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What Genetic Markers are Associated with an Increased Risk of Congenital Heart Defects, and How Can Genetic Screening be Integrated Into Prenatal Care? A Narrative Literature Review

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Abstract

Congenital heart disease (CHD) encompasses various fetal cardiac abnormalities in which immediate and effective treatment depends on early detection. Traditional diagnosis methods rely heavily on sonographic imaging, which has limitations in consistently detecting CHD. Recent advancements highlight the potential of genetic markers, such as microdeletions (e.g., 22q11 deletion) and trisomy 21, as initial indicators of CHD (Pierpont et al. 2018). Yet, further research examines how other genetic changes—such as point mutations, variances, and aneuploidies—may affect the risk of CHD. A method for early genetic assessment is non-invasive prenatal testing (NIPT), which analyzes placental cell-free DNA from maternal blood. This study briefly covers trisomy 21's involvement in CHD, specifically its effects on associated genetic markers that include MTHFR and SLC19A1, before exploring potential markers and indications. The significance of early detection and focused treatment is highlighted by examining the relationship between folate pathway deficits, single nucleotide polymorphisms (SNPs) such as rs1051266, and CHD. The findings emphasize the significance of incorporating genetic screening into prenatal care and how we can track the outcomes of prenatal genetic screening and assess the effectiveness of interventions based on these genetic findings to improve outcomes for children at risk of CHD while also addressing concerns and limitations of current technologies.

Keywords: Genetic Markers; Fetal Cardiac Issues; Congenital Heart Disease; Cardiac Abnormalities; Sonographic

Background

Early prognosis of any type of health condition allows doctors to offer patients better medical prevention plans to assist in symptom and progression management. Diagnoses for fetal cardiac issues are often made late in fetal development, which may postpone potential treatment options available for the fetus. Moreover, cardiac conditions may continue to progress during development, which limits treatment options for eight in one thousand babies diagnosed with a congenital heart defect after birth [1]. Some common conditions include fetal tachycardia progressing to hydrops, aortic stenosis progressing to hypoplastic left heart syndrome, and various other congenital heart diseases. Professionals rely heavily on using sonographic methods like fetal echocardiography to diagnose, as abnormalities can be viewed in comparison to normal fetal heart images [1]. There are limitations present in using this method, as it is predominantly visual and operator-dependent, for proper and accurate diagnosis consistently, other markers and methods are being explored. Part of the fetal echocardiography is pulsed wave "Doppler examination," which has been used to assess valvular regurgitation (like tricuspid regurgitation) present in diseased hearts [1]. If tricuspid regurgitation is present, the probability of CHD is increased [1].

Further, a more accurate and emerging method is using genetic markers, which can provide better clarity for the root causes of CHD and allow for potentially life-saving preventive treatment as well. A general genetic marker can be an abnormal karyotype observed when doing genetic testing; this places the abnormal fetal heart at a higher risk and allows for early treatment planning. With accurate testing, specific conditions or markers–including various aneuploidies, copy number variants, and point mutations–can be identified in an abnormal karyotype to predict the development of CHDs. For instance, mutations in the NKX2, GATA4, and TBX1/5 family genes play crucial roles in heart development and the potential for disease. Trisomy 21 and 22q11 are both prevalent genetic abnormalities–an aneuploidy and a copy number variant, respectively, that warrant more extensive research as they are likely markers for CHD as well [1]. Furthermore, non-invasive prenatal testing (NIPT) has emerged; the method pertains to placental cell-free DNA in the maternal blood being examined as a potential testing method for gene examination [1]. There is a sense of urgency that requires more attention diverted into exploring such genetic markers pertaining to fetal CHD as appropriate treatment plans can be formed better.

Methods

This research includes a qualitative design examining different genetic markers associated with congenital heart defects. The research paper covers different congenital heart defects such as those associated with genetic aneuploidies, microdeletions, and point mutations, and how using early genetic screening can help with intervention and early diagnosis of these genetic markers. This research paper uses data collected from previous research papers regarding fetal cardiology, where it has been shown that early genetic screening has helped prevent and diagnose congenital heart defects. The research referenced in this paper mainly focuses on prenatal patients ranging from early to late pregnancy. The most commonly used method was screening patients for genetic markers and then diagnosing and treating them. This led to a decreased risk of congenital heart defects. Research methods varied between different prenatal testing but mostly yielded similar results. The different techniques used for data analysis combined both the qualitative and quantitative data to simplify data that only yielded cardiac abnormalities specifically in early pregnancies. Then simplifies it further to yield research data that only shows how genetic screening in prenatal care has helped decrease congenital heart defects.

