What is known on angiogenesis-related rare diseases?
A systematic review of literature

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Introduction

A disease is considered rare when its low incidence becomes a problem to be added, making more difficult its accurate diagnosis and decreasing the interest in its research and the development of drugs for its treatment. According to the definition provided by the European Union, rare diseases are those with prevalence values lesser than 5/10,000 and leading patients to higher risk of death or chronic disability. Although it is difficult to estimate the exact number of rare diseases, most probably this number is within the range 6000–8000. More than 2000 rare diseases have already one or more genes assigned; see (http://www.rdplatform.org) and [1]. The greatest database on the subject, Orphanet (http://www.orpha.net/consor/cgi-bin/index.php) contains information on almost 6000 rare diseases and their associated genes.

Keywords: angiogenesis ● rare diseases ● orphanet
Angiogenesis. The formation of new vessels from the pre-existing vasculature, is one main mechanism of vascularisation during normal and specific physiological processes, such as embryonic development, growth, regeneration, wound healing and formation of corpus luteum and endometrium. Angiogenesis attracted wide interest in the scientific community when the pioneering hypothesis of Judah Folkman in 1971 that tumor progression and metastasis are dependent on angiogenesis (and, as such, cancer could be therapeutically attacked by inhibiting angiogenesis) began to be confirmed by experimental studies since the eighties [4–6]. In fact, inhibition of this process has become a major challenge in the development of new anticancer agents, with more than 40,000 scientific papers published on this subject, and about a hundred anti-angiogenic compounds entered in clinical trials, and numerous others in preclinical development [7–9]. Currently, it is well established that a deregulated and persistent angiogenesis is one of the hallmarks of cancer [10, 11]. Furthermore, there is overwhelming evidence on the involvement of deregulated angiogenesis in many other pathological situations, which are currently described as angiogenesis-dependent diseases [12]. The interest and impact of angiogenesis as a new therapeutic target from the treatment of non- oncological angiogenesis-dependent diseases is well represented by the recent concession of the Lasker-DeBakey Clinical Medical Research Award 2010 to Dr. Napoleone Ferrara for the discovery of VEGF as a major mediator of angiogenesis and the development of an effective anti-VEGF therapy for wet macular degeneration, a leading cause of blindness in the elderly [13]. This is a type of age-related macular degeneration, included as a rare disease in the Orphanet website with the Orpha number ORPHA279. Other two examples of A-RDs are POEMS syndrome (ORPHA2905) [14, 15] and Amyotrophic lateral sclerosis (ORPHA803) [16].

In fact, a number of the so far described rare diseases are infrequent types of neoplasia, most probably related to angiogenesis. Furthermore, many other rare diseases could be related to angiogenesis. However, there is a lack of an exhaustive and systematic review on the topic “angiogenesis related rare diseases”. To contribute to fill this gap is the main aim of the present review. To reach this goal, our group can make use or our previous experience in the management of databases and the implementation of bioinformatics tools [17–19]. As a research group integrated in the Spanish Network of Rare Disease Research (http://www.ciberer.es/index.php?lang=english), we are actively involved in the search of new sources of knowledge in this research area. In the present work, we aim to evaluate how much and what kind of information we are able to uncover in the context of A-RDs. Furthermore, we also evaluate what kind of information contained in Orphanet can be extracted within the frame of our systematic search.

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Methods

State of the art

The aim of this study was to perform a systematic study on the following question: what scientific information can be drawn from those rare diseases that are related to the topic called angiogenesis? To this end, we adapted the methodology stated in PRISMA statement (http://www.prisma-statement.org/statement.htm) for the systematic review of the whole set of documents that could be extracted from the databases used in this study [20, 21]. Table S1 in Supplementary material is the completed PRISMA checklist.

Strategy for the literature search

Eligibility criteria

Types of studies: This is a bibliometric study for the capture and identification of rare diseases appearing in different sources of scientific documentation and that are somehow related to angiogenesis.

Report eligibility: The scientific information specified in the previous section was exhaustively collected from scientific publications, namely, reviews, articles, case reports, proceedings and patents. The publication time ranged from 1991 to 2010 and there was no restriction concerning language or kind of publication. This search was dated in June of 2010 and updated in December of 2010. The whole set of collected rare diseases related to angiogenesis was submitted to a filter and selection procedure, according to their presence or not within a specialized database for rare diseases (Orphanet).

Information sources

For the selection of scientific publications concerning rare diseases somehow related to angiogenesis, an online search of literature was carried out in both PubMed and ISI Web of Knowledge databases.

Search terms used were “rare disease” as a generic term and “angiogen*”. The use of the two terms “rare” and “disease” juxtaposed allowed to include any pathologic with its name before the search term “disease” (i.e. Castleman disease, Von Willebrand disease, Wilson disease, Menkes disease, Crohn disease, among others) and make possible to associate the search term “rare” with other related semantic terms, such as in the cases of rare tumor, rare pathology or rare disorder, among others. Finally, the term “angiogen*” was used as a root belonging to the generic term of angiogenesis and/or all possible variants.

As mentioned above, to validate the rare diseases found in this initial literature search, Orphanet database was used. Only those rare diseases contained and indexed within this database were confirmed and used for the rest of the study.

Search

In PubMed database, search terms were introduced in Advanced search without time limit or any other limit and listed as “(rare disease) AND angiogen*”, according to the following structured search: “rare diseases”[MeSH Terms] OR “rare”[All Fields] AND “diseases”[All Fields]) OR “rare diseases”[All Fields] OR (“rare”[All Fields] AND “disease”[All Fields]) OR “rare disease”[All Fields], along with more specific terms that appear by default in Medical Subject Heading (MeSH) hierarchical structure in Medline. MeSH categories were: Orphan Drug Production / All MeSH Categories / Diseases Category / Pathological Conditions, Signs and Symptoms / Pathologic Processes / Disease Attributes / Rare Diseases. The MeSH terms were: Disease, Rare / Diseases, Rare / Rare Disease / Orphan Disease, Orphan / Diseases, Orphan / Orphan Disease. Search terms were introduced in ISI Web of Knowledge database as topics in both cases. The annotated search structure was as follows: Topic=-(rare disease) AND Topic=(angiogen*). Timespan=All Years.

Study selection

Bibliography selection

The two lists of publications mentioning one or several rare diseases somehow related to angiogenesis obtained by searching PubMed and ISI Web of Knowledge as described above were merged into a unique list containing all the entrances without repetition. In order to reduce the bias among the selected data and the data that really fit the list of search terms, all the information extracted was reviewed and verified. To reach this goal, all the publications contained in the merged list were revised one by one by making a strategic reading of them [22]. An analysis of matches was performed looking for the occurrence of the following terms “rare disease”, and/or “rare”, and/or “disease” and “angiogenic *” or “VEGF” in all titles, abstracts, author keywords and keywords plus found and MeSH terms. All the references that did not support this exclusion analysis were removed.

Rare diseases selection

Only those references containing explicit reference to one or more rare diseases (and therefore listed in Orphanet database with an Orphan identification number) were used to select those rare diseases included in the set to be further analyzed.

Data collection process and synthesis of indexed information

Data bibliographic systematic review

Once all the bibliographic information related to rare disease and angiogenesis was confirmed and validated, we proceeded to the analysis and compilation of all data of interest that Orphanet website could bring to the state of the art. All the collected data were allocated in sheets for the management of data in Excel format. This election was based on: (i) the easy access and operability of this format, (ii) the easy identification of data through the search option, and (iii) the capability to recover the original source of information through online links.

In a first column, the titles of all the selected bibliographic references in the study were included. The order or entrance was assigned according to publication dates, from the most recent to the oldest one.
All found and selected bibliographic references were categorized for each Orpha identification number validated with the applied selection criteria.

Initial classification of angiogenesis-related rare diseases
A first general classification criterion was established according to which each disease was assigned to one of the three following disjoined subsets: A (A-RDs with cancerous phenotype in all their features), B (A-RDs with cancerous phenotype only in some of their features) and C (A-RDs without cancerous phenotype). To determine the three subsets, a systematic search of the semantic terms “tumor” and “cancer” and the suffix “-ome” was carried out within the classification that Orphanet exposes for rare diseases. The terms glaucoma, angiokeratome, lysosome, pseudoxanthome and hamartome were excluded due to obvious reasons. After this, all corresponding genes and orphan drugs were seized from Orphanet database, categorized for each Orpha identification number and associated to A-RDs in different sheets.

