Seven years since the launch of the Matchmaker Exchange: the evolution of genomic matchmaking

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Abstract

The Matchmaker Exchange (MME) launched in 2015 to provide a robust mechanism to discover novel disease-gene relationships. This federated network connects databases holding relevant data, where two or more users are looking for a match for the same gene (two-sided matchmaking). The number of unique genes present across MME has steadily increased; there are currently >13,520 unique genes (˜68% of all protein coding genes) connected across MME's nodes, GeneMatcher, DECIPHER, PhenomeCentral, MyGene2, seqr, Initiative on Rare and Undiagnosed Disease, PatientMatcher, and the RD-Connect Genome-Phenome Analysis Platform. The dataset accessible across MME includes more than 120,000 cases from over 12,000 contributors in 98 countries. Discovery of potential new disease-gene relationships occurs daily and international collaborations are moving these connections forward to publication. Expansion of data sharing into routine clinical practice has ensured access to discovery for even more individuals with undiagnosed rare genetic disease. MME supports connections to the literature (PubCaseFinder) and to human and model organism resources (Monarch Initiative) and scientists (ModelMatcher). Efforts are underway to explore additional approaches to matchmaking where there is only one querier (one-sided matchmaking). Genomic matchmaking has proven its utility over the past 7 years and will continue to facilitate discoveries in years to come.

Introduction

To understand the disease relationships for all genes and variants in the Mendelian genome is nothing short of a grand challenge that represents, and will continue to represent, decades of scientific discovery. The Online Mendelian Inheritance in Man (OMIM) catalog lists 4,224 genes implicated in single gene disorders and traits (omim.org, accessed 3/4/22), yet estimates suggest more than 10,000 genes are likely to be found causal for monogenic disease *(Bamshad et al., 2019)* and typical diagnostic rates for individuals with suspected genetic disease are only around 25% *(100,000 Genomes Project Pilot Investigators et al., 2021)* . Much more variant-gene-disease discovery remains to be accomplished. As we continue to study increasingly rare Mendelian diseases, the need for responsible data sharing becomes even greater. A key driver of gene-disease discovery for rare disease is the ability to connect two or more parties looking for rare disease cases with the same candidate gene and an overlapping phenotype to expedite the gene-discovery process. This approach has been referred to as two-sided genome matchmaking and is the predominant use case for the Matchmaker Exchange (MME) (**Figure 1**)*(Philippakis et al., 2015)* .

The MME consortium was formed in 2013 as a collaborative effort to launch a federated platform to enable two-sided genomic matchmaking through a standardized application programming interface (API) and procedural conventions. While the practice of matchmaking was already occurring within individual databases before the launch of MME, the data was siloed within each node. The MME network set out to con-

nect databases into a federated network, something that had never been done before. The federated MME network launched in 2015 and the work to launch MME was described in detail by Philippakis and colleagues *(Philippakis et al., 2015)* , including formation of a steering committee and developing MME policies and approaches to queries and notifications. The federated MME network API enables exchange of information between the matchmakers through a set of required elements (https://github.com/ga4gh/mme-apis). This API is described *(Buske, Schiettecatte, et al., 2015)* , and was developed in collaboration with members of the Global Alliance for Genomics and Health (GA4GH) *(Rehm et al., 2021)* and the International Rare Diseases Research Consortium (IRDiRC) *(Boycott et al., 2017)* to ensure interoperability with other genomic services. This early work was described in a special issue of Human Mutation in 2015, The Matchmaker Exchange, which also included papers describing individual matchmaking services *(Buske, Girdea, et al., 2015; Chatzimichali et al., 2015; Gonzalez et al., 2015; Kirkpatrick et al., 2015; Lancaster et al., 2015; Mungall et al., 2015; Sobreira et al., 2015)* , case reports from clinicians, laboratories and researchers describing novel gene discoveries facilitated by genomic matchmaking *(Au et al., 2015; Jurgens et al., 2015; Loucks et al., 2015)* as well as other relevant topics *(Akle et al., 2015; Brownstein et al., 2015; Krawitz et al., 2015; Lambertson et al., 2015)* . Seven years later, we now report on the progress of the MME and advances in the field of genomic matchmaking in this special issue.

