The 2nd International Conference on Natural Resources and Life Sciences (NRLS-2018)

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PREFACE: the 2nd International Conference on Natural Resources and Life Sciences (NRLS) 2018

The 2nd International Conference on Natural Resources and Life Sciences (NRLS) 2018 has been organized by the Faculty of Biotechnology of University of Surabaya, Indonesia. The theme of this conference is *"Managing Natural Resources for Better Health"*. Focusing on biological aspects, the conference has facilitated chances of collaborations in research and development – as well as enlarged joint activities regarding natural resource management – among academics and professionals in their attempts to contribute further to the community through their respective fields.

The 2nd NRLS 2018 was held on August 23–24, 2018. This conference presented eight international speakers from five countries: Indonesia, Malaysia, the Netherlands, Singapore, and Thailand. Over 200 representatives of 48 institutions participated in this event, involving more than 74 abstracts submitted in the form of oral and poster presentations. After a rigorous selection process, the Scientific & Editorial Board have decided to publish 43 manuscripts in IOP Conference Series: Earth and Environmental Science (EES), an international proceedings indexed in Scopus, Scimago, Conference Proceedings Citation Index-Science (CPCI-S) of Clarivate Analytics's Web of Science, etc. From 43 selected ones above, 21 manuscripts were results of joint researches between Indonesia and various countries, e.g. Australia, England, Georgia, Germany, India, Japan, Latvia, Lithuania, Malaysia, the Netherlands, the Republic of Korea, Spain, and Sweden. Those manuscripts cover various biological themes, i.e. Food Biotechnology, Agricultural Biotechnology, Medical Biotechnology & Forensics, and Environmental Biotechnology & Renewable Energy. Each of the 43 manuscripts in IOP Conference Series–EES have been reviewed by at least two experts using double-blind system. The published manuscripts have passed all necessary improvement requirements (according to the IOP Proceedings standard), reviewer's comments, SI (*Système International d'Unités*), and similarity tests (with the highest threshold of 25 %) as well as editing procedure by professional editors from seven countries (Georgia, India, Indonesia, Latvia, Lithuania, Malaysia, and Sweden).

Our appreciation goes to the reviewers, editors and members of the Scientific & Editorial Board for their big efforts in reviewing and improving the manuscripts. For the generous supports in succeeding the NRLS-2018, we extend our gratitute toward the University of Surabaya's management and supporting units, our co-hosts the Faculty of Pharmacy and the Faculty of Medicine, and our sponsors VISION TEKNIK, SCIENCEWERKE, INDOLAB UTAMA, and MEGAH SEJAHTERA SCIENTIFIC.

Last but not least, we thank you all presenters and attendees for the active contribution to share scientific ideas, inspire new researches, and exchange new contacts for closer co-operations. We hope you have had enjoyable time with us and are currently encouraged to collaborate further in order to explore natural resources and life sciences in various aspects of living. We look forward to welcoming you and your team in the 3rd NRLS-2020!

Surabaya May 02, 2019
Republic of Indonesia - National Education Day

Johan Sukweenadhi, Ph.D.
Executive Chief of the 2nd NRLS-2018

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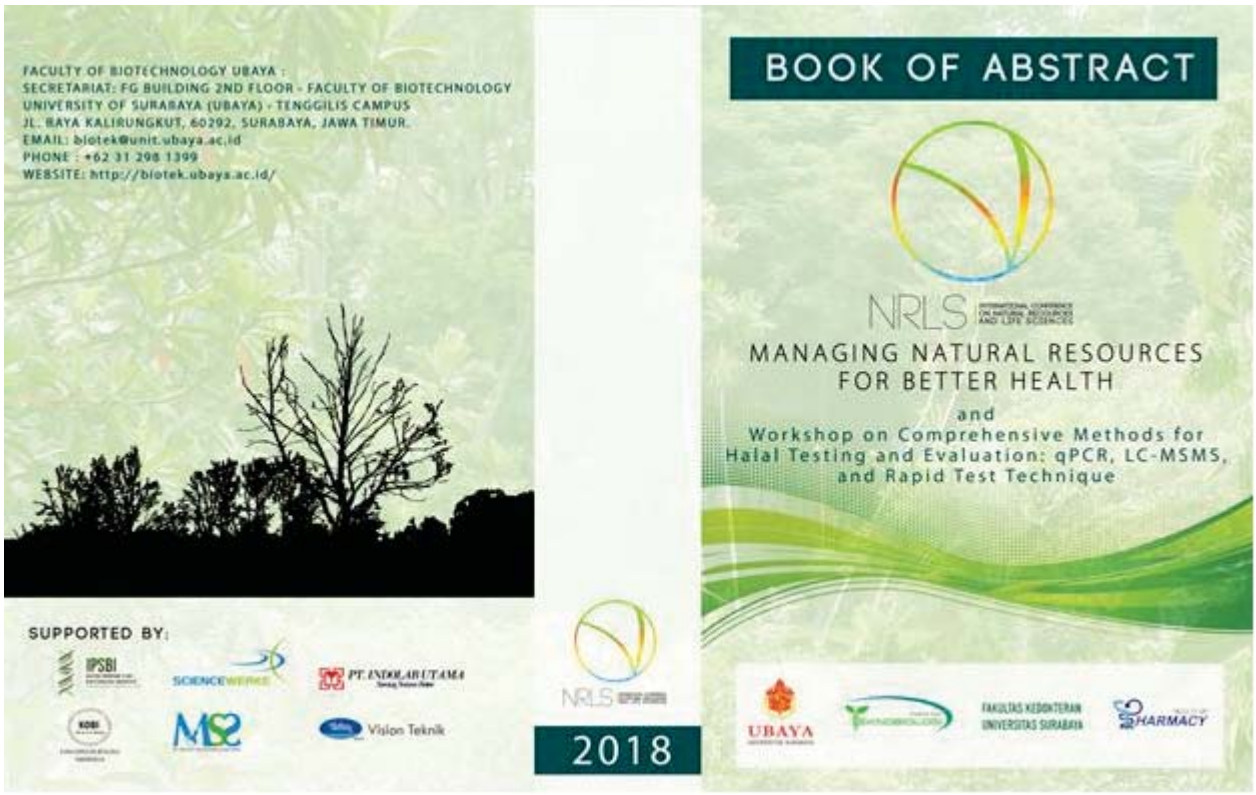
To cite this article: 2019 *IOP Conf. Ser.: Earth Environ. Sci.* **293** 011002