Bioinformatics analysis of bibliographic systematic review
To validate our manual systematic review of literature, we carried out an additional bioinformatics text mining study. The list of PubMed IDs (PMIDs) was obtained from the initial systematic review (all references of supplementary material, with the exception of references 5, 41, 44, 63 and 71) and uploaded into the text mining web application SciMiner [23]. A biomedical literature mining analysis and the subsequent enrichment analysis were carried out concerning to those Medical Subject Headings (MeSH) associated with the retrieved PMIDs from the systematic review.

Results of the literature search and Orphanet analysis

Bibliographic systematic review
As shown in the scheme depicted in Figure 1, the search in ISI Web of Knowledge yielded 284 references, whereas that carried out in PubMed yielded 263 references. From all these references, only 187 fulfilled the selection criteria for their inclusion in the set to be further analyzed. The complete set of the 187 selected bibliographic references conforms the bibliography included in the Supplementary material and they validate the entrance of 180 A-RDs indexed in the database Orphanet (see Methods). An evaluation of this bibliographic set using PMIDs was carried out as described (see Methods). To avoid the occurrence of trivial MeSH terms, we have considered statistically significant only those terms with a P-value lower than 1.0E-5 and an enrichment (t-ratio/b-ratio) greater than 40. The results are shown in Table 1. Figure S1 (Supplementary material) shows the PRISMA flow diagram corresponding to this systematic review.

Fig. 1 Flow of information through the different phases of bibliographic systematic review.
| MeSH                                      | t+ | t− | b+ | b− | WholeSize | t-Ratio | b-Ratio | t-ratio/b-ratio | P-value   |
|--------------------------------------------|----|----|----|----|-----------|---------|---------|-----------------|-----------|
| Angiogenesis inhibitors                    | 33 | 149| 8120| 19,435,023| 19,443,143| 0.18    | 4.18E-04 | 434.2           | 6.18E-76  |
| Neovascularization, pathologic             | 31 | 151| 22,709| 19,420,434| 19,443,143| 0.17    | 1.17E-03 | 145.8           | 9.89E-57  |
| Vascular endothelial growth factor A       | 18 | 164| 20,847| 19,422,296| 19,443,143| 0.1     | 1.07E-03 | 92.2            | 9.41E-30  |
| Thalidomide                                | 12 | 170| 4628| 19,438,515| 19,443,143| 0.07    | 2.38E-04 | 277             | 6.17E-26  |
| Herpesvirus 8, human                       | 9  | 173| 3009| 19,440,134| 19,443,143| 0.05    | 1.55E-04 | 319.5           | 2.49E-20  |
| Macular degeneration                       | 7  | 175| 7925| 19,435,218| 19,443,143| 0.04    | 4.08E-04 | 94.4            | 2.06E-12  |
| von Hippel–Lindau disease                  | 5  | 177| 1744| 19,441,399| 19,443,143| 0.03    | 8.97E-05 | 306.3           | 9.10E-12  |
| Lymphangioleiomyomatosis                   | 4  | 178| 569 | 19,442,574| 19,443,143| 0.02    | 2.93E-05 | 751             | 3.29E-11  |
| Endothelial cells                          | 7  | 175| 15,420| 19,427,723| 19,443,143| 0.04    | 7.93E-04 | 48.5            | 2.05E-10  |
| Carcinoma, renal cell                      | 7  | 175| 16,035| 19,427,108| 19,443,143| 0.04    | 8.25E-04 | 46.6            | 2.68E-10  |
| Exudates and transudates                   | 6  | 176| 8354| 19,434,789| 19,443,143| 0.03    | 4.30E-04 | 76.7            | 2.75E-10  |
| Hypoxia-inducible factor 1, alpha subunit  | 5  | 177| 4123| 19,439,020| 19,443,143| 0.03    | 2.12E-04 | 129.6           | 6.57E-10  |
| Vascular malformations                     | 3  | 179| 311 | 19,442,832| 19,443,143| 0.02    | 1.60E-05 | 1030.5          | 4.11E-09  |
| Telangiectasia, hereditary hemorrhagic     | 4  | 178| 1929| 19,441,214| 19,443,143| 0.02    | 9.92E-05 | 221.5           | 4.25E-09  |
| Activin receptors, type II                 | 3  | 179| 346 | 19,442,797| 19,443,143| 0.02    | 1.78E-05 | 926.3           | 5.65E-09  |
| Hemangiendothelioma, epithelioid           | 3  | 179| 459 | 19,442,684| 19,443,143| 0.02    | 2.36E-05 | 698.2           | 1.31E-08  |
| Vascular endothelial growth factors        | 5  | 177| 7692| 19,435,451| 19,443,143| 0.03    | 3.96E-04 | 69.4            | 1.44E-08  |
| Angiogenic proteins                        | 3  | 179| 482 | 19,442,661| 19,443,143| 0.02    | 2.48E-05 | 664.9           | 1.52E-08  |
| POEMS syndrome                             | 3  | 179| 486 | 19,442,657| 19,443,143| 0.02    | 2.50E-05 | 659.4           | 1.56E-08  |
| Osteolysis, essential                      | 3  | 179| 541 | 19,442,602| 19,443,143| 0.02    | 2.78E-05 | 592.4           | 2.15E-08  |
| Hemangioma, capillary                      | 3  | 179| 665 | 19,442,478| 19,443,143| 0.02    | 3.42E-05 | 481.9           | 3.97E-08  |
| Protein kinase inhibitors                  | 5  | 177| 10,840| 19,432,303| 19,443,143| 0.03    | 5.58E-04 | 49.3            | 7.82E-08  |
| Interferon-alpha                           | 5  | 177| 11637| 19,431,506| 19,443,143| 0.03    | 5.99E-04 | 45.9            | 1.11E-07  |
| Pyroles                                   | 5  | 177| 11,893| 19,431,250| 19,443,143| 0.03    | 6.12E-04 | 44.9            | 1.23E-07  |
| Von Hippel–Lindau tumor suppressor protein | 3  | 179| 1082| 19,442,061| 19,443,143| 0.02    | 5.56E-05 | 296.2           | 1.70E-07  |
| Hypoxia-inducible factor 1                 | 3  | 179| 1746| 19,441,397| 19,443,143| 0.02    | 8.98E-05 | 183.6           | 7.10E-07  |
| Endothelial growth factors                 | 4  | 178| 7866| 19,435,277| 19,443,143| 0.02    | 4.05E-04 | 54.3            | 1.12E-06  |
| Sarcoma, kaposi                            | 4  | 178| 8163| 19,434,980| 19,443,143| 0.02    | 4.20E-04 | 52.3            | 1.30E-06  |
we consider that diseases recovered in this way can be called "angiogenic rare diseases" and they can be retrieved from those 180 rare diseases related in some way with angiogenesis. These 27 angiogenic rare diseases are also highlighted in Table 2.

The most commonly used classification of diseases is WHO ICD-10 (http://www.who.int/classifications/icd/en). Tables S2–S4 (Supplementary material) list A-RDs corresponding to subsets A, B, and C, respectively, indicating their ICD-10 when available. It is noteworthy that as many as 83 A-RDs (47 in subset A, 6 in subset B and 30 in subset C) have currently no ICD code assigned.

Genes and drugs associated to angiogenesis-related rare diseases

We manually collected 244 entrances identified as genes in Orphanet. To study the relative distribution of the set of extracted and annotated genes in the list of A-RDs, and also to know their representation in the three initial subsets (A, B, C), three categories of A-RDs where established: those currently associated to no gene, those associated to one gene, and those with two or more genes associated. The number of genes in each A-RD is highlighted in Table 2. Furthermore, Tables S5 and S6 (Supplementary material) list all the A-RDs associated to a single or to more than a gene, respectively, identifying the corresponding related genes by their Orpha gene IDs.