Expansion and Impact of the Matchmaker Exchange

When the MME federated network was launched in 2015, it connected three matchmaking services (nodes) *(Philippakis et al., 2015)* : DECIPHER (DatabasE of genomiC varIation and Phenotype in Humans using Ensembl Resources) (PRODUCTION: REFERENCE APPEARS IN THE SAME SPECIAL ISSUE *(Foreman et al., 2022)*), GeneMatcher (PRODUCTION: REFERENCE APPEARS IN THE SAME SPECIAL ISSUE *(Hamosh et al., 2022)*) and PhenomeCentral (PRODUCTION: REFERENCE APPEARS IN THE SAME SPECIAL ISSUE *(Osmond, Hartley, Johnstone, et al., 2022*). Since that time, the network (**Figure 2**) has grown to include five additional genomic matchmaking nodes: MyGene2 *(Chong et al., 2016)* , *seqr* (PRODUCTION: REFERENCE APPEARS IN THE SAME SPECIAL ISSUE *(Pais et al., 2022)*), Initiative on Rare and Undiagnosed Disease (IRUD) *(Adachi et al., 2017)* , PatientMatcher (PRODUCTION: REFERENCE APPEARS IN THE SAME SPECIAL ISSUE *(Rasi et al., 2022)*), and the RD-Connect Genome-Phenome Analysis Platform (GPAP) (PRODUCTION: REFERENCES APPEARS IN THE SAME SPECIAL ISSUE *(Laurie et al., 2022)*) (**Table 1**). The "Matchmaker Exchange Participants" page on the MME website (www.matchmakerexchange.org/participants.html) provides users a set of tables comparing the types of data stored by each connected MME node, descriptions of matching and scoring output, MME connections, types of users, and summaries of matching and notification protocols. Most of the nodes provide matching services only to users who are storing their genomic data in the database and can flag candidate genes, along with additional information such as phenotype and inheritance pattern, for submission to MME. However, for many interested parties, they are lacking the means and opportunity to contribute this type of comprehensive data so use GeneMatcher *(Sobreira et al., 2015)* which has the lowest barrier to entry into the MME. As a result, GeneMatcher is the most widely used node of the MME with 11,780 submitters (PRODUCTION: REFERENCES APPEARS IN THE SAME SPECIAL ISSUE *(Hamosh et al., 2022)*).

The collective dataset accessible across the MME currently includes more than 120,000 cases from over 12,000 contributors in 98 countries. Though it is difficult to track precisely, genomic matchmaking as an approach using one or more nodes of the MME has led to well over 500 publications. The MME provides an accessible approach to matchmaking for individual research labs as well as large-scale research programs. In 2019, Bruel and colleagues *(Bruel et al., 2019)* reported the outcomes of 2.5 years' experience using GeneMatcher to share 71 novel candidate genes identified by exome sequencing (ES) and found that the subsequent follow-up of matches supported 39% of genes as causal. Care4Rare Canada has used the MME since its inception and attributes the discovery and publication of 26 novel disease-relationships to connections made via the MME over the last 7 years (unpublished data). Similarly, the Centers for Mendelian Genomics and the Undiagnosed Disease Network both use MME as a critical platform facilitating novel disease-gene discovery *(Baxter et al., 2022; Macnamara et al., 2020)* .