Results

Genetic Variations

Congenital heart disease (CHD) affects approximately 1% of all human births. Of all cases, 34% are caused by genetic variations, making it the primary etiology of CHD [2]. This review article aims to understand the genetics linked with an increased risk of CHD, and how this knowledge may be used to progress genetic screening technologies as part of prenatal

care. By referencing a range of research, focusing on six different review articles, further investigation and insight into this area were gained.

Aneuploidies

Genomic variations, categorized into aneuploidies, copy number variations (CNV), and point mutations, form this review's basis. Aneuploidies occur when there is an abnormal number of chromosomes. As there are missing, or extra chromosomes, the irregular dosage of specific genes can cause either an underexpression or overexpression, possibly leading to heart defects. Aneuploidies often cause syndromic CHDs–developmental issues that extend beyond the heart. [2] found syndromic CHDs to account for 8% to 13% of all CHDs, with the most common aneuploidies including trisomy 21 (Down syndrome), trisomy 13 (Patau syndrome), trisomy 18 (Edwards syndrome), and Monosomy X (Turner syndrome). As presented in Table 1, the incidence of CHD associated with these syndromes is 40% to 60% for trisomy 21; 60% to 80% for trisomy 13 and trisomy 18; and 20% to 40% for Monosomy X [1-3]. A key distinction is that the mere presence of the syndrome does not necessarily confirm the presence of CHD. Research by Locke et al., (2010) found that the overexpression of cystathionine β-synthase–an enzyme responsible for breaking down homocysteine–is common amongst patients with trisomy 21 and leads to abnormal heart development. Typically, it is not the syndrome itself, but rather the culmination of many genetic alterations resulting from the syndrome that increases the likelihood of CHD.

Table 1: Incidence of Congenital Heart Disease Associated with Common Aneuploidies [1-3]

Name of Syndrome	Incidence of CHD
Trisomy 21	40% to 60%
Trisomy 13	60% to 80%
Trisomy 18	60% to 80%
Monosomy X	20% to 40%

Copy Number Variants

Copy number variants are caused by segments of the genome varying from one to the next. CNVs and aneuploidies are similar as both are attributed to deletions or duplications; however, CNVs occur at specific sections whereas aneuploidies involve the entire chromosome. Approximately 10% to 15% of CHDs will be a form of a copy number variation [2]. [4] noted that two common CNVs are the 22q11 deletion syndrome and 7q11.23 duplication syndrome, often known as DiGeorge and Williams-Beuren syndromes, respectively. They are relatively prevalent microdeletions and impact the dosage of various genes, resulting in a higher risk for CHD development. Research by [5] explores additional CNVs–including 1q21.1, 2q13, 8p23.1, 11q24, 15q11.2, 16p11.2, and 22q11.2–that are characterized as "genomic hotspots." In cases of CHD, these CNVs occur more frequently and are known to affect various genes crucial for the development of the heart such as GJA5, TMEM87B, FBLN7, GATA4, ETS1, CYFIP1, TBX6, TBX1, CRKL, and MAPK1 [5].

Point Mutations

The last broad category of genetic variations is point mutations, which arise from a single nucleotide being altered in the genome caused by either inheritance or De Novo mutations. [6] highlighted that inheritance accounts for 2% of all CHD cases, while De Novo mutations form 10%. Alterations in the genome can lead to single-gene mutations. Such mutations may cause CHD by terminating gene transcription, or by either increasing or decreasing protein function [6]. Further analysis by [2] suggests that from the 400+ single-gene mutations, mutations in cardiac transcription factors (cTFs) are especially undesirable as cTFs play a key role in cardiogenesis. Examples of prevalent cTFs include the NKX2.5, GATA4, and T-Box family genes. Other groups such as structu-

ral proteins and signal factors are vital in the development of the heart, and mutations in these may lead to an increased risk of CHD as well [2]. Nodal, a signal protein, has been found to cause congenital heart defects in cases where there are disruptions in the signaling results. As Nodal signaling plays an important role in heart development, particularly in its structure and positioning within the body, abnormalities can lead to heterotaxy syndrome and other isolated defects within the major cardiovascular structures including the arteries and atrioventricular septum. Moving forward, research highlights the need for a better understanding of the connection between Nodal signals and the associated cases of CHD [7].