It is interesting to note that this relationship among genes and A-RDs is not symmetrical. Tables 3 and 4 list the whole set of 186 genes associated to one A-RD and 58 genes associated to two or more A-RDs, respectively, identifying the corresponding A-RDs by their Orpha rare disease IDs. Figure 2 shows the distribution of the annotated genes grouped in two categories (those associated to one
| n° | References | Orpha ID | Rare disease | Orpha genes | Orpha drugs |
|----|------------|----------|--------------|-------------|-------------|
| Subset A (rare oncologic diseases) |
| 1 | [1, 136] | 519 | Acute myeloid leukemia (ARD)* | 19 | 33 |
| 2 | [59] | 213772 | Adenocarcinoma of the cervix uteri | 0 | 0 |
| 3 | [128] | 1501 | Adrenocortical carcinoma | 0 | 1 |
| 4 | [47] | 163699 | Alveolar soft-part sarcoma | 2 | 0 |
| 5 | [114] | 142 | Anaplastic thyroid carcinoma | 0 | 1 |
| 6 | [52] | 86886 | Angioimmunoblastic T-cell lymphoma | 0 | 0 |
| 7 | [11] | 98731 | Arteriovenous fistula | 0 | 0 |
| 8 | [23, 26, 68, 79, 105, 143] | 211266 | Arteriovenous malformation | 0 | 0 |
| 9 | [51] | 157980 | Bladder Cancer | 0 | 0 |
| 10 | [125, 134] | 223727 | Bone sarcoma | 7 | 0 |
| 11 | [83] | 3395 | Brain tumor (ARD)* | 17 | 0 |
| 12 | [165] | 97287 | Bronchial endocrine tumor | 0 | 0 |
| 13 | [26] | 137667 | Capillary malformation-arteriovenous malformation | 1 | 0 |
| 14 | [45, 112, 143, 152] | 164 | Cerebral cavernous malformations | 0 | 0 |
| 15 | [99] | 86829 | Chronic neutrophilic leukemia | 0 | 0 |
| 16 | [61] | 99970 | Dedifferentiated liposarcoma | 0 | 0 |
| 17 | [61] | 31112 | Dermatofibrosarcoma protuberans | 2 | 0 |
| 18 | [15] | 141209 | Diffuse lymphatic malformation | 0 | 0 |
| 19 | [29, 138, 167] | 877 | Endocrine tumor | 2 | 2 |
| 20 | [29] | 100092 | Enteropancreatic endocrine tumor | 0 | 2 |
| 21 | [103] | 99871 | Eosinophilic granuloma | 0 | 0 |
| 22 | [65, 98, 139, 162] | 157791 | Epithelioid hemangioendothelioma | 0 | 0 |
| 23 | [147, 149] | 99976 | Esophageal adenocarcinoma | 0 | 0 |
| 24 | [149] | 99977 | Esophageal squamous cell carcinoma | 1 | 0 |
| 25 | [61, 134] | 319 | Ewing sarcoma | 5 | 0 |
| 26 | [51, 146, 164] | 733 | Familial adenomatous polyposis | 1 | 4 |
| 27 | [64] | 523 | Familial leiomyomatosis | 1 | 0 |
| 28 | [20] | 99361 | Familial medullary thyroid carcinoma | 0 | 0 |
| 29 | [39, 42, 47, 92, 104, 159, 160] | 151 | Familial renal cell carcinoma (ARD)* | 11 | 22 |
| 30 | [70, 135] | 63443 | Gastric cancer | 2 | 5 |
| n°  | References                                                                 | Orpha ID | Rare disease                                      | Orpha genes | Orpha drugs |
|-----|---------------------------------------------------------------------------|----------|---------------------------------------------------|-------------|-------------|
| 31  | [61, 97]                                                                  | 44890    | Gastrointestinal stromal tumor                    | 2           | 5           |
| 32  | [5, 36, 83]                                                                | 360      | Glioblastoma                                      | 8           | 33          |
| 33  | [5, 83]                                                                   | 182067   | Glioblastoma                                      | 9           | 26          |
| 34  | [45]                                                                      | 83454    | Glioblastoma                                      | 1           | 1           |
| 35  | [34]                                                                      | 99915    | Granulosa cell malignant tumor                    | 0           | 0           |
| 36  | [184]                                                                     | 58017    | Glioblastoma                                      | 0           | 2           |
| 37  | [76]                                                                      | 2126     | Glioblastoma                                      | 0           | 0           |
| 38  | [123, 137]                                                                 | 88673    | Glioblastoma                                      | 2           | 14          |
| 39  | [141]                                                                     | 227535   | Glioblastoma                                      | 0           | 0           |
| 40  | [94, 107]                                                                  | 29072    | Glioblastoma                                      | 6           | 0           |
| 41  | [166, 167]                                                                 | 97279    | Glioblastoma                                      | 0           | 3           |
| 42  | [87, 118, 144, 158, 162, 169, 172, 177, 179, 180, 181, 185, 186]            | 33276    | Glioblastoma                                      | 0           | 5           |
| 43  | [22]                                                                      | 213807   | Glioblastoma                                      | 0           | 0           |
| 44  | [22]                                                                      | 213625   | Glioblastoma                                      | 0           | 0           |
| 45  | [111]                                                                     | 65285    | Glioblastoma                                      | 1           | 0           |
| 46  | [141]                                                                     | 524      | Glioblastoma                                      | 2           | 1           |
| 47  | [173]                                                                     | 69078    | Glioblastoma                                      | 1           | 2           |
| 48  | [24, 75]                                                                   | 168811   | Glioblastoma                                      | 0           | 0           |
| 49  | [67, 112]                                                                  | 3148     | Glioblastoma                                      | 0           | 0           |
| 50  | [6]                                                                       | 98292    | Glioblastoma                                      | 1           | 1           |
| 51  | [20, 165]                                                                  | 1332     | Glioblastoma                                      | 1           | 3           |
| 52  | [56]                                                                       | 97338    | Glioblastoma                                      | 2           | 0           |
| 53  | [24, 75]                                                                   | 50251    | Glioblastoma                                      | 0           | 3           |
| 54  | [55, 77, 140, 166, 178, 184]                                               | 29073    | Glioblastoma                                      | 2           | 23          |
| 55  | [1]                                                                       | 52688    | Glioblastoma                                      | 2           | 10          |
| 56  | [61]                                                                       | 99967    | Glioblastoma                                      | 1           | 0           |
| 57  | [80]                                                                       | 209989   | Glioblastoma                                      | 0           | 1           |
| 58  | [134]                                                                     | 668      | Glioblastoma                                      | 2           | 5           |
| 59  | [59]                                                                       | 213504   | Glioblastoma                                      | 0           | 7           |
| 60  | [142]                                                                     | 2800     | Glioblastoma                                      | 0           | 0           |
| n° | References | Orpha ID | Rare disease | Orpha genes | Orpha drugs |
|----|------------|----------|--------------|-------------|-------------|
| 61 | [165]      | 217074   | Pancreatic carcinoma | 7           | 21          |
| 62 | [94]       | 717      | Pheochromocytoma and secreting paraganglioma (ARD)* | 8           | 1           |
| 63 | [14, 66, 115] | 2905    | POEMS syndrome | 0           | 0           |
| 64 | [87, 169, 172, 177, 180] | 48686  | Primary effusion lymphoma | 0           | 0           |
| 65 | [87, 144, 169, 172, 180, 181] | 99923  | Primary effusion lymphoma associated with HIV infection | 0           | 0           |
| 66 | [59]       | 213528   | Rare adenocarcinoma of the breast | 0           | 0           |
| 67 | [74]       | 180250   | Rare breast cancer (ARD)* | 12          | 0           |
| 68 | [12, 28, 39, 42, 47, 57, 63, 84, 92, 104, 122, 159, 160, 182] | 217071  | Renal cell carcinoma (ARD)* | 12          | 24          |
| 69 | [61]       | 69077    | Rhabdoid tumor | 2           | 0           |
| 70 | [165]      | 70573    | Small cell lung cancer | 0           | 4           |
| 71 | [9, 22, 56, 97, 125, 173] | 3394    | Soft tissue sarcomas | 20          | 10          |
| 72 | [162]      | 210584   | Spindle cell hemangioma | 0           | 0           |
| 73 | [93]       | 67037    | Squamous cell carcinoma of head and neck (ARD)* | 4           | 5           |
| 74 | [131]      | 99868    | Thymic carcinoma | 0           | 0           |
| 75 | [131]      | 3398     | Thymic epithelial tumor | 0           | 0           |
| 76 | [131]      | 100100   | Thymic tumor | 0           | 0           |
| 77 | [131]      | 99867    | Thymoma | 0           | 0           |
| 78 | [133]      | 1063     | Tufted angioma | 0           | 0           |
| 79 | [52]       | 86885    | Unspecified peripheral T-cell lymphoma | 0           | 4           |
| 80 | [85, 88, 159] | 39044   | Uveal melanoma | 0           | 1           |
| 81 | [61]       | 99971    | Well-differentiated liposarcoma | 0           | 0           |