While MME was primarily developed as a platform to service the research community in discovering novel causes of rare disease, it is increasingly being used directly by clinical laboratories that identify candidates through routine clinical genomic sequencing. For example, a*de novo* variant occurring in a highly constrained gene not yet implicated in disease and identified in a trio sent for clinical genomic sequencing would be highly suspicious for novel disease-gene discovery. Entering this gene into MME, along with the phenotype, can often yield matches. This can connect clinical laboratories to investigators capable of statistical and functional analysis, and ultimately facilitate a diagnosis for a patient. Proof of this can be found in three papers in this special issue report on robust clinical laboratory experiences using MME, including those from Ambry Genetics (PRODUCTION: REFERENCE APPEARS IN THE SAME SPECIAL ISSUE *(Towne et al., 2022)*), GeneDx (PRODUCTION: REFERENCE APPEARS IN THE SAME SPECIAL ISSUE *(McWalter et al., 2022)*) and Illumina (PRODUCTION: REFERENCE APPEARS IN THE SAME SPECIAL ISSUE *(Taylor et al., 2022)*). All three laboratories use GeneMatcher for their matchmaking services; GeneDx submitted entries spanning 3,507 genes, 908 (26%) of which have been validated as causal through evidence built from matchmaking; Ambry Genetics submitted cases spanning 243 unique genes with 111 (45%) now clinically characterized; Illumina has submitted 69 unique genes with 21 (30%) leading to publications or active collaborations with publication planned. Given that some of these genes will be overlapping, it still indicates that, at a minimum, over 900 novel disease genes were identified and validated through MME through just three clinical laboratories using the platform. This number represents more than 20% of the 4,224 genes underlying monogenic disorders and traits cataloged in OMIM (omim.org, accessed 3/4/22). The contributions of clinical laboratories to matchmaking cannot be understated; the 3,507 genes submitted by GeneDx comprised 25% of the 13,941 unique genes in GeneMatcher on 9/28/21 (PRODUCTION: REFERENCE APPEARS IN THE SAME SPECIAL ISSUE *(McWalter et al., 2022)*).

Seven years from its launch, it is clear that the MME is making outstanding contributions to understanding the morbid anatomy of the genome. The number of unique genes present across the MME has steadily increased over time; there are currently >14,355 genes connected across the MME's eight genomic matchmaking nodes. The discovery of potential new disease-gene relationships is happening daily and tens of thousands of patients and their family members have been directly or indirectly impacted by the discoveries facilitated by two-sided genomic matchmaking.

MME supports connections to knowledge and model organism resources

MME connects to three databases that provide additional utility to the gene discovery scientific community and these databases are considered "Connected Knowledge Sources," or "Functional Study Node", specialized MME endpoints that go beyond the initial MME design of patient-patient matchmaking (**Figure 2**). PubCaseFinder helps users identify any existing case reports for candidate genes by using phenotype-based comparisons (PRODUCTION: REFERENCE APPEARS IN THE SAME SPECIAL ISSUE *(Fujiwara et al., 2022, 2018)*). To facilitate important downstream translational research using in vitro and in vivo models *(Boycott et al., 2020; Wangler et al., 2017)* , MME connects to two additional databases; Monarch Initiative and ModelMatcher. The Monarch Initiative *(Shefchek et al., 2019)* , supports patient-disease model matches *(Mungall et al., 2015)* , by effectively matching patient phenotype profiles with a potentially existing relevant disease model. ModelMatcher (PRODUCTION: REFERENCE APPEARS IN THE SAME SPECIAL ISSUE *(Harnish et al., 2022)*) facilitates cross-disciplinary collaborations as part of a global effort to decrease the time to translational and therapeutic research by connecting scientists and other stakeholders who have interest in the same or orthologous gene *(Neff, 2021)* .