Genetic Diagnosis

There is a diverse selection of genetic diagnosis methods, each test suitable for varying situations and needs. According to [6], techniques such as karyotyping, chromosome microarrays, and whole exome sequencing are commonly used for broad screening. In contrast, tests like next-generation sequencing and fluorescence in situ hybridization involve targeting specific genes to determine a diagnosis. New and improved methods continue to emerge in this field, including non-invasive prenatal testing (NIPT), which can be integrated into prenatal care to enhance safety and effectiveness.

Discussion

Trisomy 21 Aneuploidy and Associated Point Mutations

Trisomy 21 (Down syndrome; DS) alone is not a genetic marker for CHD, yet testing done for the MTHFR c.1298A or rs1051266 single nucleotide polymorphisms (SNPs) may increase the likelihood of catching fetal CHD [8]. Caused by an extra third chromosome at position 21, trisomy 21 codes for parts of the folate pathway like SLC19A1 (folate transporter 1) and cystathionine β-synthase (CBS), which degrades homocysteine and creates cysteine from methionine [9]. In individuals with DS, this overexpression of CBS catalyzes more homocysteine breakdown, often fueling a folate deficiency, potentially changing the accuracy of DNA and RNA synthesis for proper heart development and causing the development of CHD in a fetus. So, when searching for specific markers to correlate heart defects and impacted folate mechanisms caused by aneuploidy [8], testing identified various SNPs (i.e. SLC19A1 and MTHFR) related to the synthesis of folate pathway components as the causation for CHDs formation. Polymorphisms like SNP rs1051266 and c.1298A are variants on the SLC19A1 and MTHFR gene, highly correlated to fetal CHDs; specifically, atrioventricular septal defect (AVSD). All the notable SNPs in SLC19A1 are also commonly found with the SNP rs1051266 (c.80A>G), associated with CHD in children without Down syndrome. This correlation indicates that genetic testing for these particular markers may be worthwhile in identifying CHDs for early monitoring and treatment to begin when possible.

Trisomy 13, 18, and Monosomy X Aneuploidies

As with trisomy 21, these aneuploidies commonly result in septal and outflow tract defects. Unfortunately, as most individuals with complete trisomy 13, colloquially known as Patau syndrome, do not have high survival rates past their first year of life [11], genetic research conducted with older children is limited compared to other aneuploidies like trisomy 21. There is also a comparatively low amount of research done for children with trisomy 18 and Monosomy X regarding their association with CHDs, despite the majority of syndromic individuals also having some sort of fetal CHD [4]. Moving forward, research conducted with fetal karyotypes of trisomy 13 and other aneuploidies should be considered, so that genetic markers related to these CHDs can be identified and monitored.

22q11 and 7q11.23 Copy Number Variants and Relevant Point Mutations

22q11 deletion and 7q11.23 duplication syndromes often result in a higher risk of CHDs due to de novo mutations to the TBX1 gene. TBX1 belongs to a set of genes known as the T-box family (TBX1, TBX5, TBX6), which is crucial to early embryogenesis [5,10]. Tied to fetal cardiac development, the microdeletion of TBX1 genes associated with 22q11 deletion syndrome may be further investigated to research similarities or additional causes of CHD in non-syndromic cases. By doing

so, important links such as additional presenting phenotypes of a certain mutation or the introduction of potential CHD--causing genotypes may be established. A novel example would be this isolated case of CHD (specifically, a transposition of the great arteries and ventricular septal defect, also known as TGA and VSD, respectively) resulting from a TBX1 mutation that altered an amino acid and caused significantly diminished transcriptional activity [12]. Though not directly linked to 22q11 deletion syndrome, it holds significant value in terms of diagnosing fetal CHDs for both syndromic and non-syndromic children. Overall, T-box genes show promise when searching for CHD-related correlations, as seen with their potential link to Holt-Oram syndrome (HOS): a genetic condition characterized by heart and hand malformations. Testing conducted throughout the years has shown that 75% of clinically diagnosed children with HOS have CHD and 70% of individuals with HOS have some sort of TBX5 mutation [13]. Thus, a more concrete correlation may again be useful to match more specific point mutations to a developing cardiac condition. 7q11.23DS is mainly associated with CHDs caused by microdeletions of genes including ELN (elastin), which is responsible for protein synthesis [4]. It has been partially researched that reduced elastin expression in aortic tissues due to ELN mutations can cause supravalvular aortic stenosis (SVAS) [14]. However, the link between SVAS and diminished elastin molecules should be further supported with research. Establishing controls with syndromic and non-syndromic individuals to compare with children with SVAS would be ideal for the future.

