UNIT 9 POPULATION AND DISEASE ASSOCIATION STUDIES

Contents

Learning Objectives

After reading this unit, you will be able to:

- Elucidate the definitions of blood group, blood group system, definition of antigens and their expression in other tissues;
- Explain the reasons for inherited variation and distribution in RBC antigens and present status;
- Understand about antibodies, classification and nomenclature of antigens and their applications; and
- Expose to the knowledge on the association of blood groups and diseases.

9.0 INTRODUCTION

A group of red cells (RBC) or erythrocyte surface antigens in an individual is called 'blood group', whereas blood group systems are defined as the systems of one or more antigens controlled by a single gene or closely related genes. The specific sites located on proteins, glycolipids or glycoprotein components of RBC membrane and interacting with immune system are termed as antigens (ISBTweb.org). Antigens are considered as secondary gene products whereas the glycosyltransferase enzymes to which antigens are attached as primary gene products. It has been observed that evolution of antigens occurred earlier in ecto and endodermal tissues rather than RBC and hematopoietic cells and therefore also referred as histo-blood group antigens. Decreased level of A and B antigens were reported in patients with leukaemia and a plastic anaemia (Ewald and Sumner, 2016). Besides RBC, blood group antigens are also found on leukocytes, platelets, plasma proteins, and body fluids such as amniotic fluid,

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urine, saliva, gastric secretions, sweat, breast milk and seminal fluid, neurons, epithelial and endothelial cells (Ewald and Sumner, 2016). Each blood group system is genetically unique (ISBT web.org). Those who secrete blood group antigens in their body fluids are called secretors and those unable to secrete are termed as non-secretors.

Blood Group Systems

The blood group systems have been studied by Anthropologists to understand population variation and in racial classification. A number of blood group systems were discovered. American biologist, Karl Landsteiner discovered the A, B, O of ABO blood group system in 1901. A year later, in 1902, de Castello and Steini discovered the AB blood group. Rh blood group was discovered by Karl Landsteiner and Weiner in 1940. Before that in 1927, Landsteiner and Levine discovered the MNS blood groups. M+ and N+ RBCs are found among 75% of the population and M+N+ RBCs are the most common genotype found in 50% of population. In the same year they also discovered another blood group P. Later, other blood groups like the ABH (1930), Lutheran (1946), Kell (1946), Duffy (1950), Kidd (1951), and Diego (1954) were discovered by Lehrs, Callender & Race, Coombs et al, Cutbush et al, Allen et al, Levine et al, respectively.

9.1 INHERITED VARIATION AND DISTRIBUTION IN RBC ANTIGENS AND PRESENT STATUS

Blood group of a person is determined by the presence or absence of inherited variation of RBC surface antigens. To identify any blood group antigen the governing genetic variation has to be identified, sequenced and established that it is influencing a particular phenotype. As per the International Society of Blood Transfusion (ISBT) till June, 2021, 43 blood group systems containing 345 RBC antigens and governed by 48 genes are identified (ISBT web.org). The frequency of O blood group is higher in world population followed by A, B and AB and the incidence of B is higher in India (Dean, 2005). Founder effect and in areas endemic to malaria, selection is responsible for the difference in the frequency of blood groups in world populations (Anstee, 2010). The blood group system, symbol, gene names, number of antigens and chromosome location are presented in Table 9.1. The details of antigens of blood groups are given table 9.2. The number of antigens range from one to 56. The genes of these blood groups located on chromosomes 1, 2, 3, 4, 6, 7, 9,11, 12,13,15,16, 17,18,19,20, 22 autosomes and X chromosome. The Rh blood group system is more complex due to the presence of 56 antigens and ABO system is polymorphic due to the presence of >20 sub-groups (Ewald and Sumner, 2016).

Check Your Progress

1) Till now how many blood groups are identified and inform the number of antigens and genes involved in them.