Opportunities and Challenges for the Matchmaker Exchange

With greater than 14,000 unique genes connected across the MME, most matchmaking submissions result in at least one match (**Figure 3**) and each of these matches requires review that will need additional information to inform the matching parties as to whether or not the match represents a valid novel disease-gene relationship discovery. A matchmaking outcome analysis of 194 genes submitted to MME by the Care4Rare Canada Consortium over a 2-year period highlighted the effectiveness of MME in establishing collaborations for novel candidate genes with a 15% success rate *(Osmond, Hartley, Dyment, et al., 2022)*

. The 194 genes entered by Care4Rare Canada resulted in over 1,500 matches returned by MME, with 93% receiving at least one match. Each of these needed to be evaluated, consolidated, and, in the majority of cases, have emails sent to determine the potential significance of the match; this is a laborious process that requires dedicated time and resources. Likewise, *seqr* users have supported manual communication on >6,500 matches (PRODUCTION: REFERENCE APPEARS IN THE SAME SPECIAL ISSUE *(Pais et al., 2022)* . One of the largest contributing factors to the post-match workload is the lack of phenotypic and inheritance information associated with the majority of cases in GeneMatcher, the largest node of the MME *(Osmond, Hartley, Dyment, et al., 2022)* . To date, only 2.5% of the over 63,000 submissions to GeneMatcher have included phenotype. However, the majority of records in all other primary MME nodes do include this information. The discovery community needs to carefully weigh the pros and cons of a low barrier to entry into MME with the post-match workload.

Moving forward, the MME has the opportunity to improve the efficiency of the matchmaking (**Table 2**). Inclusion of additional information (phenotype, variant details, zygosity) along with the gene will facilitate the ruling out of matches without the email back-and-forth that is difficult to scale. Osmond and colleagues (2022) showed that ˜50% of matches could be ruled out when this type of data was provided by the node at the time of match notification. It is important for users to note that inclusion of high level phenotypic data typically does not require additional consent *(Dyke et al., 2017)* . In addition, the submission of only high quality candidate genes, continuous updating of a group's submissions, removal of cases with ruled out/low priority candidate genes and removal or detailed annotation of solved cases (**Table 2**) will all promote efficient matchmaking using MME.

Several of the MME nodes have implemented additional features to help users track the large number of matches that currently require follow-up, such as those described for *seqr* (PRODUCTION: REFERENCE APPEARS IN THE SAME SPECIAL ISSUE *(Pais et al., 2022)*), PhenomeCentral (PRODUCTION: REFERENCE APPEARS IN THE SAME SPECIAL ISSUE*(Osmond, Hartley, Johnstone, et al., 2022)*), and GeneMatcher (PRODUCTION: REFERENCE APPEARS IN THE SAME SPECIAL ISSUE (Hamosh et al., 2022)) including auto-drafting emails as well as tracking match details, communications and the outcomes of matches within the database. An expanded use case for the MME is the secondary accumulation of additional cases after the initial publication of a novel disease gene relationship. Going forward, opportunities to support connections between investigators made across the MME beyond email notification will be considered, such as the equivalent of a gene 'break-out' room, to help these teams organize with less back-and-forth correspondence.

Evolution of Matchmaking

Matchmaking using MME is based on a two-sided framework where two interested parties are both looking for a match for the same gene*(Philippakis et al., 2015)* . As the past 7 years of experience has demonstrated, this approach has been very successful in advancing the discovery of novel disease-gene relationships. However, this approach only works when both interested parties have taken the time to flag a highly compelling novel candidate gene of interest. But what of all the datasets where extensive manual review has not occurred due to all sorts of factors? Discovery for these types of datasets needs to happen differently. One-sided matchmaking (**Figure 1**) can occur when one party is interested in a candidate gene and queries a database hosting genome-wide sequencing data from undiagnosed patients to identify variants in the candidate gene associated with additional information. Zero-sided matchmaking (**Figure 1**) is the term used to describe the state where there are no candidates identified but instead computational analysis across the cohort is used to identify genes with predicted damaging variants in common across phenotypes. For example, the genebass.org website allows users to query precomputed gene burden analyses across all genes for all phenotypes in the UK Biobank*(Karczewski et al., 2021)* . In another example, the Deciphering Developmental Disorders (DDD) study applies burden testing frameworks to identify genes with significant enrichments of damaging variants, such as genes with more *de novo* loss-of-function variants in the DDD cohort than expected (PMC: 7116826). Likewise, the new GREGoR consortium (gregorconsortium.org) is amassing rare disease data on the AnVIL platform *(Schatz et al., 2022)* from both the prior NIH Centers for Mendelian Genomics as well

as prospectively collected data to improve power for identifying gene-disease candidates. As more and more data are generated, this type of approach will be critical to ensure we can analyze unsolved datasets at scale.

