A Scientometric Study of Research Pertaining to the RASopathies Conditions: Costello Syndrome, Noonan Syndrome, Cardiofaciocutaneous Syndrome, Capillary Malformation-Arteriovenous Malformation Syndrome, and Legius Syndrome

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Abstract

Background: RASopathies is one of the largest known groups of malformation. Which affects 1 in 1,000 individuals in general. As a critical part of the genetic disorder research and the existing gaps in current research, a bibliometric study of the existing body of RASopathies condition is needed.

Method: Online retrieval from the Web of Science (WoS) database was performed. The collected data were analyzed by the Excel and VosViewer to identify the top authors, top journals, main themes in RASopathies, and the trend in annual research productivity about the RASopathies condition.

Results: The top author of RASopathies is Karen W Gripp and the top journal is American Journal of Medical Genetics. There are about twenty small co-authorship networks in RASopathies involving 820 authors. Further, cancer, diagnosis, and heredity are the terms that co-occurred frequently.

Conclusions: Many concepts in RASopathies research appear to be nascent, or not clearly connected to the broader body of research. Much of the research about specific RASopathies appears to be related to a specific aspect of the syndromes. The field of RASopathies research may benefit from broadening the topics explored, networks of authors producing research, and the avenues through which research findings are disseminated.

Introduction

The RASopathies is defined clinically as “a group of medical genetic conditions caused by germline mutations in genes that encode components or regulators of the Ras/mitogen-activated protein kinase (MAPK) pathway”, which mainly causes Costello syndrome, Noonan Syndrome, Cardiofaciocutaneous syndrome, Capillary malformation-arteriovenous malformation (CM-AVM) syndrome, and Legius syndrome [1]. Among those, Cardiofaciocutaneous syndrome and Costello syndrome are sporadic conditions that affect 200 to 300 people worldwide; CM-AVM syndrome affects 1 in 100,000 people; Noonan syndrome affects 1 in 1,000 to 2,500 people; and the prevalence of Legius syndrome is unknown because of its similar symptoms with neurofibromatosis type 1 [2-6]. In a common underlying RAS/MAPK pathway disorder, the RASopathies exhibits many overlapping phenotypic features that the population with RASopathies conditions generally faces a complex condition of their health, such as cardiac malformation; cutaneous, musculoskeletal, and ocular abnormalities; neurocognitive impairment; hypotonia; and an increased cancer risk [1].

As one of the largest known groups of malformation-affecting 1 in 1,000 individuals in general-large number of researchers has investigated the causes, symptoms, and treatments for symptoms of the syndromes. However, beyond these topics of etiology and diagnosis, caregivers of individuals with RASopathies also showed a strong need for information on issues such as daily care and social life [7]. Little research has been done on the topics.
Scientometric profiles of any medical topic provide researchers knowledge about research trends, opportunities for co-authorship and collaboration, and insight into the contributions of specific countries or institutions to specific medical issues [8]. Besides the bibliometric studies in general genetic researches- investigating the research trends of GENETICS for the past 100 years [9] and genetic algorithms [10], researchers also investigate the genetic disorders research output from medical perspective, such as a gene research of myocardial infarction, attention-deficit hyperactive disorder, and autism spectrum disorders [8,11,12].

As a critical part of the genetic disorder research and the existing gaps in current research, a bibliometric study of the existing body of RASopathies condition is needed. This study will identify the top researchers and publishers in the field, the topics are investigated, and the most influential types of publications across academia. Medical personnel and medical library and information science researchers may see this work as a basis on which to identify primary sources and themes for future research about the RASopathies condition.

Methods

The methods for this study are informed by the Handbook of Quantitative Science and Technology Research, the chapters about co-authorship analysis and descriptive versus evaluative bibliometrics [13]. The study is going to investigate publication trends about the RASopathies condition in the Web-of-Science database according to major authors and publishers of RASopathies condition, co-authorship networks, number of yearly publications, research hotspots, and top themes emerged from the titles and abstracts of articles. This purpose of this study is to reveal publication behaviors patterns and potentials for future RASopathies condition research.

