Navigating the Cyp2 Gene Family Research Landscape: A Comprehensive Bibliometric Analysis

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Keywords: Mapping of Science, CYP2 Gene, Precision Medicine, Bibliometrik.

Abstract: This study elucidates the role of the CYP2 gene family in the pharmacokinetics and pharmacodynamics of drugs. The variability in these genes significantly influences drug efficacy and individual response. With the increasing volume of scientific publications, a comprehensive understanding of the current research on the CYP2 gene family is crucial. Numerous studies have examined these genetic variations, yet a thorough assessment of this research landscape and the identification of unexplored areas are still needed. Through bibliometric analysis and global mapping, this study enables a more systematic interpretation of publication data, offering new insights. The aim is to perform scientific mapping and interpretation of the CYP2 gene family research corpus. Utilizing literature review methods and bibliometric analysis based on PRISMA guidelines, a search in the Scopus database with the keyword cyp2* yielded 11,867 articles. After cleaning and preparation, 9,439 articles remained for analysis. The results indicate a significant increase in CYP2 gene research, particularly between 2012-2023. Mapping reveals five main clusters, with CYP2E1 and CYP2D6 as the largest. CYP2C9 stands out for its polarization with three other clusters, indicating strong research collaboration. Identified strategic areas include opioids, atrial fibrillation, PCI, DNA methylation, hepatocellular carcinoma, and bile acid. Key genes in polymorphism studies include CYP2C19 and CYP2C8, while CYP2D6 is crucial in drug monitoring. This science mapping provides essential insights for research development in precision medicine.

1 INTRODUCTION

The CYP2 gene family holds significant importance in the field of medicine, particularly in the study of pharmacokinetics and pharmacodynamics of drugs. Genes such as CYP2C9, CYP2C19, and CYP2C16 influence how drugs are metabolized in the body (pharmacokinetics), which can affect the effectiveness of how drugs interact with their biological targets (pharmacodynamics) (Gong et al., 2023). For example, variations in these genes can impact the efficacy of drugs like warfarin, with certain genetic variants increasing the risk of side effects. Although research has deepened our understanding of these genes, there is a need to assess the entire research landscape and identify areas that are not yet fully explored. With the growing number of scientific publications, it is essential to have a comprehensive understanding of how research related to the CYP2 gene family has evolved. Understanding the "mapping of science" in this field will not only reveal current trends but also identify knowledge gaps that may not have been recognized. This is crucial for maximizing the efficiency of research efforts and directing resources to the most needy or strategic areas. Bibliometric analysis, with its ability to map and interpret publication data systematically, offers a solution to this challenge. In analyzing trends in the medical field, this tool has been effectively used, such as in orthopedic therapy studies (Jin et al., 2023). Although reviews on the CYP2 family are still scarce, utilizing this analytical approach makes exploration easier. Therefore, this study aims to delve deeper into the research landscape between topics, and highlight opportunities for future research related to precision medicine.

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Priambodo, K., HY, J. E. M., Ikawaty, R., Baharuddin, and Syafika, S. B. D.
Navigating the Cyp2 Gene Family Research Landscape: A Comprehensive Bibliometric Analysis.
DOI: 10.5220/0013671400003873

In *Proceedings of the 1st International Conference on Medical Science and Health (ICOMESH 2023)*, pages 278-285
ISBN: 978-989-758-740-5

2 MATERIALS AND METHODS

This study adhered to the bibliometric research guidelines established by Donthu (Donthu et al., 2021). We methodically executed several steps to maintain data accuracy and ensure exhaustive reporting of findings. The research involved various critical phases, starting with the formulation of the research question, followed by the creation of a controlled set of vocabulary and keywords. Following this, the process included identifying references from databases using specific filters, data preparation and cleaning, performing mathematical analysis and visualizations, and ultimately interpreting the outcomes (Donthu et al., 2021). A strategic approach for searching was developed to obtain the most relevant and accurate documents. The keywords and search queries used were:

Keyword 1: TITLE-ABS-KEY (cyp2*) AND gene AND PUBYEAR > 2011 AND PUBYEAR < 2024 AND (LIMIT-TO (SRCTYPE, "j")) AND (LIMIT-TO (PUBSTAGE, "final")) AND (LIMIT-TO (DOCTYPE, "ar")) AND (LIMIT-TO (SUBJAREA, "MEDI") OR LIMIT-TO (SUBJAREA, "PHAR") OR LIMIT-TO (SUBJAREA, "BIOC") OR LIMIT-TO (SUBJAREA, "CHEM") OR LIMIT-TO (SUBJAREA, "NEUR") OR LIMIT-TO (SUBJAREA, "IMMU") OR LIMIT-TO (SUBJAREA, "NURS") OR LIMIT-TO (SUBJAREA, "HEAL") OR LIMIT-TO (SUBJAREA, "DENT") OR LIMIT-TO (SUBJAREA, "MATH") OR LIMIT-TO (SUBJAREA, "VETE") OR LIMIT-TO (SUBJAREA, "COMP")) AND (LIMIT-TO (LANGUAGE, "English"))

The article search was conducted on October 20, 2023, using the Scopus database. In this search, we employed several filters to obtain relevant and precise documents. The following is the scheme and some filter limitations used in the search, as illustrated in Figure 1. Research Questions RQ1 How many main clusters are there in the CYP2 family studies? RQ2 What is the relationship among the clusters in the CYP2 family? RQ3 What are the strategic topics in the CYP2 family research? RQ4 Is there any dynamics in the publication of the CYP2 family?

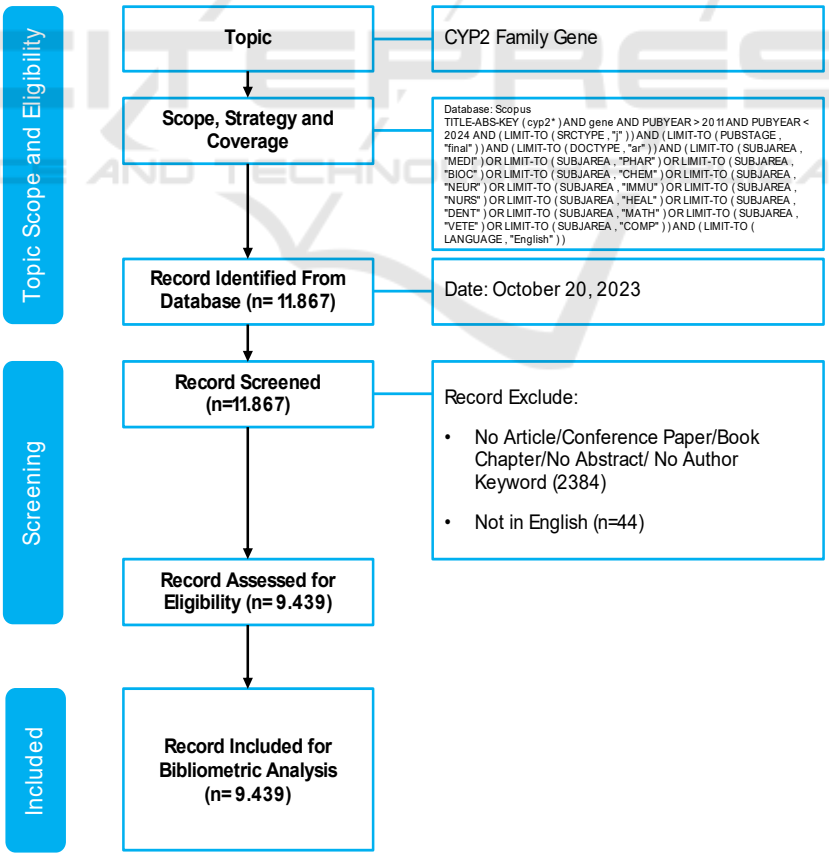

Figure 1: Document selection stages adapted from the PRISMA flow diagram (Page et al., 2021).

3 RESULT AND DISCUSSION

3.1 Research Productivity

There are two main benchmarks for gauging the productivity of research: the number of publications and the number of citations, as both aspects are closely related to the impact factor of research. The higher the number of articles produced, the more productive the researcher is in that field. In our analysis of the CYP2 gene family, we observe a significant increase in research outputs. A publication momentum occurred in the period 2019-2022, where publications exceeded the average of the previous 10 years, as seen in Figure 2.

According to the citation analysis, the countries with the greatest impact are China and the United States. In Asia, Japan represents the country with the highest citation rate in CYP2 gene family studies. This is understandable, given Japan's support from various advanced technologies Figure 3.