Several data platforms are approaching one-sided matchmaking by providing information about the existence of a specific variant and its associated information (e.g., phenotype). These databases include MyGene2 *(NHGRI/NHLBI University of Washington-Center for Mendelian Genomics (UW-CMG), Seattle, WA)* , Geno2MP *(University of Washington Center for Mendelian Genomics)* , VariantMatcher *(Wohler et al., 2021)* , and Franklin *(Genoox)* . MyGene2 and Geno2MP are public databases, with sharing driven by families in the case of MyGene2 where anyone can access the displayed variant level data associated with phenotypic terms. VariantMatcher will accept variant-specific queries, search its database of variants, and respond if the variant is present and the associated phenotype if available with dual notification to the querier and data submitter *(Wohler et al., 2021)* . Franklin is an interpretation and connection platform that supports a community of users to facilitate variant interpretation. These four data platforms are working to facilitate a federated connection to one another using Data Connect, a standard for discovery and search from GA4GH (PRODUCTION: REFERENCE APPEARS IN THE SAME SPECIAL ISSUE*(Rodrigues et al., 2022)* .

At the gene level, several databases, such as DECIPHER (PRODUCTION: REFERENCE APPEARS IN THE SAME SPECIAL ISSUE *(Foreman et al., 2022)*), RD-Connect GPAP (PRODUCTION: REFERENCES APPEARS IN THE SAME SPECIAL ISSUE *(Laurie et al., 2022)*), Genomics4RD (PRODUCTION: REFERENCES APPEARS IN THE SAME SPECIAL ISSUE *(Driver et al., 2022)*), and *seqr* if used in collaboration with the Broad Center for Mendelian Genomics (PRODUCTION: REFERENCES APPEARS IN THE SAME SPECIAL ISSUE *(Pais et al., 2022)*) are now individually approaching this challenge using internal one-sided matchmaking where an internal user with a candidate gene identified in an undiagnosed patient can query the genomic data housed in the database to see all variants identified in this candidate gene at a certain frequency, or of a certain type, across the dataset along with associated phenotypic and often inheritance data. While these approaches are currently siloed and only available to internal users due to the level of data being shared, efforts are underway to make more of this data available. For example, Geno2MP *(University of Washington Center for Mendelian Genomics)*allows searches of the rare variants generated by the majority of the Centers for Mendelian Genomics which are linked to very high-level phenotypic information *(Baxter et al., 2022)* . Genomics4RD (PRODUCTION: REFERENCES APPEARS IN THE SAME SPECIAL ISSUE *(Driver et al., 2022)*) is piloting a one-sided matchmaking platform for external users using a registered access model to facilitate multi-level filtering for both genetic variation and phenotypic information and ensuring that compound heterozygous variants in a single participant are identifiable. Beacon is a genomic discovery protocol and data access API issued by the GA4GH. Its most recent version (v2) presented in this issue describes its new and enhanced features for complex queries and richer responses (PRODUCTION: REFERENCES APPEARS IN THE SAME SPECIAL ISSUE (Rambla et al. 2022). Beacon v2 is designed to sit on top of existing solutions, can be integrated into Beacon networks and provides a way forward for the next phase of genomic matchmaking and other data queries.