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9.1.1 Antibodies

The presence of the antigens is identified by antibodies or commercially available antisera. Antibodies are proteins produced by B lymphocytes when exposed to antigens. On exposure to antigens, B lymphocytes are transformed into plasma cells and secrete antibodies. Antibodies are of five types i.e. IgG, IgM, IgD, IgE and IgA. Blood Antibodies are mostly IgG, IgM and IgD types. They are formed naturally due to their exposure to the antigens present in the environment (natural antibodies) (ABO blood group system) or RBC from other individuals (immune antibodies). Antibodies are reported to be inherited. Antibodies when exposed to the foreign antigens have been shown to reject transplanted organs in recipients and induce abortions (Ewald and Sumner, 2016).

9.1.2 Nomenclature of RBC Antigens

Blood group antigen names are given alphabetically and credit of discovery is given to the researchers who produce antibody against the blood group antigen. Each RBC antigen is given a number (6 digit number, first three numbers indicate blood group (Example ABO-001 and Rh-004) and last three digits indicate the order of the discovery of antigen. For instance, in ABO blood group, number 001 is given to A antigen because it is first discovered and 002 is given to antigen B) and assigned to blood group system or collection (antigen not meeting the criteria of blood group but linked genetically or biochemically to a particular blood group) or series (antigen not meeting either criteria of blood group or collections) (Dean, 2005). Since 1980 onwards the task of devising standards for blood group technology is shouldered by International Society of Blood Transfusion working party on Terminology for Red Cell surface antigens.

9.1.3 Classification of RBC Antigens

Blood group antigens are classified into different groups based on functions: ABO, H, Lewis, I, PIPK, Globoside, Forssamine (Transferases); Kell, Yt, Dombrock (Enzyme); Chido/Rodgers, Cromer, Knops (Complement regulations), Gerbich, MNS (Structural), Rh, RHAG, Diego, Colton, Gill, Kidd, Kx, Lan (Transport/ Channel), Indian, Lutheran, Landsteiner-Weiner, John Milton Hagen, Xg, Ok (Adhesion) and Duffy, Sciana and Raph (Receptor) (Ewald and Sumner, 2016). ISBT also classified RBC surface antigens based on functions in to different categories such as component of glycocalyx (MNS); structural component

(Diego and Gerbich); enzymes (Yt, Kell and Dombrock); receptor and adhesion molecules (Duffy and Luthern); membrane transporters (Diego and Kidd) and complement regulatory glycoproteins (Cromer and Knops) (ISBTweb.org).

9.1.4 Applications of RBC Antigens

Among blood groups identified in human beings, the ABO blood was first discovered in 1900 by Karl Land Steiner. First genetic polymorphism studies conducted using ABO blood group system and first human evolutionary tree was constructed using allele frequency data of ABO system. For management of clinical conditions, typing of blood group is done using commercial antisera. The typing involves antigen and antibody interaction. The antibody presents in the antisera bind with antigen present on the surface of RBC and cause agglutination of RBC. The blood group typing is done using various methods such as slide test, tube test, microplate, column/gel centrifugation and molecular imprinting. In clinical applications particular component of blood is used in transfusion such as plasma, platelets, packed RBC and immunoglobulins after cross matching particularly in case of ABO system. Apart from clinical applications, blood group data is also used for solving paternity disputes, identification of suspects at the crime scenes and finding evolutionary relationships between populations.