Online retrieval from the Web of Science (WoS) database was performed on August 5th, 2019. The researchers use “Costello syndrome”, “Noonan syndrome”, “Cardiofaciocutaneous syndrome”, “Capillary malformation-arteriovenous malformation syndrome”, and “Legius syndrome” as keywords to retrieve research articles between 1950 to 2019. Authors, article title, abstract, and published journal of each article are collected. Articles meet the criteria (1) The time span between 1950 to 2019; (2) Articles indexed in the WoS; (3) Articles with basic information; are included.

This research aims to answer following questions:
1. Who are the top contributors to RASopathies condition research?
   a. Who are the top authors?
   b. Who are the top journals?
2. What are the main themes in RASopathies condition research?
3. What is the trend in annual research productivity about the RASopathies condition?

Descriptive findings relevant to research questions 1 and 3, were found using simple functions in R to compile frequencies for author names, journal names, and publication years. Research question 2 were addressed with the assistance of VosViewer. VosViewer is a free software package produced by the University of Leiden that is capable of identifying meaningful relationships in bibliographic data imported from WoS and producing useful visualizations of these relationships. VosViewer visualizations are used to illustrate the co-authorship networks (authors who have published together) and abstract word co-occurrence networks (terms that are frequently used together in abstracts for RASopathies articles).

Results

Based on the selection criteria, 2647 publications relate to the RASopathies condition - Costello syndrome, Noonan syndrome, Cardiofaciocutaneous syndrome, CA-VAM syndrome, and Legius syndrome - were indexed in WoS from 1950 to 2015 were included in the study. Most of the publications are related to the Noonan syndrome (76%), followed by the Costello syndrome (17%), Cardiofaciocutaneous syndrome (3%), Legius syndrome (2%), and CA-VAM syndrome (2%). The number of publications showed gradually increasing trend from the 1950s (4) to the 1990s (367). After entering the 21st century, the number of publications showed rapid growth in the 2010s (1210). The first publication pertaining to the RASopathies condition is about the Noonan syndrome in 1956, followed by the Costello syndrome in 1985 and the Cardiofaciocutaneous syndrome in 1987. No publications related to the Legius syndrome and CM-AVM syndrome until the 2000s.

Publisher of RASopathies condition research

Over 900 scholarly journals have published articles on the RASopathies condition. Table 1 below lists the top (most articles published) publishers of RASopathies condition research. All of the publishers are journals, instead of book publishers like Routledge. Most of the publishers specifically publish medical research, except for Proceedings of the National Academy of Sciences of the United States of America - a multidisciplinary journal. Among the medical journals, most specifically publish genetic research. These top 14 publishers published 702 publications, 27% of the total RASopathies condition research.

Authorship of RASopathies condition research

Table 2 below lists the top authors of RASopathies condition research. All of the authors in the list come from medical field - genetics (13), general pediatric (3),
endocrinology (1), cardiology (1), pharmacology (1), oncology (1), and neuromuscular (1). Over half of the authors (14) have worked been postdoctoral professionals (professor or research-clinical) for more than 20 years, six of them have worked for over ten years, one has worked less than ten years. The country affiliations of the top authors include Italy (5), the United States (4), France (3), Belgium (2), Netherlands (2), Germany (2), the United Kingdom (2), and Japan (1). Europe is the

Table 1: Top publishers for the RASopathies condition.