NKX2.5 and GATA4 Point Mutations

The NKX2.5 gene encodes transcription factors relevant to cardiac function and development, with mutations commonly presenting as ASD, atrioventricular conduction defect, and occasionally tetralogy of Fallot (NKX2-5 NK2 homeobox 5 [15]. When altered or has significant microdeletions/duplications, it appears that heart development cannot be fully carried out, often being initiated but stopped early on in mammals, causing it to be a strong marker for potential CHD formation in the embryo [2]. Elucidating as to why the majority of CHDs associated with this gene result in heart malformation, additional studies to identify the cause and development of similar genetic mutations can aid researchers in developing better treatments for fetal CHDs. Similarly, the GATA4 point mutation is another gene that cannot fully carry out cardiogenesis. Alongside the NKX2.5 gene, the GATA genes are essential for the initiation of proper heart development, function, and other cardiovascular components, such as activating encoders of troponin isoforms (TNNI3, TNNC1) and cardiac myosin heavy chains (MYH6, MYH7), to name a few [2]. In particular, the GATA4, 5, and 6 mutations affect the developing heart, while the other GATA variants cause CHD in different areas. Seeing the primary significance of this gene, further studies in the field can make advancements that minimize heart problems associated with GATA4 mutations and improve the outlook for fetal CHD in the future.

Logistical Implementations and Ethical Concerns

One noteworthy limitation of this study is the use of NIPT and the costs and accessibility issues that come with it. The cost differs based on the type of test and service provider. If a test screens for more conditions, it will cost more. Also, private insurance coverage may differ, so some may not receive full coverage and miss crucial diagnoses or indications of CHD. In addition, studies have shown that the use of NIPT in socioeconomically disadvantaged neighborhoods is significantly lower. NIPT in disadvantaged neighborhoods was 20.3% compared to 47.6% in more advantaged ones [16]. The harsh difference exemplifies the impact socioeconomic factors have on the accessibility of prenatal testing. Individuals living in lower-income areas face financial barriers that limit their access to this technology. The high costs and restricted accessibility of NIPT are limitations to the incorporation of NIPT into prenatal care.

The financial limitation combined with the ethical considerations around any form of false positives and impact on parents' mental health are factors to be explored. Concerns about privacy, genetic discrimination, and permission are all increasing as NIPT becomes more common. There is also concern about the psychological impact on parents after receiving the results, as elevated stress and anxiety throughout pregnancy is an issue. The tough choices, the decision to end a pregnancy based on results also lead to ethical dilemmas.

Limitations

This study has provided valuable insights into genetic markers, but the approach has certain limitations. The scope was restricted to specific genetic markers, and the dependence on previous research and data may have created biases. However, this narrow focus has allowed for a deeper dive into crucial markers, which provides a strong foundation for future studies to explore additional markers and further refine our understanding. The sample size and demographic variety also impact the generalizability of the results. Furthermore, even though NIPT has a lot of promise, it is still a relatively new technique and cannot detect every possible genetic marker. While there is still much to learn about CHD, this study represents a significant advancement for future generations.

Conclusion

This study identifies key markers associated with risks of congenital heart defects. The research acknowledges the significance of microdeletions such as 22q11 and the indications of trisomy 21 while gathering a collection of other, rather valuable, markers. Single gene variants, aneuploidies, and copy number variants (CNVs) are some of the major contributors to congenital heart defects. Mutations in the genes families NKX2, GATA4, and TBX1/5 play crucial roles in heart development, being linked to cardiac anomalies such as atrial septal defects (ASD), ventricular septal defects (VSD), and tetralogy of Fallot (TOF). While reports on VSD and TOF are less frequent, research still shows it has associations with cardiac anomalies. These findings strongly support the thesis that non-invasive prenatal testing can effectively identify these markers, facilitating early diagnosis and intervention. This work makes a valuable contribution to the field of cardiology, enhancing our understanding of the genetic basis of CHD. It underscores the crucial role of prenatal and early genetic testing. Integrating these findings into clinical practices can significantly improve the general global management of CHD, reducing its devastating impact.

