

# Effects of changes in dna base sequences into genetic disorder inheritance



### Sickle Cell Anaemia

In 1910, sickle cell disease (SCD) was first noted in a dental student who was said to have pulmonary problems and was, and still is today, recognised by the characteristic 'sickle-shaped' erythrocytes, a term coined by Herrick after seeing the abnormal structures in his patient (Herrick, J. B, 1910). SCD is a broad term used to describe a myriad of genetic disorders that derive from a mutated form of the beta globin (HBB) gene. Normally, the HBB gene is responsible for the synthesis of beta globin, a subunit of a larger protein, haemoglobin, yet in sickle cell diseases, such as sickle cell anaemia (SCA), errors occur in the production of this polypeptide (Ballas et al 2012). A recent study had shown that in the UK alone, there are 14000 people living with SCA in the UK which is roughly the same as 1 in 4600 people (Dormandy, James, Insua and Rees 2018). Thus, with so many people suffering from such a horrific disease, we are brought to the question of what is SCA at a cellular level and how is it caused?

### From base sequence to beta globin: the formation of SCA

Berg et al (2018) points out that there is a structural hierarchy that exists within cells. With respect to SCA, this is reinforced in so far as if any error occurs within the hierarchy at any given point, in this case, at the most basic and fundamental level at the DNA base sequence, this can have direct consequences on the conformation and structural properties of enzymes and proteins. SCA is the result of sickle haemoglobin synthesized as opposed to the predominant, healthy adult form. A point frame mutation occurs at the HBB gene located on chromosome 11 whereby adenine is replaced with

thymine, resulting in the codon GTG as opposed to GAG. The consequence of this is that GTG, once translated, will lead to the synthesis of the amino acid valine as opposed to glutamic acid. Whilst this effect seems minimal, the result of this is that valine being a non-polar amino distorts the structure and folding of the polypeptide, resulting in hydrophobic interactions to form in the proteins tertiary structure, thus causing the sickle cell haemoglobin (HbS) to form (Ingram, 1956).

In contrast, in healthy haemoglobin that is composed of four polypeptide chains, two of which are alpha globin and the other two beta globin which form  $\alpha\beta$  pairs and share each an iron containing Heme group which enables the haemoglobin to associate and dissociate with oxygen in different partial pressures (Lukin, 2003). However as for sufferers of SCA, their ability to associate with oxygen is dramatically reduced. In fact, in deoxygenated conditions, strings of HbS are inclined to essentially adhere together which is facilitated by the fact that there is no nucleus in red blood cells, hence resulting in the typical biconcave shape of haemoglobin to be distorted so easily into the crescent like shape that characterises SCA (Berg et al, 2018). As of this, suffers of the disease often report to feel quickly out of breathe and experience chronic pain in regions whereby the HbS aggregates and leads to cell distortion, however, there are numerous treatments such as hydroxyurea seem hopeful in reducing such symptomologies (Charache et al, 1992).

The inheritance of SCA:

As SCA is a result of a mutation on the HBB gene, the trait can also be inherited in offspring since it is genetic. SCA is a recessive genetic conditioning, meaning individuals can either be heterozygous and thus a carrier or homozygous recessive, hence a sufferer. Thus, by the laws of monohybrid inheritance, If the parents of the offspring are both heterozygous or homozygous recessive, the chances of the offspring inheriting the disorder are increased (Neel, 1949). It would be thought then that such a unfavourable genotype would be selected against by natural selection, however it seems as though the inheritance of SCA has a heterozygous benefit, particular for populations in Africa whereby the genotype is most frequent since individuals are still able to produce some healthy HbA whilst at the same time having a some form of resistance that the mutated HBB gene seems to confer (Nagel et al, 1985). It was believed that by having the sickle cell genotype, this helped prevent the parasites ability to invade the host cell, however, recent research has proved this to be wrong. As opposed to preventing the invasion into the host cell, it appears “sickle haemoglobin makes the host tolerant to the parasite” as Miguel Soares quotes. Soares and his collages argue than the expression of the enzyme, heme oxygenase-1 (HO-1) is strongly induced by sickle cell haemoglobin. It has been shown that this enzyme produces carbon monoxide gas previously in the lab, which now scientists believe confers protection to malaria. Soares and his team elaborate, stating that when carbon monoxide is produced in response to HbS seemed to have protective effects on the infected host cell from developing malaria, whilst at the same time, not affecting the parasites life cycle inside the erythrocytes. (EurekAlert,. 2018). Thus, having this heterozygous advantage means, unlike most genetic disorders, that the <https://assignbuster.com/effects-of-changes-in-dna-base-sequences-into-genetic-disorder-inheritance/>