| Rank | Publisher                                      | Frequency |
|------|-----------------------------------------------|-----------|
| 1    | American Journal of Medical Genetics          | 327       |
| 2    | Journal of Medical Genetics                    | 52        |
| 3    | Clinical Genetics                              | 38        |
| 4    | Human Mutation                                | 31        |
| 5    | Journal of Pediatrics                          | 31        |
| 6    | Clinical Dysmorphology                         | 29        |
| 7    | European Journal of Human Genetics             | 28        |
| 8    | Hormone Research                              | 26        |
| 9    | Prenatal Diagnosis                             | 26        |
| 10   | European Journal of Medical Genetics           | 25        |
| 11   | European Journal of Pediatrics                 | 23        |
| 12   | American Journal of Human Genetics             | 22        |
| 13   | Journal of Pediatric Hematology/oncc          | 22        |
| 14   | Proceedings of the National Academy of Sciences of the United States of America | 22 |

Table 2: Top author as the first author for the RASopathies condition.

| Rank | Author                  | Frequency |
|------|-------------------------|-----------|
| 1    | Karen W Gripp           | 17        |
| 2    | Marco Tartaglia         | 10        |
| 3    | Katherine A Rauen       | 9         |
| 4    | Jean-Pierre Fryns       | 7         |
| 4    | Giulio Calcagni         | 7         |
| 4    | Christian P Kratz       | 7         |
| 4    | [Anonymous]             | 7         |
| 4    | Kees Noordam            | 7         |
| 9    | Yoko Aoki               | 6         |
| 9    | Martin Zenker           | 6         |
| 9    | Ellen A Croonen         | 6         |
| 9    | Simone Martinelli       | 6         |
| 9    | Jean-Claude Hoeffel     | 6         |
| 14   | Giovanni Neri           | 5         |
| 14   | Ellen Denaver           | 5         |
| 14   | Suzanne Schubbert       | 5         |
| 14   | Alain Verloes           | 5         |
| 14   | Olivier Dereure         | 5         |
| 14   | Maria Cristina Digilio  | 5         |
| 14   | William E Tidyman       | 5         |
| 14   | Anna Sarkozy            | 5         |
| 14   | M Sharland              | 5         |

Table 3: Articles with 100+ Citations.

| Rank | Article                                                                 | Citations |
|------|------------------------------------------------------------------------|-----------|
| 1    | Schubbert, S., Shannon, K., & Bollag, G. (2007). Hyperactive Ras in developmental disorders and cancer. Nature Reviews Cancer, 7(4), 295. | 990       |
| 2    | Tartaglia, M., Mehler, E. L., Goldberg, R., Zampino, G., Brunner, H. G., Kremer, H., ... & Kalidas, K. (2001). Mutations in PTPN11, encoding the protein tyrosine phosphatase SHP-2, cause Noonan syndrome. Nature genetics, 29(4), 465. | 957       |
| 3    | Neel, B. G., Gu, H., & Pao, L. (2003). The ‘Shp’ing news: SH2 domain-containing tyrosine phosphatases in cell signaling. Trends in biochemical sciences, 28(6), 284-293. | 758       |
| 4    | Ceconi, F., Alvarez-Bolado, G., Meyer, B. I., Roth, K. A., & Gruss, P. (1998). Apaf1 (CED-4 homolog) regulates programmed cell death in mammalian development. Cell, 94(6), 727-737. | 731       |
| 5    | Tartaglia, M., Niemeyer, C. M., Fragale, A., Song, X., Buechner, J., Jung, A., ... & Gelb, B. D. (2003). Somatic mutations in PTPN11 in juvenile myelomonocytic leukemia, myelodysplastic syndromes and acute myeloid leukemia. Nature genetics, 34(2), 148. | 662       |
| 6    | Schubbert, S., Zenker, M., Rowe, S. L., Böll, S., Klein, C., Bollag, G., ... & Nguyen, H. (2006). Germline KRAS mutations cause Noonan syndrome. Nature genetics, 38(3), 331. | 437       |
| 7    | Tartaglia, M., Kalidas, K., Shaw, A., Song, X., Musat, D. L., Van der Burgt, I., ... & Kucherlapati, R. S. (2002). PTPN11 mutations in Noonan syndrome: molecular spectrum, genotype-phenotype correlation, and phenotypic heterogeneity. The American Journal of Human Genetics, 70(6), 1555-1563. | 430       |
| 8    | Carvajal-Vergara, X., Sevilla, A., D’Souza, S. L., Ang, Y. S., Schaniel, C., Lee, D. F., ... & Ge, Y. (2010). Patient-specific induced pluripotent stem-cell-derived models of LEOPARD syndrome. Nature, 465(7299), 808. | 417       |
| 9    | Aoki, Y., Nihori, T., Kawame, H., Kurosawa, K., Ohashi, H., Tanaka, Y., ... & Matsubara, Y. (2005). Germline mutations in HRAS proto-oncogene cause Costello syndrome. Nature genetics, 37(10), 1038. | 413       |
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area with the most top authors, followed by the North American and Asia. These authors have contributed to 153 publications in total.