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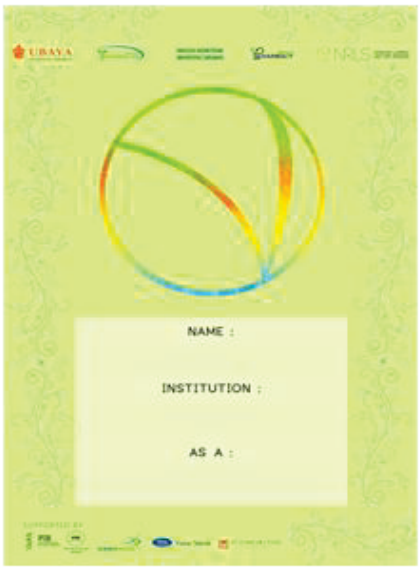
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Themed "MANAGING NATURAL RESOURCES FOR BETTER HEALTH"
Faculty of Biotechnology University of Surabaya
Surabaya, August 23-24, 2018
Dean of Faculty of Biotechnology
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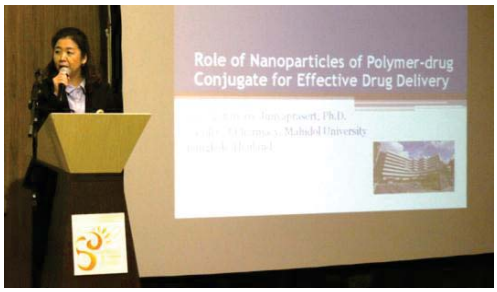

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Oral Presentation Session

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Peer review statement

To cite this article: 2019 *IOP Conf. Ser.: Earth Environ. Sci.* **293** 011005

Peer review statement

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IOP Conference Series: Earth and Environmental Science

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2019
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Scientific & Editorial Boards the 2nd NRLS-2018

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IOP Conference Series: Earth and Environmental Science, Volume 293, The 2nd International Conference on Natural Resources and Life Sciences (NRLS-2018) 23–24 August 2018, Ibis Styles Hotel, Surabaya, Indonesia

Citation 2019 *IOP Conf. Ser.: Earth Environ. Sci.* **293** 011004

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Abstract

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Review article: Myopia - Genetically inherited or environmental influences

Review article: Myopia - Genetically inherited or environmental influences

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Abstract. Myopia or nearsightedness is a condition in which a person cannot see distant objects clearly. It is currently the most common eye disorder. It is predicted that half of the world's population will develop myopia by 2050. Myopia has been associated with both environmental and genetic influences affecting eye growth. The mechanism by which genetics can lead to myopia is still uncertain. Much remains to be elucidated about the interplay between environmental and genetic factors that play a role in the onset of myopia. The main purpose of this article is to describe molecular (genetic and epigenetic) and environmental (lifestyle influenced) causes of myopia in order that drugs, therapies, and other treatments can be found to cure and prevent myopia. As the conclusion, a picture of interconnectivity between genetic, environment, and myopia was constructed
Keyword: Eyes, habit, hereditary, nature, nearsightedness

1. Introduction

Myopia is a condition in which a person cannot see distant objects clearly. It occurs because the eyeball is elongated or the cornea is too curved [1]. Myopia can also be defined as a state in which the eye experiences refractive error, such that light entering the eye that should be focused directly on the retina, is instead focused in front of the retina [2].

Myopia is currently the most common eye disorder diagnosed and also associated with other eye disorders that have the potential to cause blindness, such as glaucoma [3], *ablasio retina* (retinal detachment) [4], and cataracts [5]. According to the National Eye Institute (NEI), the percentage of patients with nearsighted eyes aged 12 yr to 54 yr in the United States grew from 25 % (1971 to 1972) to 46.1 % (1999 to 2004). In Europe, in 2010, the percentage of patients with nearsightedness reached 30.6 % [6]. In Asia, rates of nearsighted people vary. In East Asia they reach 90 % [7–11]. The summary can be seen in table 1.