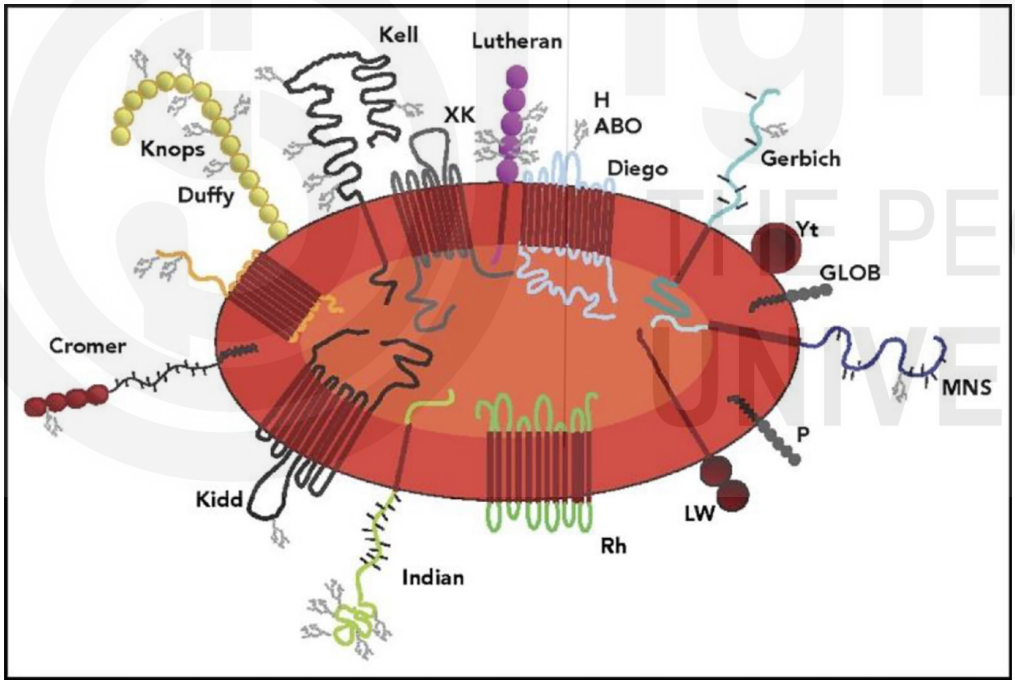

Fig. 9.1 : RBC membrane with representative blood group antigens
(***Source:*** https://onlinelibrary.wiley.com/doi/full/10.1111/voxs.12593

9.2 BLOOD GROUPS AND DISEASES

Blood group antigens play an important role in the causation or prevention of diseases. Presence and absence of antigens cause changes in the RBC membrane and functions associated with these membranes make the carriers of blood groups susceptible to diseases. Non-secretors are at increased risk of infection due to the binding of organisms to the polysaccharide on RBC surface

whereas in case of secretors the presence of antigens in body fluids prevent their binding (Abegaz, 2021). Difference in the expression of RBC antigens has been shown to either increase or decrease the susceptibility of individual to the infections (Fan et al.2020). These diseases are mostly found to be associated with phenotypes of ABO blood group system (Ewald and Sumner, 2016). The blood groups which are reported to be associated with different disease are presented in Table 9.3. From this table till now the involvement of ABO, Rh, Lewis, Duffy, MN, Knops, RHAG and Raph blood groups in causation of communicable and non-communicable diseases were reported. The cause and effect relationship between blood groups and diseases needs to be proved by validated mechanisms.

Check Your Progress

2) Name the blood groups which are associated with malaria?

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Table 9.1: Blood Group Systems in Humans

S. No.	Blood Group System	Symbol	Genes (s)	Antigens (n)	Chromosome location
1	ABO	ABO	*ABO*	4	9q34.2
2	Rh	RH	*RHD, RHCE*	56	1p36.11
3	MNS	MNS	*GYPA, GYPB*	50	4q31.21
4	Duffy	FY	*ACKR1*	5	1q21-q22
5	Kell	KEL	*KEL*	36	7q33
6	Lutheran	LU	*BCAM*	*27*	*19q13.2*
7	P1PK	P1PK	A4GALT	3	22q13.2
8	Lewis	LE	*FUT3*	6	19p13.3
9	Kidd	JK	*SLC14A1*	3	18q11-q12
10	Diego	DI	*SLC4A1*	23	17q21.31
11	Yt	YT	*ACHE*	5	7q22
12	Xg	XG	*XG,CD99*	2	Xp22.32
13	Scianna	SC	*ERMAP*	9	1p34.2
14	Dombrock	DO	*ART4*	10	12p13-p12
15	Colton	CO	*AQP1*	4	7p14
16	Landsteiner-Wiener	LW	*ICAM4*	3	19p13.2
17	Chido/Rodgers	CH/RG	*C4A, C4B*	9	6p21.3
18	H	H	*FUT1; FUT2*	1	19q13.33
19	Kx	XK	*XK*	1	Xp21.1
20	Gerbich	GE	*GYPC*	13	2q14-q21
21	Cromer	CROM	*CD55*	20	1q32