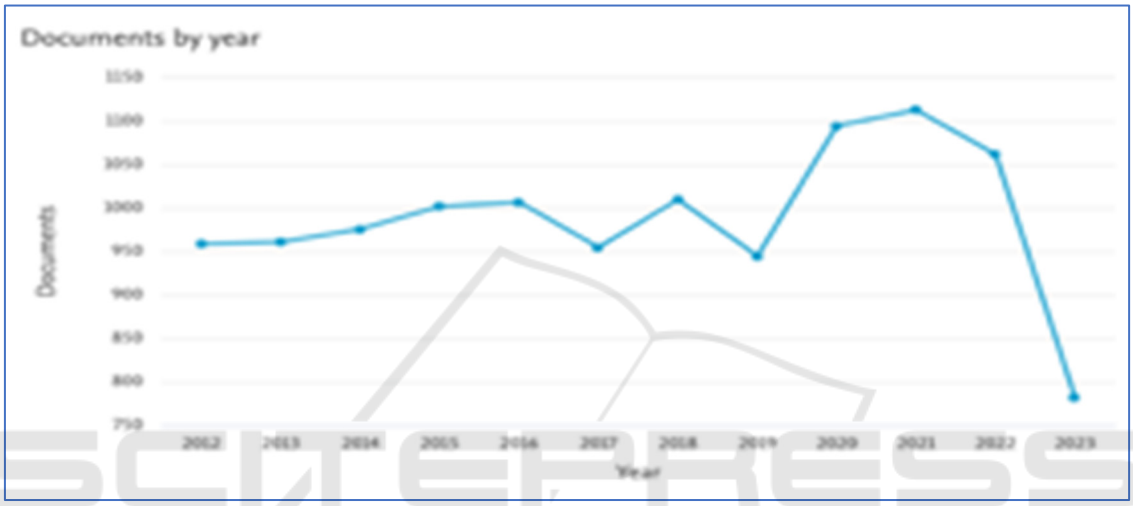

Figure 2: Number of documents by year. Data sourced from Scopus.

Figure 3: Number of citations by country.

3.2 CYP2 Gene Family Clusters

The optimized visualization of the CYP2 gene family clusters reveals five primary clusters, distinguished by different colors: red, green, blue, purple, and yellow. The largest cluster is CYP2E1, colored red, while the smallest is CYP2C19. As the largest cluster, CYP2E1 is strongly associated with hepatotoxicity, oxidative stress, and inflammation. There is also a strong relationship between each topic in the CYP2 study. This section addresses RQ1-2 in this research and is detailed further in the sub-studies. The visualization also highlights strategic studies, which are situated at the centrality with large nodes. In the evolving research of the CYP2 gene family, there are two aspects that consistently serve as bridges between clusters, located centrally. The nodes acting as bridges are metabolism and polymorphism Figure 4 and Figure 5.

Figure 4. Visualization of Global Co-occurrence of Topics Based on Author Keywords.

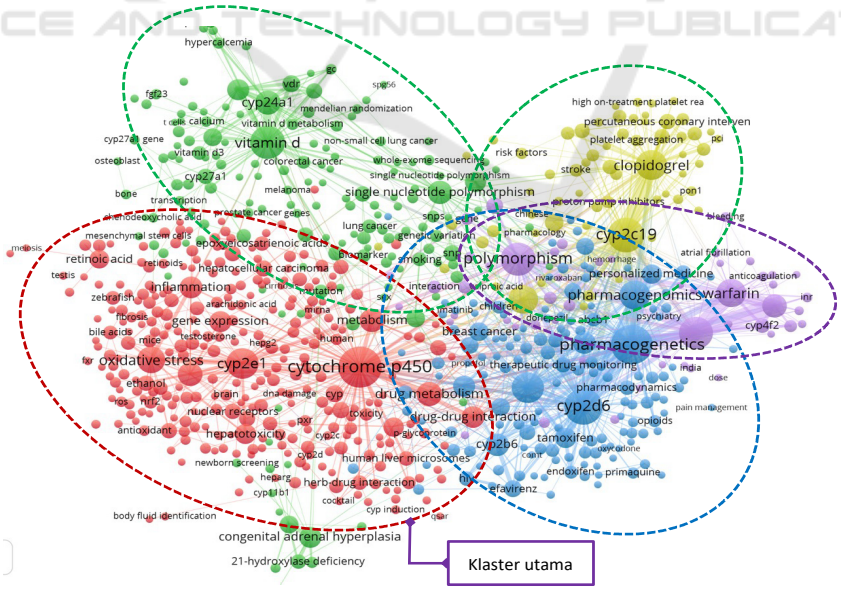

Figure 5. Visualization of Global Co-occurrence of Topics Based on Author Keywords and Cluster Areas.