Concluding Remarks

Over the past seven years, the MME has made outstanding contributions to the discovery of novel disease-gene relationships and is relied on heavily by both the research and clinical rare disease communities. Moving forward, there are opportunities to improve the efficiency of the MME, particularly by encouraging all submissions to share phenotypic and inheritance information with submissions. Although most nodes in MME have from the outset included information about phenotype and inheritance alongside variant submissions, most entries in GeneMatcher, the most widely used node, have not, and therefore we call on the community to quickly move in this direction. Genomic matchmaking approaches continue to evolve and novel approaches to discovery are now underway to ensure that no dataset gets left behind. Connections to literature, model organism resources and scientists, as well as patient-driven matchmaking are all innovative approaches contributing to the ultimate goal of being able to provide diagnostic clarity, biological insight, and social support for the thousands of rare genetic diseases.

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CONFLICT OF INTERESTS

The authors declare that there are no conflicts of interests.

WEB RESOURCES

- DECIPHER -*https://decipher.sanger.ac.uk/*
- Franklin - https://franklin.genoox.com
- GeneMatcher -*https://www.genematcher.org/*
- Geno2MP - https://geno2mp.gs.washington.edu/Geno2MP
- Matchmaker Exchange - https://www.matchmakerexchange.org/
- ModelMatcher - https://www.modelmatcher.net/
- Monarch Initiative -*https://monarchinitiative.org/*
- MyGene2 -*https://www.mygene2.org/*
- PatientMatcher -*https://www.scilifelab.se/facilities/clinical-genomics-stockholm/*
- PhenomeCentral -*https://www.phenomecentral.org/*
- PubCaseFinder - https://pubcasefinder.dbcls.jp/
- RD-Connect GPAP -*https://platform.rd-connect.eu/*
- *seqr* -*https://seqr.broadinstitute.org/matchmaker/matchbox/*
- VariantMatcher - https://variantmatcher.org/

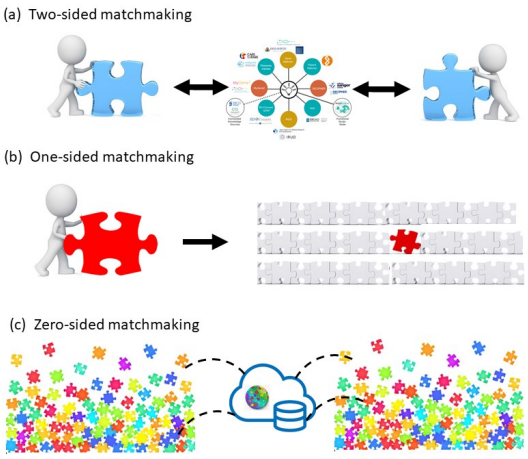

FIGURE 1 Three types of genomic matchmaking to enable novel disease-gene relationship discoveries. (a) Two-sided matchmaking refers to the scenario where two or more parties have the same novel candidate gene and are trying to find each other. This type of matchmaking is facilitated by the current MME. (b) One-sided matchmaking refers to the scenario where one party has a novel candidate variant or gene and queries a database housing structured genome-wide sequencing data from undiagnosed patients. (c) Zero-sided matchmaking refers to the scenario where computer algorithms are used to identify potentially matching undiagnosed cases with rare variants in the same gene and overlapping phenotypes.