22	Knops	KN	*CR1*	12	1q32.2
23	Indian	IN	*CD44*	6	11p13
24	Ok	OK	*BSG*	3	19p13.3
25	Raph	RAPH	*CD151*	1	11p15.5
26	John Milton Hagen	JMH	*SEMA7A*	8	15q22.3-q23
27	I	I	*GCNT2*	1	6p24.2
28	Globoside	GLOB	*B3GALNT1*	2	3q25
29	Gill	GIL	*AQP3*	1	9p13
30	Rh-associated glycoprotein	RHAG	*RHAG*	4	6p12.3
31	FORS	FORS	*GBGT1*	1	9q34.13-q34.3
32	JR	JR	*ABCG2*	1	4q22.1
33	LAN	LAN	*ABCB6*	1	2q36
34	Vel	VEL	*SM1M1*	1	1p36.32
35	CD59	CD59	*CD59*	1	11p13
36	Augustihe	AUG	*SLC29A1*	4	6p221.1
37	Kanno	KANNO	*PRNP*	1	20p13
38	SID	SID	*B4GALNT2*	1	17q21.32
39	CTL2	CTL2	*SLC44A2*	2	19p13.2
40	PEL	PEL	*ABCC4*	1	13q32.1
41	MAM	MAM	*EMP3*	1	19q13.33
42	EMM	EMM	*PIGG*	1	4p16.3
43	ABCC1	ABCC1	*ABCC1*	1	16p13.11

Source: **www. isbtweb.org**

Table 9.2: Antigens of Blood Groups in Humans

S.No	Blood group system	Antigens
1	ABO	A, B, A B, A1
2	Rh	D, C,E,c,e,f,Ce,Cw,Cx,V,Ew,G,Hro,Hr,hrs,VS,CG,CE,Dw, c-like, cE, hrH, Rh29, Goa, hrB, Rh32,Rh33,HrB,Rh35,Bea, Evans, Rh39, Tar, Rh41, Rh42, Crawford, Nou, Riv, Sec, Dav, JAL, STEM, FPTT, MAR, BARC, JAHK, DAK, LOCR, CENR, CEST, CELO, CEAG, PARG,CEVF,CEWA,CETW
3	MNS	M, N, S,s, U, He, Mia, Mc, Vw, Mu, Mg, Vr, Me, Mta, Sta, Ria, CIa, Nya, Hut, Hil, Mv, Far, SD, Mit, Dantu, Hop, Nob, Ena, ENKT, 'N' Or,DANE, TSEN,MINY, MUT,SAT, ERIK,OSa, ENEP,ENEH, HAG, ENAV, MARS, ENDA, ENEV,MNTD,SARA,KIPP, JENU,SUMI,
4	Duffy	FYa, FYb,FY3,FY5,FY6
5	Kell	K,k,Kpa,Kpb,Ku,Jsa,Jsb,UIa,K11,K12,K13,K14,K16 ,K17,K18,K19, Km,Kpc,K22,K23,K24,VLNA, TOU, RAZ,VONG,KALT,LTIM, KYO, KUCI, KANT, KASH, KELP,KETI,KHUL,KYOR,KEAL
6	Lutheran	Lua,Lub,Lu3,Lu4,Lu5,Lu6,Lu7,Lu8,Lu9,Lu11,Lu12,Lu13, Lu14,Lu16,Lu17,Aua,Aub,Lu20, Lu21,LURC,LUIT,LUGA, LUAC, LUBI, LUYA,LUNU, LURA