Table 1. Prevalence of myopia in some countries

Country/age	Prevalence	Source
USA/ (12 to 54) yr.	46.1 %	NEI
Europe/ (25 to 89) yr	30.6 %	[6]
Iran/ (40 to 64) yr	30.2 %	[7]
China/ 19 yr	95.5 %	[9]
South Korea/ 19 yr	83.3 % to 96.5 %	[8, 10]
India/ (11.6 ± 2.2) yr	13.1 %	[11]

The number of nearsighted people continue to increase every year. It is predicted that the global percentage will reach 33.9 % by 2020 and by 2050, is predicted to be 49.8 % [12]. Myopia can cause a decrease in global productivity because slow at reading, missing some important information, and

others. The current global burden caused by myopia reaches USD 121.4 × 10 [13]. The average total cost required for the treatment is USD 755 × 10^6 per year [14, 15].

With the increasing rate and the potential effect on the economy, this condition is a problem that needs our attention. Myopia is strongly correlated with environmental factors. Habits and lifestyle have traditionally been along with genetics have a role in the onset of myopia. This review article discusses causes of myopia, so that they may be used as a basis for prevention or treatment.

2. Environmenal influences on myopia

Myopia is influenced by the environment because it involved changes and adjustments to the eye. These changes and adjustments depend on the object seen by the eye as the main signal. The eye will focus the object on the retina. The eye has several mechanisms to regulate the focus of the eyes. First, the eyeball extends by changing the sclera structure, second, retinal retraction will occur with thinning of the blood vessels (choroid), and third, there is also a retinal signal from the brain, in the form of retinoic acid which regulates eye changes and adjustments.

All of this is related to the use of the eye in daily life. If an eye adjustment occurs continuously, the change will become permanent, causing myopia, via a long eyeball structure or choroid thinning. This phenomenon was reviewed by Wallman and Winawer [16].

2.1. Myopia and lifestyle (work and education)

All habits that force the eyes to work hard increase the likelihood of developing myopia. Continuous reading, reading at close range, reading in dark conditions, playing video games too often, and watching television at close range have been shown to cause myopia [11, 17, 18].

Education level is also have a correlation. The longer the time in school and the higher the level of education, the higher the risk of suffering myopia [19]. Educational level or duration is often associated with the time used for learning and reading. Both of these activities often interfere with the work of the eye so that if it continues to be done inappropriately, the eye will experience adjustment and cause myopia.

Work or daily activities are also associated with the onset of myopia. Like indoor activities, for example staring at computer very long, sewing, weaving, etc. [20–23]. In fact, not all jobs are at risk of causing myopia. An example is outdoor activities. The longer the activity outside the room the lower the risk of having myopia [24, 25]. Higher light intensity outside the room, will stimulate dopamine production. Feldkaemper and Schaeffel have proposed a mechanism that dopamine can decrease elongation of the eyeball and decrease the risk of people to become myopia [26]

2.2. Myopia and ethnicity-geography

The prevalence of myopia also varies between ethnicities. In several studies, it was found that ethnic groups from Asia had a higher myopia prevalence than other ethnicities. New cases of the appearance of myopia are more common in Asians than in Hispanics, Native Americans, African-Americans, and Whites [27]. In the UK, the number of nearsighted people from Asia is higher than that from Africa, Caribbean, and Europe [28]. In fact, data shows that Asian children in the United States are more likely to develop myopia than children from other ethnicities [29]. In Asia alone, only certain ethnicities have high prevalence of myopia, namely those from East Asia, Chinese compared to others [7–11, 30–32]. Within China, there is no particular ethnicity with a higher prevalence rate [33].

The number of myopia in Asians is often associated with high rates of diabetics in Asia [34]. This is supported by a review by Umezurike, et al [35]. One of the data found that people with diabetes mellitus tended to be myopia compared to non-diabetic controls. This is related to the lifestyle of Asians whose staple food is rice. But it's not clear whether myopia in Asians is influenced by the lifestyle or other factors.

3. Genetic influence on myopia

Children who have two parents who suffer from myopia are at the highest risk of developing myopia compared with those who have one parent with myopia. Children with parents who do not suffer from myopia are at a lower risk of developing myopia [36–40]. Myopia is inherited between generations. This shows that in addition to environmental factors, genetics also plays a role in the onset of myopia.

In addition, genetic causes of myopia is supported by twin studies. In one study, its heritability reached 80 % [41]. From these data, it is known that myopia is not completely due to environmental or genetic alone. Data on heritability among other twin pairs has also been described in a review by Dirani et al. [42].

Variation of myopia by ethnic group, population studies and twin studies illustrate the role of genetics in addition to the environment influences. To better understand this factor, research has been conducted to link myopia with certain genes. Linkage analysis has been performed on a group of families with myopia. Using linkage analysis, several genes have been mapped to their position on the chromosome. Most of the, the genes that play a role are related to eye development. If polymorphism or mutation occurs in these genes, it can cause changes in eye growth that leads to myopia. Data on the name of the locus and its location on the chromosome can be seen in Yamashiro and Yoshimura's review [43].