Subset B (A-RDs with cancerous phenotype only in some of their features)

| n° | References | Orpha ID | Rare disease | Orpha genes | Orpha drugs |
|----|------------|----------|--------------|-------------|-------------|
| 1  | [111]      | 109      | Bannayan-Riley-Ruvalcaba syndrome (ARD)* | 1           | 0           |
| 2  | [89, 184]  | 521      | Chronic myeloid leukemia (ARD)* | 3           | 12          |
| 3  | [69]       | 53721    | Cobb syndrome | 0           | 0           |
| 4  | [60, 109]  | 191      | Cockayne syndrome | 5           | 0           |
| 5  | [95]       | 2414     | Congenital pulmonary lymphangiectasia | 0           | 0           |
| 6  | [111]      | 201      | Cowden syndrome (ARD)* | 3           | 0           |
| 7  | [17]       | 324      | Fabry disease | 1           | 3           |
| 8  | [15, 16, 73, 118] | 73      | Gorham-Stout disease | 0           | 0           |
| n° | References | Orpha ID | Rare disease | Orpha genes | Orpha drugs |
|----|------------|----------|--------------|-------------|------------|
| 9  | [35, 110]  | 90308    | Klippel-Trenaunay syndrome (ARD)* | 1           | 0          |
| 10 | [90]       | 389      | Langerhans cell histiocytosis     | 0           | 1          |
| 11 | [174]      | 79383    | Lymphedema (ARD)*                | 4           | 0          |
| 12 | [50]       | 2451     | Mucocutaneous venous malformations (ARD)* | 1           | 1          |
| 13 | [166, 167] | 652      | Multiple endocrine neoplasia type 1 | 2           | 2          |
| 14 | [89, 148]  | 824      | Myelofibrosis with myeloid metaplasia | 1           | 2          |
| 15 | [2, 61]    | 636      | Neurofibromatosis type 1 (ARD)*   | 3           | 2          |
| 16 | [53]       | 2869     | Peutz-Jeghers syndrome             | 1           | 0          |
| 17 | [91]       | 42775    | PHACE syndrome                     | 0           | 0          |
| 18 | [89]       | 729      | Polycythemia vera                 | 1           | 5          |
| 19 | [174]      | 77240    | Primary lymphedema                 | 2           | 0          |
| 20 | [8, 13, 23, 45, 79, 105, 143] | 774 | Rendu-Osler-Weber disease (ARD)* | 3           | 1          |
| 21 | [37, 88]   | 3205     | Sturge-Weber syndrome              | 0           | 0          |
| 22 | [12, 29, 39, 42, 84, 88, 92, 122, 130, 161, 170, 182] | 892 | Von Hippel–Lindau disease (ARD)* | 1           | 2          |
| 23 | [187]      | 913      | Zollinger-Ellison syndrome         | 1           | 3          |

Subset C (A-RDs without cancerous phenotype)

| n° | References | Orpha ID | Rare disease | Orpha genes | Orpha drugs |
|----|------------|----------|--------------|-------------|------------|
| 1  | [25]       | 93585    | Acquired thrombotic thrombocytopenic purpura due to anti-ADAMTS 13 antibodies | 0           | 1          |
| 2  | [54]       | 79126    | Acute interstitial pneumonia     | 0           | 0          |
| 3  | [19, 27, 32, 40, 43, 48, 62, 88, 176] | 279 | Age-related macular degeneration | 6           | 1          |
| 4  | [58, 126]  | 803      | Amyotrophic lateral sclerosis (ARD)* | 17          | 10         |
| 5  | [35, 110]  | 2346     | Angio-osteo hypertrophic syndrome (ARD)* | 2           | 0          |
| 6  | [25]       | 2134     | Atypical hemolytic uremic syndrome (ARD)* | 6           | 3          |
| 7  | [154]      | 3453     | Autoimmune polyendocrinopathy type 1 | 1           | 0          |
| 8  | [46]       | 117      | Behcet disease                   | 0           | 2          |
| 9  | [21]       | 131      | Budd-Chiari syndrome             | 0           | 0          |
| 10 | [30, 120]  | 36258    | Buerger’s disease                | 0           | 0          |
| 11 | [152]      | 136      | CADASIL syndrome                 | 1           | 0          |
| 12 | [31, 179, 185] | 160 | Castleman disease                | 0           | 2          |
| 13 | [154]      | 178029   | Central diabetes insipidus       | 1           | 0          |
| 14 | [68]       | 98044    | Central nervous system malformation | 0           | 0          |
| 15 | [40]       | 179      | Chorioretinopathy, Birdshot type | 1           | 0          |
| n° | References | Orpha ID | Rare disease                                                                 | Orpha genes | Orpha drugs |
|----|------------|----------|------------------------------------------------------------------------------|-------------|-------------|
| 16 | [155]      | 2137     | Chronic autoimmune hepatitis                                                 | 0           | 1           |
| 17 | [117]      | 183      | Churg-Strauss syndrome                                                       | 0           | 1           |
| 18 | [40, 109]  | 190      | Coats disease                                                                | 1           | 0           |
| 19 | [78]       | 2041     | Coronary arterial fistulas                                                   | 0           | 0           |
| 20 | [6, 103, 133] | 206  | Crohn disease                                                               | 5           | 0           |
| 21 | [116]      | 137688   | Cytomegalovirus disease in patients with impaired cell mediated immunity deemed at risk | 0           | 1           |
| 22 | [68]       | 97339    | Dural sinus malformation                                                     | 0           | 0           |
| 23 | [40]       | 40923    | Eales disease                                                                | 0           | 0           |
| 24 | [165]      | 99889    | Ectopic Cushing syndrome                                                     | 0           | 1           |
| 25 | [72]       | 199323   | Endophthalmitis                                                              | 0           | 0           |
| 26 | [183]      | 337      | Fibrodyplasia ossificans progressiva (ARD)*                                 | 1           | 0           |
| 27 | [45]       | 2092     | Focal dermal hypoplasia                                                      | 1           | 0           |
| 28 | [3]        | 221126   | Fowler syndrome                                                              | 1           | 0           |
| 29 | [17]       | 355      | Gaucher disease                                                              | 2           | 5           |
| 30 | [17]       | 77260    | Gaucher disease, type 2                                                      | 1           | 4           |
| 31 | [17]       | 77261    | Gaucher disease, type 3                                                      | 1           | 4           |
| 32 | [154]      | 95509    | Granulomatous hypophysitis                                                   | 0           | 0           |
| 33 | [121]      | 855      | Hashimoto struma                                                            | 1           | 0           |
| 34 | [90]       | 158032   | Hemophagocytic syndrome                                                      | 14          | 1           |
| 35 | [132, 152] | 85458    | Hereditary cerebral hemorrhage with amyloidosis                             | 2           | 0           |
| 36 | [132]      | 100006   | Hereditary cerebral hemorrhage with amyloidosis, Dutch type                 | 0           | 0           |
| 37 | [157]      | 422      | Idiopathic and/or familial pulmonary arterial hypertension (ARD)*           | 3           | 17          |
| 38 | [21]       | 69665    | Intrahepatic cholestasis of pregnancy                                        | 2           | 0           |
| 39 | [100]      | 2778     | Juvenile chronic recurrent multifocal osteomyelitis                         | 0           | 0           |
| 40 | [82]       | 2331     | Kawasaki disease                                                            | 0           | 1           |
| 41 | [156]      | 1571     | Knobloch syndrome (ARD)*                                                     | 1           | 0           |
| 42 | [101, 163] | 530      | Lipoid proteinosis (ARD)*                                                    | 1           | 0           |
| 43 | [7, 108]   | 538      | Lymphangioleiomyomatosis                                                     | 2           | 0           |
Table 2. Continued