7	P1PK	P1, Pk, NOR
8	Lewis	Lea,Leb, Leab,LebH,ALeb, BLeb
9	Kidd	Jka, Jkb,Jk3
10	Diego	Dia,Dib,Wra,Wrb,Wda,Rba,WARR,ELO,Wu,BPa,Moa,Hga, Vga,Swa,BOW,NFLD,Jna,KREP,Tra,Fra,SW1,DISK,DIST
11	Yt	Yta,Ytb,YTEG,YTLI,YTOT
12	Xg	Xga, CD99
13	Scianna	Sc1,,Sc2,Sc3,Rd,STAR,SCER,SCAN,SCAR,SCAC
14	Dombrock	Doa,Dob,Gya,Hy,Joa,DOYA,DOMR,DOLG,DOLC, DODE
15	Colton	Coa, Cob, Co3, Co4
16	Landsteiner-Wiener	Lwa,LWab,LWb
17	Chido/ Rodgers	Ch1, Ch2, Ch3, Ch4, Ch5, Ch6, WH, Rg1, Rg2
18	H	H
19	Kx	Kx
20	Gerbich	Ge2,Ge3,Ge4, Wb,Lsa,Ana,Dha,GEIS,GEPL,GEAT,GETI,G ECT,GEAR
21	Cromer	Cra,Tca,Tcb,Tcc,Dra,Esa,IFC,WESa,WESb, UMC,GUTI, SERF, ZENA, CROV, CRAM, CROZ,CRUE,CRAG,CROK,CORS
22	Knops	Kna,Knb,McCa,SI1,YKa,McCb,SI2,SI3,KCAM,KDAS,DA CY,YCAD
23	Indian	Ina,Inb,INFI,INJA,INRA,INSL
24	Ok	Oka, OKGV,OKVM
25	Raph	MER2
26	John Milton Hagen	JMH,JMHK,JMHL, JMHG, JMHM,JMHQ, JMHN,JMHA
27	I	I
28	Globoside	P, PX2
29	Gill	Gill
30	Rh-associated glycoprotein	Duclos, OIa, DSLK,Kg
31	FORS	FORS1
32	JR	Jra
33	LAN	Lan
34	Vel	Vel
35	CD59	CD59.1
36	Augustihe	AUG1, Ata, ATML, ATAM
37	Kanno	KNNO1
38	SID	Sda
39	CTL2	VER, RIF
40	PEL	PEL
41	MAM	MAM
42	EMM	Emm
43	ABCC1	WLF

Source: **www. isbtweb.org**

Table 9.3: Association of Blood Groups and Diseases

Communicable Diseases	
Blood Group	**Disease (s)**
A	Infections of Hepatitis B virus (Wang et al., 2012a), HIV, (Mohammadali and Pourfathollah, 2014), *Helicobacter pylori* (Wang et al., 2012b),COVID-19 (Alkout et al., 2020), H1N1 (Lebiush et al.,1981), *E. Coli* (Zhou and Welsby, 2014), Small Pox and *Pseudomonas Aerugionosa* (Ewald and Sumner, 2016)
B	Infections of Falciparum malaria (Panda et al., 2011), Gonorrhoea, *Streptococus pneumoniae* (Garatty , 2005), H3N2, a Type A influenza (Mackenzie and Fimmel,1978), Hepatitis-C (Erhabor et al., 2015), Tuberculosis, *E. Coli*, S. Pneumoniae , and Salmonella (Ewald and Sumner, 2016)
O	Infections of *E. coli* (Blackwell et al.2002), hepatitis-B, C (Jiang et al.2020; Aljooni et al., 2012) and Noro virus (Hutson et al.,2002; Liao et al., 2020), Plague, Cholera, Tuberculosis, Mumps (Garatty, 2005), SARS (Cheng et al., 2005) and Dengue virus (Harshan et al.,2020)
AB	Infections of HIV-2 (Abdulazeez et al., 2008) influenza A & and B (Aho et al.,1980; Naïkhin et al., 1989), Dengue hemorrhagic fever (Muruganathan et al., 2018), Smallpox, *E. Coli* and salmonella (Ewald and Sumner, 2016)
Rh	Infections of Hepatitis-B virus infection (Mohammadali and Pourfathollah, 2014)
M	Yaws (Garatty , 2005)
Knops	*Plasmodium falciparum* Malaria (Ewald and Sumner, 2016)
Duffy	*Plasmodium vivax Malaria* (Ewald and Sumner, 2016)
Lewis	Cholera (Ewald and Sumner, 2016)
Non-communicable Diseases	
A	Myocardial infarction, venous thrombo-embolism, ischemic stroke (Wiggins et al., 2009), Pancreatic cancer (Wang et al., 2012a), gastric cancer (Wang et al.2012b), nasopharyngeal cancer (Sheng et al., 2013), hyperlipidaemia, heart failure and atherosclerosis (Groot et al., 2020),diabetes, heart disease(Zhou and Welsby, 2014), Breast, Basal Cell, Non-small cell lung, Gastric, Skin, Nasopharyngeal, Hepato cellular, Bladder, Lung, Gall bladder, Ovarian, Oral, Cervical, Oesophageal, Oral and salivary gland cancers (Amjadi et al.,2015)
B	Ovarian cancer (Gates et al., 2011), Type 2 diabetes (Qureshi and Bhatti, 2003), exocrine pancreatic cancer (Ewald and Sumner, 2016) hypertension (El-Sayed and Amin, 2015); Hodgkin's lymphoma (Ewald and Sumner, 2016), myocardial infarction (Groot et al., 2020), Gastrointestinal tract, Gall bladder, central nervous system, oral and non-squamous cell, Laryngeal, Genitourinary, Liver, Ovarian, Breast, Pancreatic and Cardiac cancers (Amjadi et al.,2015), Hodgkin's lymphoma (Ewald and Sumner, 2016)
AB	Myocardial infarction, venous thrombo-embolism (Wiggins et al., 2009); Preeclampsia (Hiltunen et al.2009), nasopharyngeal cancer (Sheng et al., 2013), cognitive impairment (Ewald and Sumner,2016), Lung, Nasopharyngeal and Gastrointestinal carcinoma (Amjadi et al., 2015)