3.1. Genes that related with myopia

Analysis of several genes that can affect the growth of eyeballs has also been carried out. Myopia is associated with an elongated eye shape or a weak sclera. Some genes related to eye shape and sclera have been identified. Several studies have been conducted to link these genes to patients with myopia.

Collagen, type I, alpha 1 (*COL1A1*) is a gene that encodes the protein component of the extracellular matrix. This gene is usually expressed in the sclera. People with myopia have an increased rate of polymorphisms in these genes. This was demonstrated using the Single Nucleotide Polynorphism (SNP) markers (rs2075555 and rs2269336) [44]. Polymorphism in these genes causes weak sclera structure, so it cannot resist elongation of the eyes.

Collagen, type II, alpha 1 (*COL2A1*) is a gene that plays a role in the production of extracellular matrix components in the sclera. Polymorphism in the *COL2A1* gene is also associated with the onset of myopia. In the study by Metlapally, et al. [45], there were five SNP markers associated with patients with myopia (rs1034762, rs1635529, rs1793933, rs3803183, and rs17122571).

Paired Box 6 (*PAX6*) is a regulator that responsible for eye growth and development. If there is a polymorphism or mutation in this gene, eye growth is susceptible to myopia. The 1410delC, Arg240Stop, and Glu93Stop mutations are reported to be related to myopia [46]. Polymorphism in the *PAX6* gene is also claimed to cause myopia. There are seven SNP markers associated with patients with myopia (rs3026390, rs3026393, rs3026354, rs667773, rs2071754, rs644242, and rs662702) [47–49].

The transforming growth factor-beta2 (TGFB-2) is an important component of the scleral extracellular matrix. Reduction in the matrix will affect the shape of the eye. Polymorphism in this gene will affect the the onset of myopia. In a study from Lin, et al. [50] it was found that SNP markers rs7550232 associated with nearsighted patients.

Insulin-like growth factor 1 (*IGF-1*) has a role in insulin regulation. If there is a damage to this gene, it will cause insulin resistance. High insulin concentration in the blood will affect elongation of the eye. This condition can cause myopia. There are three SNP markers associated with nearsighted patients (rs12423791, rs7956547, and rs5742632) [51].

There are still many other genes involved in eye development and have been investigated in relation to myopia. For example, *RDH8*, has a role in the production of the enzyme retinol dehydrogenase. This enzyme be responsible in the formation of retinoic acid, the retinal signal that regulates eye growth. *Matrix metalloproteinase 2* (*MMP2*) and *Tissue inhibitors of metalloproteinase-2* and *-3* (*TIMP2* and *TIMP3*), play a role in the degradation of the scleral extracellular matrix. When the eye is elongated, the sclera reduces the production of the extracellular matrix and increases the production of matrix-degrading enzymes [17]. *Transforming growth factor, beta 1* (*TGFB1*), has a role in controlling scleral growth. However, the associations with myopia of *RDH8* [52], *Matrix metalloproteinase 2* (*MMP2*), *Tissue inhibitors of metalloproteinase-2* and *-3* (*TIMP2* and *TIMP3*) [53] and *Transforming growth factor, beta 1* (*TGFB1*) [54] have not been found to date.

As described before, myopia is not only caused by environmental but also genetic influences. A summary of studies that show the relationship between myopia and the environment and/or genetics can be seen in the table 2.

Table 2. Summary of environmental and / or genetic effects on the occurrence of myopia.

Study	Environment	Genetic	Resume/ Finding	Explanation	Source
Habits, Jobs, and Education	✓		- Nearwork activities have a higher risk to the onset of myopia - Outdoor activities decrease the risk to the onset of myopia	Habits in work and learning as well as daily habits are environmental factors that cause myopia.	[12, 18–24]
Between Families	✓	✓	Risk for children who have myopic parents are higher than children who have no myopic parent	Myopia can be inherited between family members. Not only that, similarities in habits, lifestyle, and the environment in one family can cause myopia	[36–39]
Between Twins	✓	✓	Heritability estimates ranging from 0.11 to 0.94 in vary ages from 3 yr to 79 yr.	Just as between families, twin couples who live together share the same environment so that genetic is not an important factor in the onset of myopia	[40–42]
Linkage analysist		✓	In linkage analysis using microsatellites markers has identified 19 loci for myopia: MYP1 – MYP19	Genetic inheritance is proven by the relationship between genes that are not separated during meiosis and are passed down between generations.	[43]
Candidate gene		✓	- *COL1A1* - *COL2A1* - *PAX6* - *IGF-1* - *TGFB2*	The genes that analyzed are related to eye development. Polymorphism or gene mutation will cause myopia. This can be inherited.	[44–51]

4. Environment and genetic interactions on myopia

An improper dietary pattern is also estimated to cause myopia. According to a study, high blood sugar levels cause high insulin levels. High insulin levels in the blood affect the growth of the eyeball. This phenomenon has been demonstrated in test animals [55]. Galvis et al. [56] have proposed a hypotheses regarding the possible of the effect of insulin on eye growth. This evidence shows that a high sugar diet will affect genetics and cause myopia. This proves that the environment and genetic interactions on myopia exist.

