoter has multiple C/EPBb transcription bindingsites between 600 and 500 bp, indicating potential regulation of the gene by interleukin-6 [38]. Another potential candidate for regulating the human FcRn transcription AP-1 [41], was not detected in the bovine promoter. In the more distant segment upstream of the transcriptional start site (between 1800 and 800) multiple potential binding sites were localized, such as the prolactin response factor MGF/STAT5 binding site which has also been found in the possum promoter sequence based on a similar database search [42]. Possible binding sites for interferon response elements IRF1, IRF2 and members of the nuclear factor kB family were also proposed in the bovine promoter which may indicate responsiveness of the bFcRn in inflammatoryreactions.

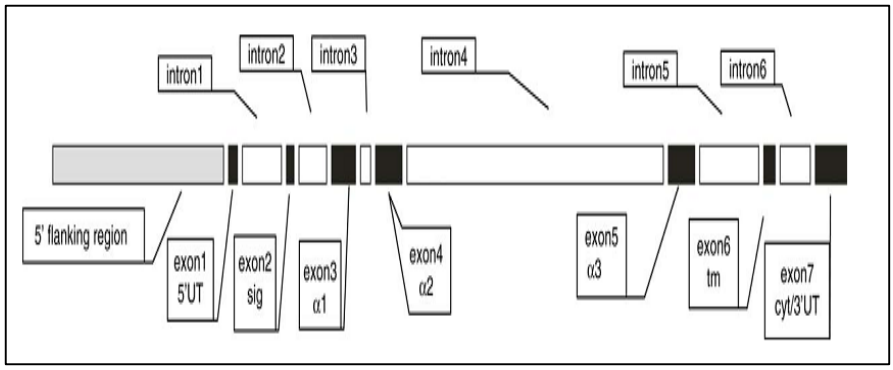


Fig 4: Bovine FCGRT gene exons

Bovine Beta 2 microglobulin gene

The beta-2-microglobulin (β2 m), is a non-covalently associated protein with MHC classes I molecules stabilizing their heavy chain has marked similarity to the structures of Ig domains [43]. Bovine β2 m, with a MW 11,630 Da has been found on the surfaces of nearly all cells. The β2 m genes are conserved across species, including mammals and birds containing four exons and three introns. It is located outside of the MHC region (present on 10th autosome of bovine). In bovines it contains 98 amino acid residues as compared with 99 for the human, rabbit, guinea pig, and murine proteins. The valine residue at 49th position in all the aforementioned species is deleted in the bovine variant. The primary function of β2 m is antigen recognition and peptide presentation to $CD8^+$ T cells to initiate cell mediated cytotoxicity. The β2 m also interacts with many non-classical MHC class I molecules such as HLA-E, -F, -G, and HFE in human and CD1, the neonatal Fc receptor, and H2-Q supporting their functions [44].

Role of β2m in passive immune transfer

Bovine neonatal calves get their preliminary immunity through the process of passive transfer i.e. due to feeding of colostrums containing immunoglobulin (mainly IgG). Immunoglobulin concentration in milk has been found to be influenced both by genetic and environmental factors [45]. IgG can be selectively transferred from serum to milk in mammary gland and milk to blood in intestinal epithelium of neonates by the Fc receptor (FcRn) mediated mechanism. The

FcRn binds with IgG at a weak acidic pH on basolateral surface of mammary gland epithelium and following transcytosis, and then it releases the IgG into milk upon exposure to neutral pH (Fig. 5). The β2 m acts as an integral component of FcRn heterodimer for its cell surface expression [46] and in its absence, FcRn is retained in endoplasmic reticulum. Furthermore, in absence of β2m, IgG binding is decreased compared with that of native FcRn.

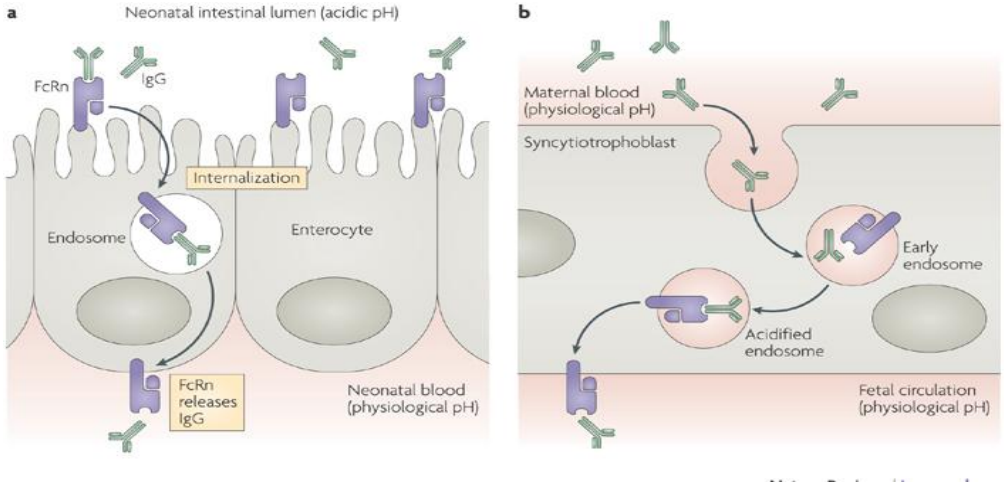


Fig 5: Binding of FcRn with IgG at a weak acidic pH on basolateral surface of mammary gland epithelium

Polymorphism in β2 m gene and its association

Although β2 m gene is closely associated with MHC class I molecule (highly polymorphic), still it is minimally polymorphic within the species. Two single nucleotide polymorphisms (SNPs) and one insertion/deletion (indel) of two base pairs, assorted into four haplotypes,
were identified. Twelve single nucleotide polymorphisms (SNPs), assorted into eight haplotypes, were identified by sequencing exons II and IV regions of β2 m in cattle [47]. The calves homozygous for one of the eight haplotypes were at increased risk of failure of passive transfer (FPT) which indicates that this haplotype is in linkage disequilibrium with genetic risk factors affecting passive transfer of IgG in calves. The dairy cows with homozygous deletion of β2 m were also found to be with the lowest milk IgG concentration and mass.

Conclusion

Immunity in neonates is controlled by environment as well as genetic factors. However genetic control of immunity is heritable. So scientific community is constantly searching for the genes responsible or genes associated with the control of immunity. The transfer of immunity from mother to neonates may be one of the processes of natural selection where neonates are weathered to develop similar immunity as that of mother which is developed in similar immunological situation. So, genomic research for passive transfer of immunity will pave the way for development of immunotolerant animals in future.

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