Further research should expand upon these findings by identifying additional genetic markers associated with CHD while delving deeper into less researched factors. More extended studies can track the outcomes of prenatal genetic screening and assess the effectiveness of interventions based on these genetic findings. Researching the ethical implications of universal genetic screening in prenatal care is crucial, particularly in understanding the possibilities and consequences of false positives and psychological impacts on parents expecting children with these conditions.

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References

1. Pierpont ME, Brueckner M, Chung WK, Garg V, Lacro RV, et al. (2018) American Heart Association Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; and Council on Genomic and Precision Medicine. Genetic Basis for Congenital Heart Disease: Revisited: A Scientific Statement From the American Heart Association. Circulation, 138: e653-711.

2. Chhatwal K, Smith JJ, Bola H, Zahid A, Venkatakrishnan A, Brand T (2023). Uncovering the Genetic Basis of Congenital Heart Disease: Recent Advancements and Implications for Clinical Management. CJC Pediatric and Congenital Heart Disease, 2: 464-80.

3. Diz OM, Toro R, Cesar S, Gomez O, Sarquella-Brugada G, Campuzano O (2021) Personalized Genetic Diagnosis of Congenital Heart Defects in Newborns. Journal of personalized medicine, 11: 562.

4. Fahed AC, Gelb BD, Seidman JG, Seidman CE (2013) Genetics of Congenital Heart disease: the glass half empty. Circulation Research, 112: 707-20.

5. Ehrlich L, Prakash S (2022) Copy-number variation in congenital heart disease. Elsevier.

6. Simmons MA, Brueckner M (2017) The Genetics of Congenital Heart Disease. Understanding and Improving Long-Term Outcomes in Congenital Heart Disease: A Review for The General Cardiologist and Primary Care Physician. Current Opinion in Pediatrics, 29: 520-8.

7. Barnes RM, Black BL (2016) Nodal Signaling and Congenital Heart Defects. National Library of Medicine National Center for Biotechnology Information.

8. Locke AE, Dooley KJ, Tinker SW, Cheong SY, Feingold E, Allen EG, et al. (2010) Variation in Folate Pathway Genes Contributes to Risk of Congenital Heart Defects Among Individuals with Down Syndrome. Genetic Epidemiology, 34: 613-23.

9. Pogribna M, Melnyk S, Pogribny I, Chango A, Yi P, James SJ (2001) Homocysteine Metabolism in Children with Down Syndrome: In Vitro Modulation. American Journal of Human Genetics, 69: 88-95.

10. Papaioannou VE (2014) The T-box Gene Family: Emerging Roles in Development, Stem Cells and Cancer. Development (Cambridge, England), 141: 3819-33.

11. Trisomy 13 (Patau Syndrome). Trisomy 13 (Patau Syndrome) - Mississippi State Department of Health (2023) https://msdh.ms.gov/page/41,0,285,980.html

12. Zhang M, Li FX, Liu XY, Hou JY, Ni SH, Wang J, et al. (2017) TBX1 loss-of-function mutation contributes to congenital conotruncal defects. Experimental and therapeutic medicine, 15: 447-53.

13. Aoki H, Horie M (2018) Electrical disorders in atrial septal defect: genetics and heritability. Journal of Thoracic Disease, 10.

14. Zhou J, Wu Y, Xu X, Zhang Y, Zhang X, Chen H, et al. (2022) Identification and Characterization of Novel Elastin Gene Mutations in Eleven Families with Supravalvular Aortic Stenosis. Frontiers in Genetics, 13: 1059640.

15. U.S. National Library of Medicine. (n.d.). Nkx2-5 NK2 homeobox 5 [homo sapiens (human)] - Gene-NCBI. National Center for Biotechnology Information.