Dirani, et al. [57] conducted a study to determine the effect of environmental and genetic interactions on myopia. This study compared the rate of myopia from monozygotic twin and dizygotic twin with their differences in studying or education attainment. They found that not only the genetics represented by zygosity and the environment factors represented by education attainment were responsible for the onset of myopia, but also their interactions. This shows that the genotype is influenced by the environment and vice versa. Further studies on this subject began to be directed to epigenetic studies.

4.1. Epigenetic patterns in myopia

The environment also affects gene expression and lead to the onset of myopia through a genetic mechanism. This is demonstrated by recent epigenetic research. In test animals that are intentionally induced to be myopia, *COL1A1* expression decreases. Cells regulate this by increasing methylation in the *COL1A1* promoter. DNA methylation in the *COL1A1* promoter will cause collagen synthesis in the sclera to decrease, resulting in a weak sclera structure that cannot contain eye growth, and the eye will grow longer than normal.

Methylation of the *COL1A1* promoter also decreases when test animals gradually recover from myopia. This shows that the methylation in the *COL1A1* promoter is influenced by the environment, including feedback regarding the growth of the eye itself. If eye growth leads to myopia, *COL1A1* promoter methylation will increase, and vice versa [58, 59].

Overall, it is known that myopia is caused by environmental influences, genetic, and interaction of both called epigenetic. A summary scheme of factors that cause myopia can be seen in the figure 1.

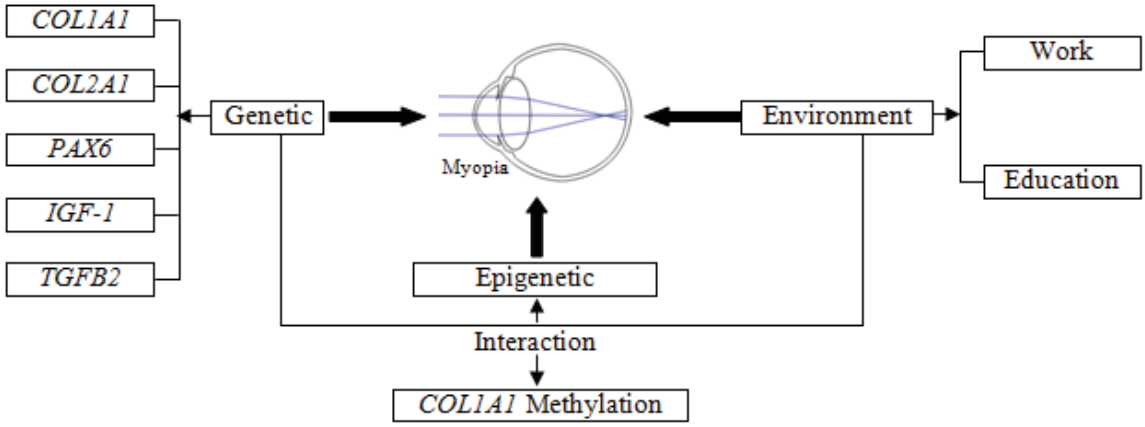

Figure 1. Factors that cause myopia

5. Future prospect

Research on myopia has placed more emphasis on the influence of the environment on eye growth than on the influence of genetics. As a result of this, treatment methods for patients with myopia is currently limited to therapy or physical treatment directly on the patient's eyeball [60]. In fact, such treatment is usually temporary, because myopia is based on eye growth. If eye growth is still not normal, then myopia can reappear.

The lack of information on the specific mechanisms causing the occurrence of myopia makes it difficult to find suitable drugs and therapies to cure myopia. Current research has begun to link genetic and epigenetic patterns to the onset of myopia. Some polymorphisms and epigenetic patterns of several genes believed to be involved in the onset of myopia have been found. But this discovery only links these genes to the onset of myopia. Further research should be directed at specific molecular mechanisms leading to eye growth, including interactions between genes and the environment. This is necessary in order to find the complex mechanism for the onset of myopia.

Genetics, epigenetics, and lifestyle taken together have potential to improve predictions of a person's risk of myopia and lead to efforts to prevent myopia before it occurs. In the future, research will be focused to find a treatment of myopia at the molecular level.

6. Conclusion

The environment, lifestyle, and habits are believed to be the main factors associated with eye growth through vision as the main signals. But genetics is also an important factor in the cause of myopia. This condition is heritable and genes that play a role are usually related to eye growth and develpment. It is also likely that there are interactions between genes and the environment that cause myopia, as seen from epigenetic patterns in patients with myopia. Hopefully, this article can be used as a basis for prevention or treatment for patients with myopia.

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by Sulistyo Tjoa

Submission date: 01-Feb-2021 02:07PM (UTC+0700)
Submission ID: 1498884840
File name: myopia-_genetically_inherited.pdf (761.79K)
Word count: 5692
Character count: 29162

Review article: Myopia - Genetically inherited or environmental influences

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Abstract. Myopia or nearsightedness is a condition in which a person cannot see distant objects clearly. It is currently the most common eye disorder. It is predicted that half of the world's population will develop myopia by 2050. Myopia has been associated with both environmental and genetic influences affecting eye growth. The mechanism by which genetics can lead myopia is still uncertain. Much remains to be elucidated about the interplay between environmental and genetic factors that play a role in the onset of myopia. The main purpose of this article is to describe molecular (genetic and epigenetic) and environmental (lifestyle influenced) causes of myopia in order that drugs, therapies, and other treatments can be found to cure and prevent myopia. As the conclusion, a picture of interconnectivity between genetic, environment, and myopia was constructed

Keyword: Eyes, habit, hereditary, nature, nearsightedness

1. Introduction

Myopia is a condition in which a person cannot see distant objects clearly. It occurs because the eyeball is elongated or the cornea is too curved [1]. Myopia can also be defined as a state in which the eye experiences refractive error, such that light entering the eye that should be focused directly on the retina is instead focused in front of the retina [2].