Highly-Cited RASopathies condition research

Table 3 displays all of the RASopathies condition research articles - 92 in total - cited at least 100 times. The most cited article, *Hyperactive RAS in developmental disorders and cancer* with 990 citations, was coauthored by Suzanne Schubbert, Kevin Shannon, and Gideon Bollag. This article provides the first indication that besides carcinogenesis, mutant Ras proteins may also contribute to human developmental disorders [14]. The other article with over 900 citations, *Mutations in PTPN11, encoding the protein tyrosine phosphatase SHP-2, cause Noonan syndrome*, cited by 957 times, is coauthored by Marco Tartaglia. The three articles cited over 500 times are pertaining to the Noonan syndrome, one publication on the researching of Costello syndrome, CM-AVM syndrome, and Cardiofaciocutaneous Syndrome. This situation may be caused by the occurrence of each syndrome.

Co-Authorship analysis

While there are about twenty small co-authorship networks in RASopathies, there is only one very large network. This network is displayed in Figure 1. There are 820 individual authors within this network. Each circle within the visualization represents a single author, with the size of the circle representing the relative number of publications by that author. Each connection line between authors represents co-authorship on at least one publication between those two authors. Each color within the visualization indicates a smaller group of authors who regularly publish together. This network actually consists of about seven smaller, tighter networks, with several publications between authors in these seven groups that create the large network.

Each of the smaller networks has at least one author that is prominent, or has a large circle/number of publications with a large number of co-authors. These authors include Karen Gripp, Martin Zenker, Marco Tartaglia, Alexander Jorge, Ineke van der Burgt, Amy Roberts, Katherine Rauen, Benjamin Neel, Yoko Aoki, and Tetsuya Niihori. These align with the “top” authors in Table 2. Figure 1 shows that the work of all these individuals is connected via co-authorship of...
challenges from having this tight of a network, such as an insulating effect towards external or competing ideas. If all researchers within a small field are so interconnected in their work, it makes it difficult to introduce new or competing ideas that would challenge the work of colleagues. As all other co-authorship networks are comparatively extremely small, there is little competition to the authority of this group of authors. This effectively creates a "collective of knowledge," such that most knowledge of the RA-

Figure 1: Work of all the individuals connected via co-authorship of research.

There can be benefits to having a tight network like that of the RASophathies. It likely indicates that researchers in this field are knowledgeable about developments in the field and that information flow among the group is strong. However, there may be challenges from having this tight of a network, such as an insulating effect towards external or competing ideas. If all researchers within a small field are so interconnected in their work, it makes it difficult to introduce new or competing ideas that would challenge the work of colleagues. As all other co-authorship networks are comparatively extremely small, there is little competition to the authority of this group of authors. This effectively creates a “collective of knowledge,” such that most knowledge of the RA-

Figure 2: Visualization of term co-occurrence in the abstracts of RASophathies articles.
Sophathies conditions, and what topics/idea are popular/likely to be accepted for publication and cited in this area of research, may be controlled by a single group of highly-interconnected authors.

**Term co-occurrence**

Figure 2 displays the visualization of term co-occurrence in the abstracts of RASopathies articles. In this visualization, the size of a circle represents the relative number of occurrences of that term, while a connection between two circles indicates that these terms are frequently used together in abstracts. Color indicates that terms share some semantic relationship, while distance indicates how closely terms are used together.