| No | References | Orpha ID | Rare disease                                      | Orpha genes | Orpha drugs |
|----|------------|---------|--------------------------------------------------|-------------|-------------|
| 44 | [17]       | 93448   | Lysosomal storage disease with skeletal involvement | 22          | 0           |
| 45 | [86]       | 101338  | Mediterranean spotted fever                       | 0           | 0           |
| 46 | [168]      | 54370   | Membranoproliferative glomerulonephritis          | 1           | 0           |
| 47 | [10, 127, 145] | 565 | Menkes disease                                   | 1           | 0           |
| 48 | [68, 106]  | 2573    | Moyamoya disease                                  | 1           | 0           |
| 49 | [87, 144, 169, 172, 177, 180] | 93686 | Multicentric Castleman disease                    | 0           | 0           |
| 50 | [176]      | 94058   | Neovascular glaucoma                              | 1           | 0           |
| 51 | [129]      | 649     | Norrie disease                                    | 1           | 0           |
| 52 | [25]       | 447     | Paroxysmal nocturnal hemoglobinuria               | 0           | 2           |
| 53 | [17]       | 85212   | Perinatal-lethal Gaucher disease                  | 1           | 0           |
| 54 | [18]       | 563     | Peripartum cardiomyopathy                         | 0           | 0           |
| 55 | [40]       | 758     | Pseudoxanthoma elasticum                          | 1           | 0           |
| 56 | [4, 113, 157] | 182090 | Pulmonary arterial hypertension                    | 0           | 3           |
| 57 | [96, 153]  | 199241  | Pulmonary capillary hemangiomatosis               | 0           | 2           |
| 58 | [113]      | 71198   | Rare pulmonary hypertension                       | 0           | 1           |
| 59 | [38]       | 60032   | Recurrent respiratory papillomatosis              | 0           | 0           |
| 60 | [40, 102, 171, 176] | 90050 | Retinopathy of prematurity                        | 1           | 2           |
| 61 | [33]       | 49041   | Retroperitoneal fibrosis                          | 0           | 0           |
| 62 | [86]       | 102021  | Rickettsiae disease                               | 0           | 0           |
| 63 | [17, 82]   | 797     | Sarcoïdosis                                       | 1           | 2           |
| 64 | [81, 124]  | 801     | Scleroderma                                       | 0           | 3           |
| 65 | [166]      | 36426   | Stevens-Johnson syndrome                          | 0           | 0           |
| 66 | [99]       | 3243    | Sweet syndrome                                    | 0           | 0           |
| 67 | [116, 119, 154] | 536 | Systemic lupus erythematosus                      | 2           | 1           |
| 68 | [81]       | 90291   | Systemic sclerosis                                | 0           | 3           |
| 69 | [135]      | 93573   | Thrombotic microangiopathy                        | 0           | 0           |
| 70 | [25, 151]  | 54057   | Thrombotic thrombocytopenic purpura               | 1           | 5           |
| 71 | [25]       | 90038   | Typical hemolytic uremic syndrome                  | 0           | 1           |
| 72 | [117]      | 52759   | Vasculitis                                        | 0           | 0           |
| 73 | [49, 109, 129] | 98668 | Vitreoretinopathy (ARD)*                          | 14          | 0           |
| 74 | [86, 151, 175] | 903   | Von Willebrand disease                            | 1           | 3           |
A-RD and those associated to two or more A-RDs in the whole set and the three subsets of A-RDs.

In the case of drugs, in this study 285 entrances were manually identified in Orphanet database as orphan drugs. As in the case of genes, three categories of A-RDs where established: those currently associated to no drug, those associated to one drug, and those with two or more drugs associated. The number of drugs in each A-RD is highlighted in Table 2. Furthermore, Tables S7 and S8 (Supplementary material) list all the A-RDs associated to a single or to more than a drug, respectively, identifying the corresponding related drugs by their Orpha drug IDs. As in the case of genes, the relationship A-RDs-drugs is also asymmetrical. Tables S9 and S10 list the whole set of 198 drugs associated to one A-RD and 87 drugs associated to two or more A-RDs, respectively, identifying the corresponding A-RDs by their Orpha rare disease IDs. Figure 3 shows the distribution of the annotated drugs grouped in two categories (those associated to one A-RD and those associated to two or more A-RDs) in the whole set and the three subsets of A-RDs.

**Discussion of the literature search and orphanet analysis**

**Bibliographic systematic review**

Our bibliographic systematic review (see Fig. 1) has allowed us to select 187 references (see bibliography in Supplementary material) and 180 A-RDs (that is, 180 rare diseases related with the neovascularization process, see Table 2A-C). This systematic review has also made possible the extraction of a great amount of data in an exhaustive and trustworthy manner. In the present work, these extracted data could be synthetized, validated and interrelated through the use of a reproducible methodology, based in PRISMA statements (20, 21) (see PRISMA checklist in Table S1 and PRISMA flow diagram in Figure S1). When we recovered those A-RDs that are cited three or more times in our set of selected references (29 of the 180 A-RDs), we found that in most cases vascular diseases (or malformations) or angioproliferative disorders were retrieved, with the exceptions of Multicentric castlemann disease (ORPHRA93686), Multiple myeloma (ORPHA29073), Primary effusion lymphoma associated with HIV infection (ORPHA99923) and Primary effusion lymphoma (ORPHA48686). Renal cell carcinoma (ORPHA217071) was the angioproliferative disease more times referenced (in fact, it is mentioned in 14 of the 187 selected references included in supplementary material).

On the other hand, a text mining analysis has been used as an automatic and independent validation of the results achieved in the systematic review. We can observe that the enriched MeSH terms of the 187 bibliographic references, obtained from the systematic review, are notably related to angiogenesis and pathological conditions (see Table 1). These results of the text mining analysis confirm that our selection of the bibliography has consistent information related to angiogenesis and biological process involved in the pathogenesis. Under these conditions, more than a half of PMIDs linked to MeSH terms related to pathologies (*i.e.* Neovascularization, Pathologic, Herpesvirus 8, Macular Degeneration, Pathologic-von Hippel-Lindau Disease, lymphangioleiomyomatosis, Renal Cell Carcinoma, Hereditary Hemorrhagic Telangiectasia, Hemangioendothelioma, POEMS Syndrome, Essential osteolyis, Capillary Hemangioma Kaposi Sarcoma, Rare Diseases and Lipoid proteinosis of Urbach and Wiethe) match with those PMIDs that are linked to MeSH terms related to angiogenesis (Angiogenesis inhibitors, Vascular Endothelial Growth Factor A, Thalidomide, Vascular Endothelial Growth Factors, Angiogenic Proteins, Vascular Endothelial Growth Factor Receptors). It is interesting to note that only three PMIDs are indicated for the term called “Rare disease”, which highlights the lack of identification with this type of disease in the scientific literature (see Table 1).

**Initial classification of angiogenesis-related rare diseases**

Orphanet has its own classification of rare diseases, based on a hierarchy of descriptive categories. These categories are pathological descriptions based in published scientific data and information provided by experts in the field. These pathological descriptions are referred to as manifestations along the tables presented in this work. The close relationship between angiogenesis and tumor progression was used for the initial classification of A-RDs into three differentiated subsets (see Table 2). The analysis of this classification confirmed that this procedure gave rise to a consistent separation. The dominant subset was “rare neoplasias” (subset A), as expected. Concerning A-RDs included in subset B, they are mostly vascular malformations (as angiomas and hemangiomas), as well as dysplasias and hamartomas. They are non neoplastic pathologies associated to an increased risk to develop tumors. Finally, subset C included a whole array of non-tumoral rare diseases tightly related with (and, in many cases, dependent on) angiogenesis.
Table 3. Genes associated to a single angiogenesis-related rare disease