Myopia is currently the most common eye disorder diagnosed and also associated with other eye disorders that have the potential to cause blindness, such as glaucoma [3], *ablasio retina* (retinal detachment) [4], and cataracts [5]. According to the National Eye Institute (NEI), the percentage of patients with nearsighted eyes aged 12 yr to 54 yr in the United States grew from 25 % (1971 to 1972) to 46.1 % (1999 to 2004). In Europe, in 2010, the percentage of patients with nearsightedness reached 30.6 % [6]. In Asia, rates of nearsighted people vary. In East Asia they reach 90 % [7–11]. The summary can be seen in table 1.

Table 1. Prevalence of myopia in some countries

Country/age	Prevalence	Source
USA/ (12 to 54) yr.	46.1 %	NEI
Europe/ (25 to 89) yr	30.6 %	[6]
Iran/ (40 to 64) yr	30.2 %	[7]
China/ 19 yr	95.5 %	[9]
South Korea/ 19 yr	83.3 % to 96.5 %	[8, 10]
India/ (11.6 ± 2.2) yr	13.1 %	[11]

The number of nearsighted people continue to increase every year. It is predicted that the global percentage will reach 33.9 % by 2020 and by 2050, is predicted to be 49.8 % [12]. Myopia can cause a decrease in global productivity because slow at reading, missing some important information, and

others. The current global burden caused by myopia reaches USD 121.4 × 10 [13]. The average total cost required for the treatment is USD 755 × 10^6 per year [14, 15].

With the increasing rate and the potential effect on the economy, this condition is a problem that needs our attention. Myopia is strongly correlated with environmental factors. Habits and lifestyle have traditionally been along with genetics have a role in the onset of myopia. This review article discusses causes of myopia, so that they may be used as a basis for prevention or treatment.

2. Environmenal influences on myopia

Myopia is influenced by the environment because it involved changes and adjustments to the eye. These changes and adjustments depend on the object seen by the eye as the main signal. The eye will focus the object on the retina. The eye has several mechanisms to regulate the focus of the eyes. First, the eyeball extends by changing the sclera structure, second, retinal retraction will occur with thinning of the blood vessels (choroid), and third, there is also a retinal signal from the brain, in the form of retinoic acid which regulates eye changes and adjustments.

All of this is related to the use of the eye in daily life. If an eye adjustment occurs continuously, the change will become permanent, causing myopia, via a long eyeball structure or choroid thinning. This phenomenon was reviewed by Wallman and Winawer [16].

2.1. Myopia and lifestyle (work and education)

All habits that force the eyes to work hard increase the likelihood of developing myopia. Continuous reading, reading at close range, reading in dark conditions, playing video games too often, and watching television at close range have been shown to cause myopia [11, 17, 18].

Education level is also have a correlation. The longer the time in school and the higher the level of education, the higher the risk of suffering myopia [19]. Educational level or duration is often associated with the time used for learning and reading. Both of these activities often interfere with the work of the eye so that if it continues to be done inappropriately, the eye will experience adjustment and cause myopia.

Work or daily activities are also associated with the onset of myopia. Like indoor activities, for example staring at computer very long, sewing, weaving, etc. [20–23]. In fact, not all jobs are at risk of causing myopia. An example is outdoor activities. The longer the activity outside the room the lower the risk of having myopia [24, 25]. Higher light intensity outside the room, will stimulate dopamine production. Feldkaemper and Schaeffel have proposed a mechanism that dopamine can decrease elongation of the eyeball and decrease the risk of people to become myopia [26]

2.2. Myopia and ethnicity-geography

The prevalence of myopia also varies between ethnicities. In several studies, it was found that ethnic groups from Asia had a higher myopia prevalence than other ethnicities. New cases of the appearance of myopia are more common in Asians than in Hispanics, Native Americans, African-Americans, and Whites [27]. In the UK, the number of nearsighted people from Asia is higher than that from Africa, Caribbean, and Europe [28]. In fact, data shows that Asian children in the United States are more likely to develop myopia than children from other ethnicities [29]. In Asia alone, only certain ethnicities have high prevalence of myopia, namely those from East Asia, Chinese compared to others [7–11, 30–32]. Within China, there is no particular ethnicity with a higher prevalence rate [33].

The number of myopia in Asians is often associated with high rates of diabetics in Asia [34]. This is supported by a review by Umezurike, et al [35]. One of the data found that people with diabetes mellitus tended to be myopia compared to non-diabetic controls. This is related to the lifestyle of Asians whose staple food is rice. But it's not clear whether myopia in Asians is influenced by the lifestyle or other factors.