3.3 The Role of CYP2 in Inflammation

Inflammation is a critical process in complex biological systems, particularly in infection conditions. It arises due to the body's response to external antigens. CYP2E1 can metabolize arachidonic acid into epoxyeicosatrienoic acids (EETs), which have anti-inflammatory effects. However, CYP2E1 is also known to produce reactive oxygen species (ROS) as a by-product of metabolism, which can contribute to oxidative stress and inflammation. The stimulative effect of ROS has been demonstrated by Abdelmeed and team, who proved the role of CYP2E1 in non-alcoholic steatohepatitis (NASH) (Abdelmegeed et al., 2012). Another member, CYP2J2, also metabolizes arachidonic acid into EETs, providing anti-inflammatory and vasoprotective effects. Given the complexity of the CYP2 gene family and its varied functions, these genes play a significant role in both the promotion and resolution of inflammation, depending on the context and the specific CYP2 enzyme involved Figure 6. Nevertheless, a serious concern is that the regulation of oxidative stress can manifest as hepatotoxicity (Jiang et al., 2021).

3.4 The Role of CYP2 in Polymorphism

Intensive research into polymorphisms is necessary to provide evidence for the causes of drug metabolism variation at the genomic level. However, monitoring the direction of research development is crucial to balancing the projection of where this research will evolve. In this study, there are intriguing findings regarding the CYP2 gene family and polymorphism. Not all genes have the same weight in studies; not all are strongly linked to polymorphism studies (Figure 4). In this study, the genes strongly associated with genetic polymorphism are CYP24A1, CYP2C19, CYP2D6, CYP2C9, and CYP2E1. In terms of clusters, CYP24A1, as a centrality, has the most distant relationship (green cluster) (Figure 7).

Figure 6. The Role of CYP2E1 in the Inflammation Process.