16. U.S. National Library of Medicine. Van der Meij, KRM, Kooij C, Bekker MN, Galjaard RJH, Henneman L, Dutch NIPT Consortium. (2021) Non-invasive prenatal test uptake in socioeconomically disadvantaged neighborhoods. Prenatal Diagnosis.

17. U.S. National Library of Medicine. (n.d.). Non-invasive prenatal testing: A review of the cost effectiveness and guidelines. National Center for Biotechnology Information.

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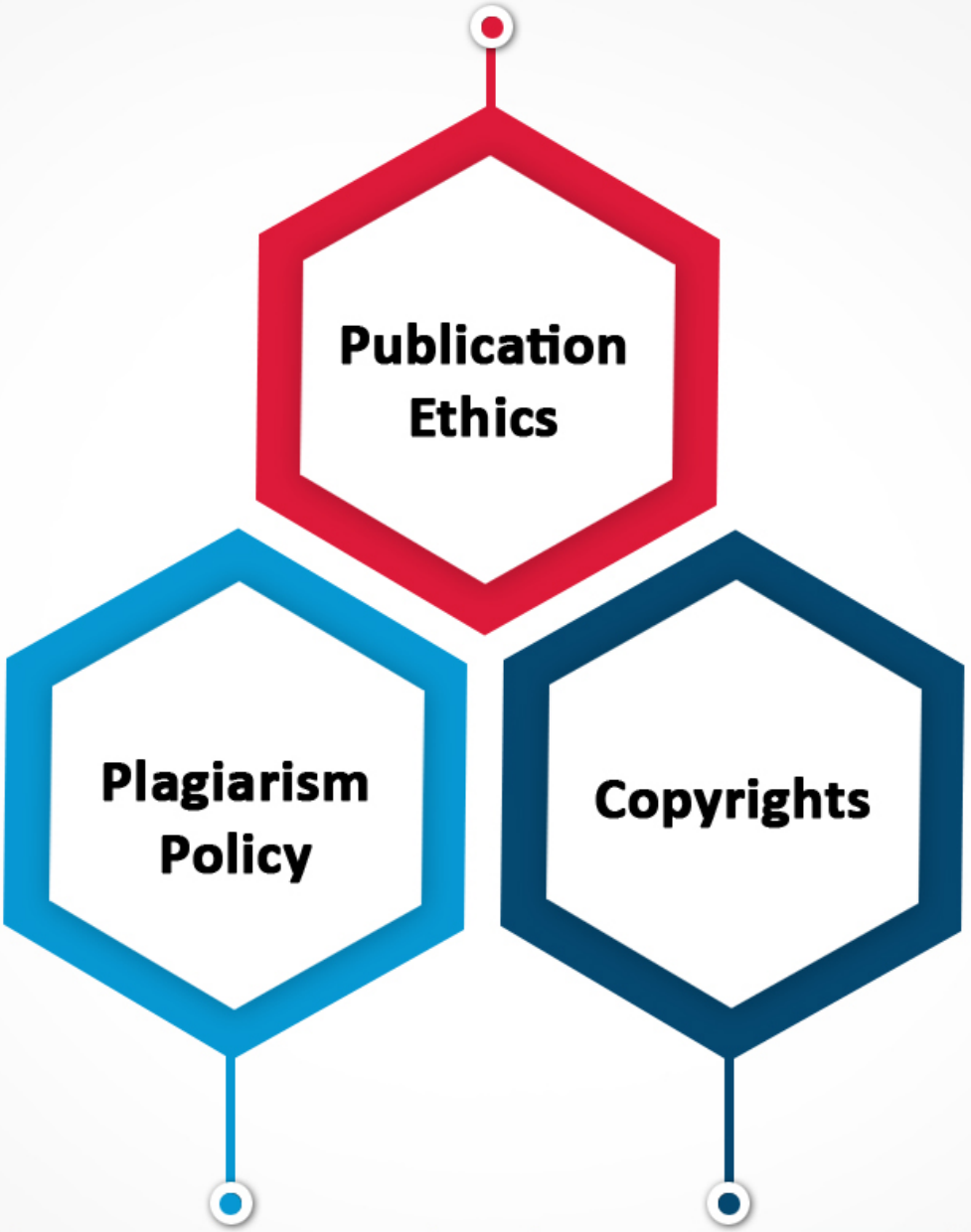

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