O	Meta static tumour (Ewald and Sumner, 2016) neuroendocrine tumours (Weisbroad et al., 2013), peptic ulcer (Ewald and Sumner, 2016; Garatty, 2005), Malignant Melanoma (Amjadi et al., 2015), Multiple Endocrine Neoplasia Type1, Von Hippel-Lindau and Neuroendocrine, acute lymphoblastic leukaemia, Primary and Secondary Non-Hodgkins central nervous system lymphoma (Ewald and Sumner, 2016)
Rh	Haemolytic disease of new born (Anstee, 2010), Chronic and auto immune haemolytic anaemia (Ewald and Sumner, 2016)
RHAG	Chronic and auto immune haemolytic anaemia (Ewald and Sumner, 2016)
Lewis	Peptic ulcer (Garatty, 2005)
Raph	Renal disease (Garatty, 2005)

9.3 SUMMARY

The specific sites located on proteins, glycolipids or glycoprotein components of RBC membrane and interacting with immune system are termed as antigens. Besides RBC, blood group antigens are also found on leukocytes, platelets, plasma proteins, and body fluids such as amniotic fluid, urine, saliva, gastric secretions, sweat, breast milk and seminal fluid, neurons, epithelial and endothelial cells. As per the International Society of Blood Transfusion (ISBT) till June, 2021, 43 blood group systems containing 345 RBC antigens and governed by 48 genes are identified. Founder effect and natural selection (in areas endemic to malaria and other communicable and non-communicable diseases) are responsible for the difference in the frequency of various blood groups in world populations. Antibodies are proteins produced by B lymphocytes when exposed to antigens. They are formed naturally due to their exposure to the antigens present in the environment (natural antibodies) (ABO blood group system) or RBC from other individuals (immune antibodies). Blood group antigen names are given alphabetically and credit of discovery is given to the researchers who produce antibody against the blood group antigen. Based on the functions of antigens they are classified into different categories. In clinical, forensic, medico-legal and evolutionary studies data of blood groups is useful. Till now the involvement of ABO, Rh, Lewis, Duffy, MN, Knops, RHAG and Raph blood groups in the causation of communicable and non-communicable diseases is only known.

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9.5 ANSWERS TO CHECK YOUR PROGRESS

1) As per the International Society of Blood Transfusion (ISBT) till June, 2021, 43 blood group systems containing 345 RBC antigens and governed by 48 genes are identified.

2) Blood groups B, Duffy and Knops are associated with *Plasmodium falciparum* ad Vivax Malaria.