| n° | Genes | Rare diseases Orpha ID |
|----|-------|-----------------------|
| 1  | ACTA2 | 2573 (C) |
| 2  | ATF1  | 97338 (A) |
| 3  | ACVR1 | 337 (C) |
| 4  | ADAMTS13 | 54057 (C) |
| 5  | AP3B1 | 158032 (C) |
| 6  | ARMS2 | 279 (C) |
| 7  | APP   | 85458 (C) |
| 8  | ALS2  | 803 (C) |
| 9  | ALK   | 3395 (A) |
| 10 | ANG   | 803 (C) |
| 11 | (TATCCGGAGGCTCGCCATGCTGCT) | 94058 (C) |
| 12 | AVP   | 178029 (C) |
| 13 | ARSB  | 93448 (C) |
| 14 | AGA   | 93448 (C) |
| 15 | ATG16L1 | 206 (C) |
| 16 | ATP8B1 | 69665 (C) |
| 17 | ATP7A | 565 (C) |
| 18 | ATP7B | 905 (C) |
| 19 | ABCA4 | 279 (C) |
| 20 | ABCB4 | 69665 (C) |
| 21 | ABCC6 | 758 (C) |
| 22 | AIRE  | 3453 (C) |
| 23 | BEST1 | 98668 (C) |
| 24 | BLOC1S3 | 158032 (C) |
| 25 | BMPR2 | 422 (C) |
| 26 | BARD1 | 180250 (A) |
| 27 | BRI1P | 180250 (A) |
| 28 | BCR   | 521 (B) |
| 29 | BRCA1 | 180250 (A) |
| 30 | CDH1  | 63443 (A) |
| 31 | CREB3L1 | 3394 (A) |

Table 3. Continued

| n° | Genes | Rare diseases Orpha ID |
|----|-------|-----------------------|
| 32 | CREB3L2 | 3394 (A) |
| 33 | Cathepsin A—CTSA | 93448 (C) |
| 34 | CEBPA | 519 (A) |
| 35 | CD46 | 2134 (C) |
| 36 | CXCR4 | 51636 (C) |
| 37 | CHGB | 803 (C) |
| 38 | COL2A1 | 98668 (C) |
| 39 | COL9A1 | 98668 (C) |
| 40 | COL11A1 | 98668 (C) |
| 41 | COL11A2 | 98668 (C) |
| 42 | CR1 | 536 (C) |
| 43 | C3 | 2134 (C) |
| 44 | CFB | 2134 (C) |
| 45 | CFI | 2134 (C) |
| 46 | CBFB | 519 (A) |
| 47 | CDKN1B | 652 (B) |
| 48 | CDKN2A | 217074 (A) |
| 49 | CST3 | 85458 (C) |
| 50 | CTLA4 | 536 (C) |
| 51 | DAO | 803 (C) |
| 52 | DEK | 519 (A) |
| 53 | DTNB1P | 158032 (C) |
| 54 | ENG | 774 (B) |
| 55 | ETV6 | 519 (A) |
| 56 | ERCC1 | 191 (B) |
| 57 | ERCC2 | 191 (B) |
| 58 | ERCC5 | 191 (B) |
| 59 | ERCC6 | 191 (B) |
| 60 | ERCC8 | 191 (B) |
| 61 | EXT1 | 223727 (A) |
| 62 | ECM1 | 530 (C) |
| 63 | FCGR3B | 855 (C) |
| n'  | Genes  | Rare diseases Orpha ID |
|-----|--------|------------------------|
| 64  | FLVCR2 | 2211 (C)               |
| 65  | FBLN5  | 279 (C)                |
| 66  | FIG 4  | 803 (C)                |
| 67  | FLT3   | 519 (A)                |
| 68  | FOXC2  | 79383 (B)              |
| 69  | FOXO1  | 3394 (A)               |
| 70  | FZD4   | 98668 (C)              |
| 71  | FUCA1  | 93448 (C)              |
| 72  | GALNS  | 93448 (C)              |
| 73  | GLA    | 324 (B)                |
| 74  | GLB1   | 93448 (C)              |
| 75  | GLMN   | 83454 (A)              |
| 76  | GNS    | 93448 (C)              |
| 77  | GUSB   | 93448 (C)              |
| 78  | HMCN1  | 279 (C)                |
| 79  | HGSNAT | 93448 (C)              |
| 80  | HPS1   | 158032 (C)             |
| 81  | HPS3   | 158032 (C)             |
| 82  | HPS4   | 158032 (C)             |
| 83  | HPS5   | 158032 (C)             |
| 84  | HPS6   | 158032 (C)             |
| 85  | HTRA1  | 279 (C)                |
| 86  | HYAL1  | 93448 (C)              |
| 87  | IDS    | 93448 (C)              |
| 88  | IDUA   | 93448 (C)              |
| 89  | IGHG1  | 29073 (A)              |
| 90  | ING1   | 67037 (A)              |
| 91  | ING3   | 67037 (A)              |
| 92  | INSM1  | 877 (A)                |
| 93  | IRF4   | 29073 (A)              |
| 94  | IL10   | 206 (C)                |
| 95  | IL23R  | 206 (C)                |
| 96  | LRP5   | 98668 (C)              |
| 97  | LYST   | 158032 (C)             |
| 98  | HLA-A  | 179 (C)                |
| 99  | HLA-DRB1 | 797 (C)               |
| 100 | MAN2B1 | 93448 (C)              |
| 101 | MANBA  | 93448 (C)              |
| 102 | MECOM  | 52688 (A)              |
| 103 | MKL1   | 519 (A)                |
| 104 | MANF   | 217074 (A)             |
| 105 | MUTYH  | 63443 (A)              |
| 106 | MLL    | 519 (A)                |
| 107 | MYH11  | 519 (A)                |
| 108 | MYST3  | 519 (A)                |
| 109 | GNPTAB | 93448 (C)              |
| 110 | GNPTG  | 93448 (C)              |
| 111 | NAGLU  | 93448 (C)              |
| 112 | NF1    | 636 (B)                |
| 113 | NEFH   | 803 (C)                |
| 114 | NME1   | 3395 (A)               |
| 115 | SGSH   | 93448 (C)              |
| 116 | NR1H3  | 803 (C)                |
| 117 | NR2E3  | 98668 (C)              |
| 118 | NPM1   | 519 (A)                |
| 119 | NUP214 | 519 (A)                |
| 120 | NUP98  | 519 (A)                |
| 121 | NOD2   | 206 (C)                |
| 122 | OPTN   | 803 (C)                |
| 123 | PAX3   | 3394 (A)               |
| 124 | PAX7   | 3394 (A)               |
| 125 | PHOX2B | 3395 (A)               |
| 126 | PON1   | 803 (C)                |
| 127 | PON2   | 803 (C)                |
On the other hand, the systematic review of the collected data allowed us to detect a number of incoherencies in the Orphanet classification of rare diseases. Some of them are highlighted here:

- **Cerebral cavernous malformations** (ORPHA164) are rare brain vascular malformations that are also named as brain cavernous angioma. The term “angioma” showed concurrence with

| n° | Genes   | Orpha ID |
|----|---------|----------|
| 128 | PON3    | 803 (C)  |
| 129 | PTCH2   | 3395 (A) |
| 130 | PRF1    | 158032 (C)|
| 131 | PRPH    | 803 (C)  |
| 132 | PLCE1   | 99977 (A) |
| 133 | PDGFRα  | 44890    |
| 134 | PORCN   | 2092 (C) |
| 135 | KCNJ13  | 98668 (C)|
| 136 | PRLR    | 180250 (A)|
| 137 | PML     | 519 (A)  |
| 138 | PSAP    | 355 (C)  |
| 139 | RAB27A  | 158032 (C)|
| 140 | RAD51   | 180250 (A)|
| 141 | RAD51C  | 180250 (A)|
| 142 | RB1     | 668 (A)  |
| 143 | RARA    | 519 (A)  |
| 144 | RS1     | 98668 (C)|
| 145 | RMST    | 3394 (A) |
| 146 | RPS1A   | 52688 (A) |
| 147 | RNF135  | 636 (B)  |
| 148 | RBM15   | 519 (A)  |
| 149 | RUNX1   | 521 (B)  |
| 150 | RUNX1T1 | 519 (A)  |
| 151 | SETX    | 803 (C)  |
| 152 | STK11   | 2869 (B) |
| 153 | SET     | 519 (A)  |
| 154 | NEU1    | 93448 (C)|
| 155 | SMAD9   | 422 (C)  |
| 156 | SLC17A5 | 93448 (C)|
| 157 | SLC22A4 | 206 (C)  |
| 158 | SLC44A4 | 93448 (C)|
| 159 | SOX18   | 79383 (B)|

(A), (B), (C) correspond to subset A, B and C respectively.