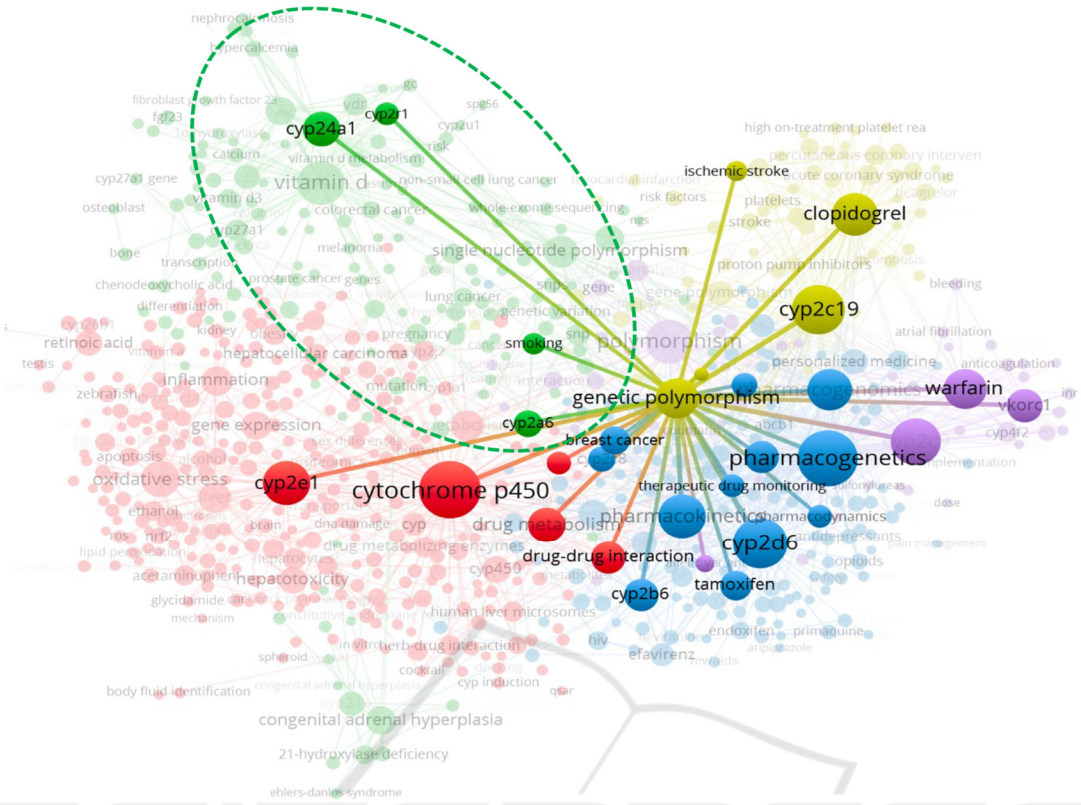

Figure 7. Relationship of Genetic Polymorphism Studies to the CYP2 Gene Family.

In several studies, CYP24A1 is associated with drugs like deferasirox, tenofovir disoproxil fumarate (TDF), and telaprevir. Polymorphisms in CYP24A1 are presumed to be related to changes in the pharmacokinetic profile of these drugs (Cusato et al., 2015). There are 12 variant annotations recorded in PharmGKB, of which 5 variants have clinical annotations but with a level of evidence 3. This indicates a lack of evidence linking CYP24A1 variants to changes in drug levels (*CYP24A1*, n.d.). Furthermore, polymorphisms in CYP24A1 are not yet listed in the Clinical Pharmacogenetics Implementation Consortium (CPIC), suggesting insufficient evidence of the effects of CYP24A1 variants on drugs (*CPIC*, 2023).

Interestingly, within the green cluster, the topic of "smoking" is closely associated with genetic polymorphism. The closest general clusters are yellow, purple, and red. The closest topic is breast cancer. Genetic polymorphisms often affect an individual's susceptibility to breast cancer and their response to treatment (Lum et al., 2013). For example, certain genetic variations can affect drug metabolism, impacting the efficacy and toxicity of breast cancer therapies. Various studies have shown the role of CYP2D6 in reducing the efficacy of Tamoxifen (TMX) (Bezerra et al., 2018). Additionally, genetic polymorphisms in genes related to DNA repair, cell cycle, and hormonal pathways can also affect the risk of developing breast cancer.

3.5 Therapeutic Drug Monitoring

Therapeutic drug monitoring (TDM) is a critical component in assessing the effects of drugs on the body. This examination allows for determining the amount of drug exposure, thereby maintaining drug levels within a therapeutic range (Voulgaridou et al., 2023). Variations in the CYP2 genes can cause changes in drug levels in the blood, leading to variations and strategies in treatment. Numerous studies have demonstrated the significant role of the CYP2D6 gene in drug metabolism (De Rose et al., 2020). In our analysis, there are 134 articles discussing TDM. For example, TDM can be used for dose optimization of the antidepressant escitalopram (S-CIT) by understanding genetic variations in (Tsai et al., 2010). In this study, we found 22 documents discussing TDM and CYP2D6.

Figure 8. Research Trends of the CYP2 Gene Family.

3.6 CYP2 Family Research Trends

Research on the CYP2 family is focused on the density of the P450 cluster. Identified strategic areas include opioids, atrial fibrillation, PCI, DNA methylation, hepatocellular carcinoma, and bile acid. Several studies related to the CYP2D6 gene analyze intermediate and poor metabolizers (IMs and PMs) and pain management (Smith et al., 2019). The trend node in the trend phase can be easily identified due to its bright yellow visual (Figure 8).

4 CONCLUSIONS

The analysis of 9,439 articles related to the CYP2 gene family reveals a broad spectrum of study, evidenced by the formation of five clusters: red, green, yellow, blue, and purple. The inter-cluster relationships are strong, as demonstrated by the intersection of the purple and green clusters. Based on the mapping, it is evident that the CYP2 genes play a crucial role in drug metabolism, inflammation, and drug monitoring.

ACKNOWLEDGEMENTS

The present study was funded by LPPM. We would like to express our deepest gratitude to Lembaga Penelitian dan Pengabdian kepada Masyarakat (LPPM) Universitas Surabaya for their generous support through the research funding scheme for publication 2023. This financial support has been instrumental in the realization of our research and its dissemination.

Additionally, we extend our sincere thanks to the Faculty of Medicine, Universitas Surabaya, for their unwavering support and valuable contributions, which have significantly facilitated the successful completion of our research. Their guidance and assistance have been crucial in achieving the objectives of our study.

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