3. Genetic influence on myopia

Children who have two parents who suffer from myopia are at the highest risk of developing myopia compared with those who have one parent with myopia. Children with parents who do not suffer from myopia are at a lower risk of developing myopia [36–40]. Myopia is inherited between generations. This shows that in addition to environmental factors, genetics also plays a role in the onset of myopia.

In addition, genetic causes of myopia is supported by twin studies. In one study, its heritability reached 80 % [41]. From these data, it is known that myopia is not completely due to environmental or genetic alone. Data on heritability among other twin pairs has also been described in a review by Dirani et al. [42].

Variation of myopia by ethnic group, population studies and twin studies illustrate the role of genetics in addition to the environment influences. To better understand this factor, research has been conducted to link myopia with certain genes. Linkage analysis has been performed on a group of families with myopia. Using linkage analysis, several genes have been mapped to their position on the chromosome. Most of the, the genes that play a role are related to eye development. If polymorphism or mutation occurs in these genes, it can cause changes in eye growth that leads to myopia. Data on the name of the locus and its location on the chromosome can be seen in Yamashiro and Yoshimura's review [43].

3.1. Genes that related with myopia

Analysis of several genes that can affect the growth of eyeballs has also been carried out. Myopia is associated with an elongated eye shape or a weak sclera. Some genes related to eye shape and sclera have been identified. Several studies have been conducted to link these genes to patients with myopia.

Collagen, type I, alpha 1 (*COL1A1*) is a gene that encodes the protein component of the extracellular matrix. This gene is usually expressed in the sclera. People with myopia have an increased rate of polymorphisms in these genes. This was demonstrated using the Single Nucleotide Polynorphism (SNP) markers (rs2075555 and rs2269336) [44]. Polymorphism in these genes causes weak sclera structure, so it cannot resist elongation of the eyes.

Collagen, type II, alpha 1 (*COL2A1*) is a gene that plays a role in the production of extracellular matrix components in the sclera. Polymorphism in the *COL2A1* gene is also associated with the onset of myopia. In the study by Metlapally, et al. [45], there were five SNP markers associated with patients with myopia (rs1034762, rs1635529, rs1793933, rs3803183, and rs17122571).

Paired Box 6 (*PAX6*) is a regulator that responsible for eye growth and development. If there is a polymorphism or mutation in this gene, eye growth is susceptible to myopia. The 1410delC, Arg240Stop, and Glu93Stop mutations are reported to be related to myopia [46]. Polymorphism in the *PAX6* gene is also claimed to cause myopia. There are seven SNP markers associated with patients with myopia (rs3026390, rs3026393, rs3026354, rs667773, rs2071754, rs644242, and rs662702) [47–49].

The transforming growth factor-beta2 (TGFB-2) is an important component of the scleral extracellular matrix. Reduction in the matrix will affect the shape of the eye. Polymorphism in this gene will affect the the onset of myopia. In a study from Lin, et al. [50] it was found that SNP markers rs7[illegible]0232 associated with nearsighted patients.

Insulin-like growth factor 1 (*IGF-1*) has a role in insulin regulation. If there is a damage to this gene, it will cause insulin resistance. High insulin concentration in the blood will affect elongation of the eye. This condition can cause myopia. There are three SNP markers associated with nearsighted patients (rs12423791, rs7956547, and rs5742632) [51].

There are still many other genes involved in eye development and have been investigated in relation to myopia. For example, *RDH8*, has a role in the production of the enzyme retinol dehydrogenase. This [illegible]zyme be responsible in the formation of retinoic acid, the retinal signal that regulates eye growth. *Matrix metalloproteinase 2* (*MMP2*) and *Tissue inhibitors of metalloproteinase-2* and *-3* (*TIMP2* and *TIMP3*), play a role in the degradation of the scleral extracellular matrix. When the eye is elongated, the sclera reduces the production of the extracellular matrix and increases the production of matrix-degrading enzymes [17]. *Transforming growth factor, beta 1* (*TGFB1*), has a role in controlling scleral growth. However, the associations with myopia of *RDH8* [52], *Matrix metalloproteinase 2* (*MMP2*), *Tissue inhibitors of metalloproteinase-2* and *-3* (*TIMP2* and *TIMP3*) [53] and *Transforming growth factor, beta 1* (*TGFB1*) [54] have not been found to date.

As described before, myopia is not only caused by environmental but also genetic influences. A summary of studies that show the relationship between myopia and the environment and/or genetics can be seen in the table 2.

Table 2. Summary of environmental and / or genetic effects on the occurrence of myopia.