On the other hand, the systematic review of the collected data allowed us to detect a number of incoherencies in the Orphanet classification of rare diseases. Some of them are highlighted here:

- **Cerebral cavernous malformations** (ORPHA164) are rare brain vascular malformations that are also named as brain cavernous angioma. The term “angioma” showed concurrence with
this and other search terms included in the three subsets, in spite of the fact that an angioma is not a tumor [24]. Our analysis led to include cerebral cavernous malformations (ORPHA164) within subset A, although the Orphanet classification for this disease remained undefined (“This disease will be assigned to a classification in the near future”). Furthermore, the clinical description of this disease in Orphanet was unclear enough as to make possible its inclusion in any of the other subsets (either B or C). On the other hand, ICD-10 codes this disease as Q28.3 (“Congenital malformations, deformations and chromosomal abnormalities”), as it is also the case for other angiomas (glomuvenous malformation (ORPHA83454), among others).

- **POEMS syndrome** (ORPHA2905) is a rare paraneoplasia that only presented concurrency with search terms in some of their classifications. However, it is a multisystemic disease in most of the cases associated to osteosclerotic myeloma. This is the main reason why it was finally included into subset A, although there were also reasons to include it into subset B. ICD-10 codes it within R16 (“Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified”).

- **Chronic myeloid leukemia** (ORPHA521) appears included in subset B (Table 2) because at the moment in which this systematic review and analysis was carried out Orphanet offered four general categories of classification (namely, classification of hematopoietic and lymphoid tumors, classification of disease with platelet number and function anomalies, Orphanet classification of rare hematological diseases and Orphanet classification of rare tumors) for this disease, one of which (namely, classification of disease with platelet number and function anomalies) had no concurrence with search terms. However, updates arranged in Orphanet after our systematic review and analysis offer only two general classification for this disease (namely, Orphanet classification of rare hematological diseases and Orphanet classification of rare tumors), which would be consistent with the inclusion of this disease within subset A. In fact, ICD-10 codes this disease as C92.1 (“Neoplasms”).

These previously commented cases and others reveal the importance of establishing correct and unambiguous denominations to these diseases in databases such as Orphanet. A systematic, unambiguous classification and the actual way in which the information is documented and transmitted can help physicians during health assistance. We have also detected that ICD-10 have no code assigned for 46% (83 out of 180) of the A-RDs listed (see Tables S2–S4 in Supplementary material). The announced release of ICD-11 (which will
include a systematic classification based on worldwide accepted clinical criteria) should standardize the classification of rare diseases. This undoubtedly will make it easier the documentation procedure and the curation of the collected information concerning this kind of vaguely described disorders.

It should be mentioned that several classifications of rare diseases available in Orphanet at the moment of carrying out this systematic review were deleted from Orphanet website in more recent actualizations of the site. This was the case of Orphanet classification of red cell diseases, classification of hematopoietic and lymphoid tumors and classification of disease with platelet number and function anomalies. The recent emergence of a new category in the Orphanet classification: Inherited cancer-predisposing syndrome (ORPHA140162) should also be mentioned.

As mentioned, from the 180 selected A-RDs, these 27 highlighted with an asterisk in Table 2 can be considered as angiogenic rare diseases. Three of them have same genetic and molecular profiles closely related to angiogenesis: Angio-osteohypertrophic syndrome (ORPHA2346), Neurofibromatosis type I (ORPHA636) and Rendu-Osler-Weber disease (ORPHA774). Orphanet also includes information about this. The other angiogenic rare diseases are pathologies whose genetic and molecular profiles are related to certain aspects of angiogenesis such as VEGF expression, anti-angiogenic therapies or related with vascular proliferation process, among others. In many of these cases further investigation is required. A problem arises with Orphanet updates and corrects its database. For instance, up to four angiogenic rare diseases were outdated in the course of our systematic review. Glioma, now called Glial tumor (ORPHA182067), does not remain associated with the gene called PTEN, which in its original link (MIN ID605 691) is identified as a tumor suppressor. Oligodendrogial tumor (ORPHA6484) is linked in UniProt (ID60484) too and it is just a subcategory of glial tumor. In addition, two genes are listed among the diseases included under this term, search for in the Classifications menu), we think that many other diseases could be retrieved.

Another problem for systematic studies is also the way in which Orphanet updates and corrects its database. For instance, up to four angiogenic rare diseases were outdated in the course of our systematic review. Glioma, now called Glial tumor (ORPHA182067), does not remain associated with the gene called PTEN, which in its original link (MIN ID605 691) is identified as a tumor suppressor. Oligodendrogial tumor (ORPHA6484) is linked in UniProt (ID60484) too and it is just a subcategory of glial tumor. In addition, two genes are listed among the diseases included under this term.
Table 4 Genes associated to two or more angiogenesis-related rare diseases

| n° | Genes | Orpha ID | Rare diseases | Orpha ID | Rare diseases | Orpha ID | Rare diseases | Orpha ID | Rare diseases | Orpha ID | Rare diseases | Orpha ID |
|----|-------|----------|---------------|----------|---------------|----------|---------------|----------|---------------|----------|---------------|----------|
| 1  | PTEN  | 3395 (A) | 180250 (A) | 182067 (A) | 67037 (A) | 201 (B) | 109 (B) | 65285 (A) | 2890 |
| 2  | FUS   | 3394 (A) | 519 (A) | 803 (C) | 69078 (A) | 99967 (A) | 2890 |
| 3  | SDHD  | 180250 (A) | 717 (A) | 29072 (A) | 201 (B) | 877 (A) | 2890 |
| 4  | TP53  | 3395 (A) | 182067 (A) | 360 (A) | 217074 (A) | 524 (A) | 2890 |
| 5  | CHEK2 | 180250 (A) | 223727 (A) | 524 (A) | 668 (A) | 2890 |
| 6  | EWSR1 | 3394 (A) | 223727 (A) | 319 (A) | 97338 (A) | 2890 |
| 7  | GBA   | 355 (C) | 77260 (C) | 77261 (C) | 85212 (C) | 2890 |
| 8  | NDP   | 98668 (C) | 190 (C) | 649 (C) | 90050 (C) | 2890 |
| 9  | SDHB  | 180250 (A) | 717 (A) | 29072 (A) | 201 (B) | 2890 |
| 10 | TFE3  | 3394 (A) | 217071 (A) | 151 (A) | 163699 (A) | 2890 |
| 11 | VHL   | 217071 (A) | 151 (A) | 717 (A) | 892 (B) | 2890 |
| 12 | CFH   | 279 (C) | 2134 (C) | 54370 (C) | 2890 |
| 13 | DMBT1 | 3395 (A) | 182067 (A) | 360 (A) | 2890 |
| 14 | EGFR  | 3395 (A) | 182067 (A) | 360 (A) | 2890 |
| 15 | FH    | 217071 (A) | 151 (A) | 523 (A) | 2890 |
| 16 | GLTSCR1 | 3395 (A) | 182067 (A) | 360 (A) | 2890 |
| 17 | GLTSCR2 | 3395 (A) | 182067 (A) | 360 (A) | 2890 |
| 18 | GLI1  | 3395 (A) | 182067 (A) | 360 (A) | 2890 |
| 19 | LRRN2 | 3395 (A) | 182067 (A) | 360 (A) | 2890 |
| 20 | YEATS4 | 3395 (A) | 182067 (A) | 360 (A) | 2890 |
| 21 | OGG1  | 217071 (A) | 151 (A) | 2890 |
| 22 | ACVRL1 | 422 (C) | 774 (B) | 2890 |
| 23 | APC   | 3395 (A) | 733 (A) | 2890 |
| 24 | ASPSCR1 | 3394 (A) | 163699 (A) | 2890 |
| 25 | AGGF1 | 2346 (C) | 90308 (B) | 2890 |
| 26 | BRCA2 | 180250 (A) | 217074 (A) | 2890 |
| 27 | CTNNB1 | 3395 (A) | 88673 (A) | 2890 |
| 28 | COL1A1 | 3394 (A) | 31112 (A) | 2890 |
| 29 | COL18A1 | 98668 (C) | 1571 (C) | 2890 |
| 30 | DIRC1 | 217071 (A) | 151 (A) | 2890 |
| 31 | DIRC2 | 217071 (A) | 151 (A) | 2890 |
for Brain tumor: PTEN and CTNB1. On the other hand, two genes (PML and RBM15) were listed for Acute myeloid leukemia (ORPHA519). Currently, the symbol RBM15 (RNA binding motif protein 15) does not appear in Orphanet database. In Uniprot (ID Q96T37), Acute megacaryoblastic leukemia (ORPHA518) is listed as an Orphan disease.