allelic frequency for sickle cell anaemia in the whole population will not be subject to selective removal, yet in fact, will even be selected for in places whereby malaria acts as a big selection pressure killing thousands such as in sub-Saharan Africa affecting up to 3% of births (Grosse, S. D et al, 2011)

### Haemophilia – ‘ The Royal disease’

SCA however is not the only genetic disorder that one can inherit, nor is monohybrid inheritance the only way we can inherit genetic disorders. Haemophilia, which means love (“ philia”) of blood (“ haemo”) seems to be an ironic name to give to the sex linked disorder, characterised by prolonged and excessive bleeding (Fijnvandraa, K. et al 2012). Haemophilia has been called a “ royal disease” largely because the haemophilia gene was passed from Queen Victoria, who became Queen of England in 1837, to the ruling families of Russia, Spain, and German (Sciencecases. lib. buffalo. edu, 2018). During the formation of a blood clot, precursor proteins such as factor VIII enter a cascade of enzymatic events to lead to the synthesis of Fibrin, a protein that enables blood clots to form to prevent excessive bleeding. However, it has been noted in recent years that there are polymorphisms in the factor VIII genes in sufferers of the disease (Bowen, DJ. 2012). Haemophilia can be separated into Haemophilia A and B which arise because of a different, yet similar, precursor protein gene involved in blood clot formation being mutated. Haemophilia A is four times more present in the population as opposed to Haemophilia B, with Haemophilia affecting 1 in 30, 000 males whereas Haemophilia A affects 1 in 50, 000 males (Lilicrap D, 1998).

### The biochemistry of Haemophilia –

45% of cases being a result of inversion mutations, yet this does vary – for example, studies have reported numerous cases of substitution mutations also. Consequently, this changes the conformation of primary structure of factor VIII (Bowen, DJ. 2012). Recent molecular studies have shown that in at least five Haemophilic patients, a A> G mutation changes AAT to GAT, and in turn neutral amino acid asparagine becomes negatively charged aspartic acid. This can therefore disrupt the non-covalent e. g. ionic bonding between R groups in the proteins tertiary structure, thus leading to a non-functional form of factor VIII in its A2 domain. Due to this deficient protein, Haemophiliacs have a lack of Fibrin that circulates their body, thus, even a simple bump on the head can cause bleeding into the brain for some people who have severe haemophilia (Owaidah, TM et al. 2009).

### The inheritance of Haemophilia:

Any gene that is found either on the X or Y chromosome is said to be sex linked. However, the X chromosome is much longer than the Y chromosome, meaning that for most of the length of the X chromosome, there is no equivalent homologous portion on the Y chromosome. Thus, characteristics that are controlled by recessive alleles on this non-homologous portion of the X chromosome, such as haemophilia will appear more frequently in the male, whose genotype is XY – thus, any recessive sex-linked disorder means that males will always be most affected as they cannot be heterozygous unlike women, hence why haemophilia occurs in about 1 of every 5, 000. However, this is not exclusive to just men, as if a female was to inherit a homozygous

recessive genotype, she too could be a sufferer, or yet, a carrier if she was to have the heterozygous genotype. However, haemophilic females is often rare since they are subject to death with the onset of menstruation at puberty (Centres for Disease Control and Prevention, 2018). As expected, this has resulted in the selective removal of this gene by the population, making its occurrence relatively rare, affecting about one person in 20, 000 in Europe alone. (Centres for Disease Control and Prevention, 2018). Thus, if a carrier female and a normal male were to produce offspring, there would be a 50% chance that they could have male or female offspring who are not affected. However, there would then be a 25% chance that they could produce a carrier female and also a 25% chance they could produce a 25% haemophilic male.