This visualization shows several loosely-related terms encircling a shared core of terms. At the bottom of the visualization, in purple, is “clinical diagnosis”; to the right is “authorship”; to the upper-right is “legius syndrome”; to the upper-left is “adolescent”; to the middle-left is “giant cell lesion”; and to the bottom-left is “Costello.” What this may indicate is that, though these conditions share some topicality with other aspects of RASopathies research, they are not presently connected in significant ways with these aspects in the literature and/or have simply not been researched with great frequency (which is also indicated in the size of these terms’ circles, which compared to circles in the central mass are quite small.

Within the central mass of terms, there are five large groups of terms. In green appear to be terms related to cancer, including, “leukemia,” “cancer,” “shp2,” “shp,” “disease,” “dysregulation,” and “malignancy.” Costello and Noonan syndromes are also part of this grouping, which may indicate that the majority of research about these two syndromes relates to the increased risk of cancer associated with them, rather than other medical and health elements.

In red are terms that are largely related to diagnosis, such as, “prenatal diagnosis,” “pregnancy,” “correlation,” “genetics,” “cases,” and “differential diagnosis.”

In dark blue are terms that may be related to familial attributes of these disorders, or heredity. These terms include, “mother,” “son,” “father,” “sibling,” and “trisomy.” Also included in this group is Turner syndrome, a syndrome which only occurs in females. This group may be related to the group in orange, which includes terms related to (growth) hormones and has extensive connections to Turner syndrome, as growth hormones has been identified as one potential treatment for this condition.

Finally, in light blue appears to be terms related to chromosomal origins of these syndrome, including terms like, “clinical phenotype,” “chromosome,” “deletion,” “hras mutation,” and “genetic heterogeneity.”

**Discussion**

In regard to the journals in which RASopathies research is published there are a very small number of very powerful producers in the field. In fact, the journal with the most RASopathies publications, the American Journal of Medical Genetics, has six times as many publications as its nearest alternative. This fact grants this journal considerable power over flow of new knowledge within the field of RASopathies research. As many of the articles in this journal are not open-access, this also makes research within this field very difficult to access for researchers from developing countries, or other situations where the individual or their institution’s library may not subscribe to the journal.

Research pertaining to the RASopathies also has a very tight network of authors. This network is responsible for over half of the research related to the RASopathies, thus exerting a high-level of power in this field. More diversity/new research groups may improve the field by offering new ideas or challenging existing ones that may be taken for granted within this large network of authors.

Presently, there appear to be five major areas of research with the RASopathies: Chromosomes, hormones, heredity, diagnosis, and cancer. These topics focus on the etiology and diagnosis of RASopathies but do not cover factors like lifespan healthcare and education. Research from birth onward appears to be severely lacking. This leaves caregivers, and the medical professionals that support them and utilize peer-reviewed publications to make informed decisions and guidance, in a precarious position. There are limited answers to questions like, “what should I do if my Costello child is vomiting every morning upon waking?” This results in a state of information poverty, wherein caregivers must turn to less reliable sources of information (like first-hand experience of other caregivers, shared through social media groups) to satisfy their needs [7].

**Conclusion**

Several trends in RASopathies research indicate important authors and topics in the field. There appears to be a very well-defined network of researchers in this field, which may be beneficial in this small area of research, but could also have an insulating effect on the field. Many concepts in RASopathies research appear to be nascent, or not clearly connected to the broader body of research. Much of the research about specific RASopathies appears to be related to a specific aspect of the syndromes, such as cancer for Costello and Noonan Syndrome, and gender for Turner Syndrome. This indicates a gap in more comprehensive research about the diversity of challenges individuals with these syndromes and their caregivers face. The field of RASopathies research may benefit from broadening the topics...
explored, networks of authors producing research, and the avenues through which research findings are disseminated.

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