Study	Environment	Genetic	Resume/ Finding	Explanation	Source
Habits, Jobs, and Education	✓		- Nearwork activities have a higher risk to the onset of myopia - Outdoor activities decrease the risk to the onset of myopia	Habits in work and learning as well as daily habits are environmental factors that cause myopia.	[12, 18–24]
Between Families	✓	✓	Risk for children who have myopic parents are higher than children who have no myopic parent	Myopia can be inherited between family members. Not only that, similarities in habits, lifestyle, and the environment in one family can cause myopia	[36–39]
Between Twins	✓	✓	Heritability estimates ranging from 0.11 to 0.94 in vary ages from 3 yr to 79 yr.	Just as between families, twin couples who live together share the same environment so that genetic is not an important factor in the onset of myopia	[40–42]
Linkage analysist		✓	In linkage analysis using microsatellites markers has identified 19 loci for myopia: MYP1 – MYP19	Genetic inheritance is proven by the relationship between genes that are not separated during meiosis and are passed down between generations.	[43]
Candidate gene		✓	- *COL1A1* - *COL2A1* - *PAX6* - *IGF-1* - *TGFB2*	The genes that analyzed are related to eye development. Polymorphism or gene mutation will cause myopia. This can be inherited.	[44–51]

4. Environment and genetic interactions on myopia

An improper dietary pattern is also estimated to cause myopia. According to a study, high blood sugar levels cause high insulin levels. High insulin levels in the blood affect the growth of the eyeball. This phenomenon has been demonstrated in test animals [55]. Galvis et al. [56] have proposed a hypotheses regarding the possible of the effect of insulin on eye growth. This evidence shows that a high sugar diet will affect genetics and cause myopia. This proves that the environment and genetic interactions on myopia exist.

Dirani, et al. [57] conducted a study to determine the effect of environmental and genetic interactions on myopia. This study compared the rate of myopia from monozygotic twin and dizygotic twin with their differences in studying or education attainment. They found that not only the genetics represented by zygosity and the environment factors represented by education attainment were responsible for the onset of myopia, but also their interactions. This shows that the genotype is influenced by the environment and vice versa. Further studies on this subject began to be directed to epigenetic studies.

4.1. Epigenetic patterns in myopia

The environment also affects gene expression and lead to the onset of myopia through a genetic mechanism. This is demonstrated by recent epigenetic research. In test animals that are intentionally induced to be myopia, *COL1A1* expression decreases. Cells regulate this by increasing methylation in the *COL1A1* promoter. DNA methylation in the *COL1A1* promoter will cause collagen synthesis in the sclera to decrease, resulting in a weak sclera structure that cannot contain eye growth, and the eye will grow longer than normal.

Methylation of the *COL1A1* promoter also decreases when test animals gradually recover from myopia. This shows that the methylation in the *COL1A1* promoter is influenced by the environment, including feedback regarding the growth of the eye itself. If eye growth leads to myopia, *COL1A1* promoter methylation will increase, and vice versa [58, 59].

Overall, it is known that myopia is caused by environmental influences, genetic, and interaction of both called epigenetic. A summary scheme of factors that cause myopia can be seen in the figure 1.

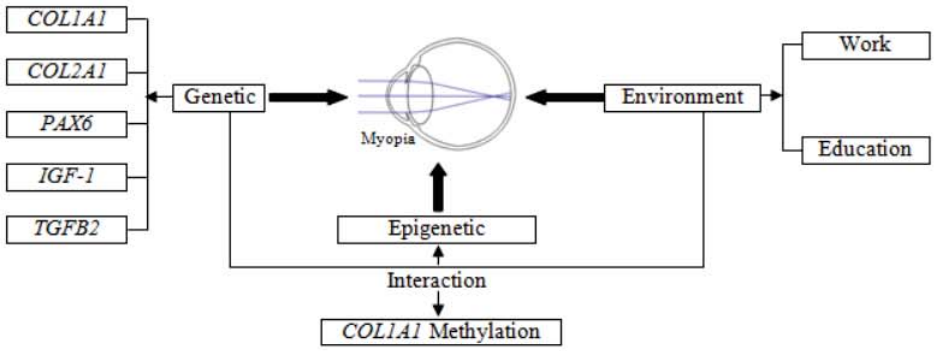

Figure 1. Factors that cause myopia

5. Future prospect

Research on myopia has placed more emphasis on the influence of the environment on eye growth than on the influence of genetics. As a result of this, treatment methods for patients with myopia is currently limited to therapy or physical treatment directly on the patient's eyeball [60]. In fact, such treatment is usually temporary, because myopia is based on eye growth. If eye growth is still not normal, then myopia can reappear.

The lack of information on the specific mechanisms causing the occurrence of myopia makes it difficult to find suitable drugs and therapies to cure myopia. Current research has begun to link genetic and epigenetic patterns to the onset of myopia. Some polymorphisms and epigenetic patterns of several genes believed to be involved in the onset of myopia have been found. But this discovery only links these genes to the onset of myopia. Further research should be directed at specific molecular mechanisms leading to eye growth, including interactions between genes and the environment. This is necessary in order to find the complex mechanism for the onset of myopia.

Genetics, epigenetics, and lifestyle taken together have potential to improve predictions of a person's risk of myopia and lead to efforts to prevent myopia before it occurs. In the future, research will be focused to find a treatment of myopia at the molecular level.

6. Conclusion

The environment, lifestyle, and habits are believed to be the main factors associated with eye growth through vision as the main signals. But genetics is also an important factor in the cause of myopia. This condition is heritable and genes that play a role are usually related to eye growth and develpment. It is also likely that there are interactions between genes and the environment that cause myopia, as seen from epigenetic patterns in patients with myopia. Hopefully, this article can be used as a basis for prevention or treatment for patients with myopia.

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