### Genes and drugs associated to angiogenesis-related rare diseases

Figure 4 shows frequency distributions of A-RDs taking into account the number of genes or the number of drugs to which they are related (information abstracted from Tables 2-4 and S5-S10). As Figure 4

| \( n^\circ \) | Genes | Rare diseases Orpha ID |
|---|---|---|
| 32 | ETV4 | 223727 (A) | 319 (A) |
| 33 | ETV1 | 223727 (A) | 319 (A) |
| 34 | FLT4 | 79383 (B) | 77240 (B) |
| 35 | FLCN | 217071 (A) | 151 (A) |
| 36 | FHIT | 217071 (A) | 151 (A) |
| 37 | FLJ1 | 223727 (A) | 319 (A) |
| 38 | GJC2 | 79383 (B) | 77240 (B) |
| 39 | HSPBAP1 | 217071 (A) | 151 (A) |
| 40 | JAK2 | 824 (B) | 729 (B) |
| 41 | MET | 217071 (A) | 88673 (A) |
| 42 | MEN1 | 652 (B) | 913 (B) |
| 43 | NOTCH3 | 136 (C) | 95509 (C) |
| 44 | PRCC | 217071 (A) | 151 (A) |
| 45 | PALB2 | 180250 (A) | 217074 (A) |
| 46 | PDGFB | 3394 (A) | 31112 (A) |
| 47 | RASA1 | 2346 (C) | 137667 (A) |
| 48 | RET | 717 (A) | 1332 (A) |
| 49 | RNF139 | 217071 (A) | 151 (A) |
| 50 | SMAD4 | 217074 (A) | 774 (B) |
| 51 | SDHAF2 | 717 (A) | 29072 (A) |
| 52 | SDHA | 717 (A) | 29072 (A) |
| 53 | SDHC | 717 (A) | 29072 (A) |
| 54 | SMARCA4 | 3394 (A) | 69077 (A) |
| 55 | SMARCB1 | 3394 (A) | 69077 (A) |
| 56 | TMEM127 | 717 (A) | 29072 (A) |
| 57 | ERG | 223727 (A) | 319 (A) |
| 58 | KIT | 44890 (A) | 98292 (A) |

(A), (B), (C) correspond to subset A, B and C respectively.
shows, approximately half of A-RDs are linked to no gene and no drug. The highest percentage of A-RDs linked to two or more genes or drugs corresponds to subset A. This reflects the actual current state of knowledge in this research area, which—as expected—is much higher in neoplastic A-RDs (those included in subset A).

Lysosomal storage disease with skeletal involvement (ORPHA93448) is the A-RD linked to the highest number of genes (22), but at the same time is linked to no drug. On the other hand, both Acute myeloid leukemia (ORPHA519) and Glioblastoma (ORPHA360) are the two A-RDs with the highest number of linked drugs (33 in each case), being the third and the 12th respectively according to their linked genes (see Table 2 and Table S6).

As Figure 2 shows, most of the genes are linked to only one A-RD. The majority of those genes linked to two or more A-RDs in fact are related with A-RDs of the subset A. A similar situation is found in the case of drugs (Fig. 3).

Phosphatase and tensin homolog (mutated in multiple advanced cancers 1)—PTEN is one of the genes with more links to A-RDs (Table 4).

It is noteworthy that Orphanet updated versions used when this systematic review and analysis was carried out identified the entrance Antisense Oligonucleotide (TATCCGGAGGCTCGCATGTC) as both a gene (which is obviously false) and as a drug (see Table 3 and Table S9). In both cases, this entrance was linked to an only A-RD: to Neovascular glaucoma (ORPHA94058) in Table 3 and to Retinopathy of prematurity (ORPHA90050) in Table S9. We have maintained both entrances according to the results yielded by our systematic methodology. This highlights that this systematic approach allows for a more correct curation of the collected data. In more recent updates of Orphanet some of the detected error have been corrected.

Concluding remarks

1 The obvious great current interest in angiogenesis and in rare diseases demanded a systematic review of the current state of knowledge in the Boolean intersection of these two research areas, namely, the still not well defined set of angiogenesis-related rare diseases. The present review report contributes to satisfy such a demand.

2 Current technology allows researchers to have access to great databases containing overwhelming amounts of data. Furthermore, there are a number of biocomputational tools that makes it easier the access, extraction and analysis of biological data contained in databases and they can enhance the molecular knowledge emerged from the systematic review results. We claim that the critical use of such tools makes possible and affordable to carry out systematic reviews of the current state of knowledge of specific research areas. These systematic reviews are aimed to add value to the classical bibliographical reviews thanks to their potential to extract new emergent information. The present systematic review on angiogenesis-related rare diseases can be considered an initial contribution in this way.

3 Herein we propose a simple classification of angiogenesis-related rare diseases trying to discriminate the tight relationships of those linked to cancer.

4 We have detected that both the Orphanet classification of rare diseases and the WHO International Classification of Diseases ICD-10 urgently require deep revisions and updates.

5 Much more research is urgently needed for the identification of genes and drugs related to many angiogenesis-related rare diseases and for the exploration of new diagnostic, prognostic and therapeutic procedures.

6 Orphanet database is a useful resource for all scientists and physicians engaged with rare diseases, as well as for patients’ associations. However, form a scientific point of view, Orphanet still lacks of an actual semantic classification of rare disease. Furthermore, a deep upgrade of the scientific information contained in Orphanet is urgently required.

7 This systematic review of available literature on angiogenesis rare diseases has ordered and connected the currently available but up to now dispersed wealth of information on the topic, as reflected by the full set of accompanying figures and tables. This information will be useful for those interested in knowing the full set of described angiogenesis-related rare diseases, and what genes and drug treatments a specific angiogenesis-related rare disease shares with other ones. In particular, this information can be a very useful start point for new, deep reviews focused on concrete angiogenic rare diseases.

8 Taking the ordered information contained in the accompanying figures and tables of the present work as a starting point, functional enrichment and network analysis tools could be used in the near future to make predictions of new gene targets, drugs and/or treatments for some rare diseases based in their shared spectra with the full set of angiogenesis-related rare diseases herein reviewed.

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Competing interests

The authors declare that they have no competing interests.

Authors’ contributions

All the five authors were personally involved bibliographic research and discussion of collected data as well as in the design of the manuscript contents. L.R.C. carried out the primary bibliographic
search. A.R.P. was involved in the text-mining analysis with SciMiner. A.R.Q. and F.S.J. critically reviewed the first draft of the manuscript and contributed to its definitive version. M.A.M. supervised the whole procedures and wrote the manuscript.

Supporting information

Additional Supporting Information may be found in the online version of this article:

Figure S1. PRISMA flow diagram of the bibliographic systematic review.
Table S1. PRISMA checklist
Table S2. Analysis of the angiogenesis-related rare disease in subset A according to International Classification of Diseases
Table S3. Analysis of the angiogenesis-related rare disease in subset B according to International Classification of Diseases
Table S4. Analysis of the angiogenesis-related rare disease in subset C according to International Classification of Diseases
Table S5. Angiogenesis-related rare diseases associated to a single gene
Table S6. Angiogenesis-related rare diseases associated to two or more genes
Table S7. Angiogenesis-related rare diseases associated to a single drug
Table S8. Angiogenesis-related rare diseases associated to two or more drugs
Table S9. Drugs associated to a single angiogenesis-related rare disease
Table S10. Drugs associated to two or more angiogenesis-related rare diseases

Data S1. Selected bibliographic references related to the 187 angiogenesis-related rare diseases covered by this work.

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