- Herrick J. B. Peculiar elongated and sickle-shaped red blood corpuscles in a case of severe anemia. *Arch. Int. Med.* 1910; 6: 517-52
- Ballas, S. K., Gupta, K. and Adams-Graves, P., 2012. Sickle cell pain: a critical reappraisal. *Blood* , pp. blood-2012
- Dormandy, E., James, J., Inusa, B. and Rees, D., 2017. How many people have sickle cell disease in the UK?. *Journal of Public Health*
- Berg, J., Tymoczko, J. and Stryer, L. (2018). *Biochemistry* . [online] Ncbi. nlm. nih. gov. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK21154/> [Accessed 22 Oct. 2018].
- Ingram, V. M., 1956. A specific chemical difference between the globins of normal human and sickle-cell anaemia haemoglobin. *Nature* , 178 (4537), p. 792.

- Lukin, J. A., Kontaxis, G., Simplaceanu, V., Yuan, Y., Bax, A. and Ho, C., 2003. Quaternary structure of hemoglobin in solution. *Proceedings of the National Academy of Sciences* , 100 (2), pp. 517-520.
- Berg, J., Tymoczko, J. and Stryer, L. (2018). *Biochemistry* . [online] Ncbi. nlm. nih. gov. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK21154/> [Accessed 22 Oct. 2018].
- Charache, S., Dover, G. J., Moore, R. D., Eckert, S., Ballas, S. K., Koshy, M., Milner, P. F., Orringer, E. P., Phillips, G. J. and Platt, O. S., 1992. Hydroxyurea: effects on hemoglobin F production in patients with sickle cell anemia [see comments]. *Blood* , 79 (10), pp. 2555-2565.
- Neel, J. V., 1949. The inheritance of sickle cell anemia. *Science* , 110 (2846), pp. 64-66.
- Nagel, R. L., Fabry, M. E., Pagnier, J., Zohoun, I., Wajcman, H., Baudin, V. and Labie, D., 1985. Hematologically and genetically distinct forms of sickle cell anemia in Africa: the Senegal type and the Benin type. *New England Journal of Medicine* , 312 (14), pp. 880-884.
- EurekAlert!. (2018). *Mystery solved: How sickle hemoglobin protects against malaria* . [online] Available at: [https://www.eurekalert.org/pub\\_releases/2011-04/igdc-msh042311.php](https://www.eurekalert.org/pub_releases/2011-04/igdc-msh042311.php) [Accessed 24 Oct. 2018].
- Grosse, S. D., Odame, I., Atrash, H. K., Amendah, D. D., Piel, F. B., & Williams, T. N. (2011). Sickle cell disease in Africa: a neglected cause of early childhood mortality. *American journal of preventive medicine* , 41 (6 Suppl 4), S398-405.



- Figjnvandraa Karin, Cnossen Marjon H, LeebeekFrank WG, Peters Marjolein. Diagnosis and management of haemophilia *BMJ* 2012; 344; e2
- Sciencecases. lib. buffalo. edu. (2018). [online] Available at: <http://sciencecases.lib.buffalo.edu/cs/files/hemo.pdf> [Accessed 24 Oct. 2018].
- Bowen DJ Haemophilia A and haemophilia B: molecular insights *Molecular Pathology* 2002; 55-1-18
- Lillicrap, D. Haemophilia. 1998 *The molecular basis of haemophilia B*. Jul; 4(4): 350-7
- Owaidah TM, Alkhail HA, Zahrani HA, Musa AA, Saleh MA, Riash MA, Alodaib A, Abu Amero K
- Blood Coagul Fibrinolysis. 2009 Sep; 20 . *Molecular genotyping of hemophilia A in Saudi Arabia: report of 2 novel mutations (6): 415-8.*
- Centers for Disease Control and Prevention. (2018). *Basics About Hemophilia / NCBDDD / CDC* . [online] Available at: <https://www.cdc.gov/ncbddd/hemophilia/facts.html> [Accessed 24 Oct. 2018].