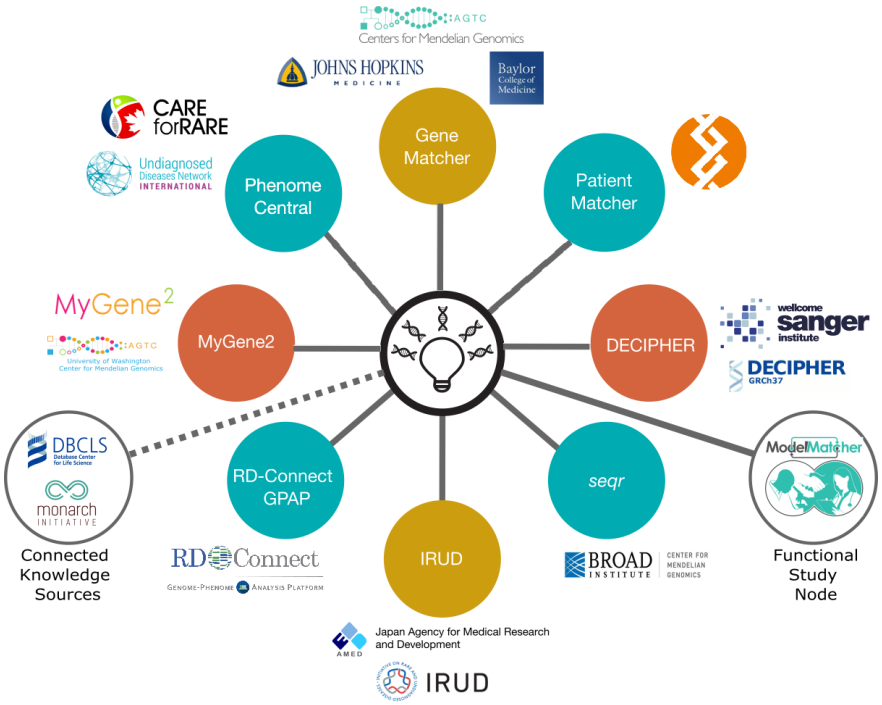

FIGURE 2 The MME currently connects eight genomic matchmaking nodes (solid lines) representing >14,355 unique genes and 120,000 cases from over 12,000 contributors in 98 countries. The MME also connects to three databases that provide additional utility to the gene discovery scientific community and these databases are considered "Connected Knowledge Sources," or "Model Organism Nodes", specialized MME endpoints that go beyond the initial MME design of patient-patient matchmaking. The MME is a driver project of the GA4GH and the MME has been leveraging the expertise of the GA4GH working groups for guidance on pertinent aspects of the project.

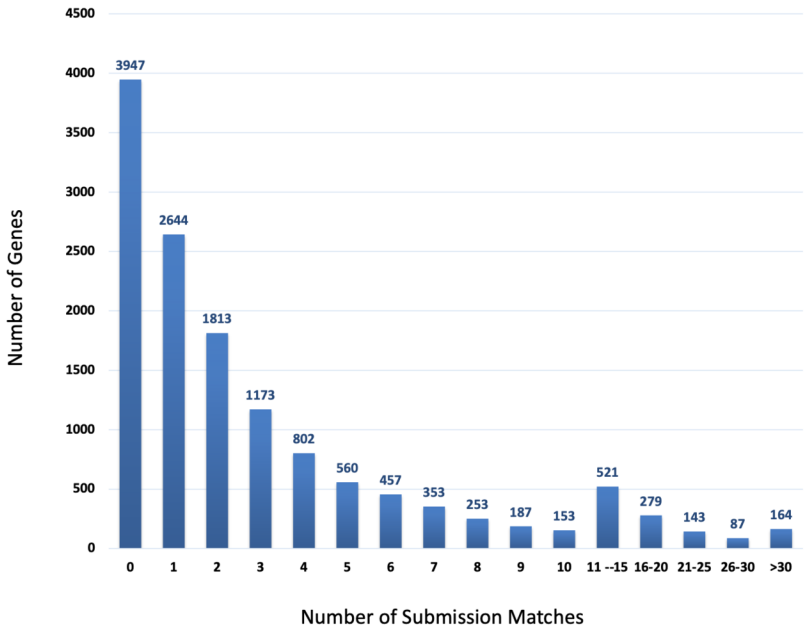

FIGURE 3 Matches per gene in GeneMatcher. Among the 14,355 unique genes submitted to GeneMatcher as of March 1st, 2022, 3,947 (27%) have no match. The number of matches for genes with >30 matches ranges from 31 to 142 matches; about 0.1% (15) of unique genes in GeneMatcher have more than 60 matches.

TABLE 1 Details of the connected MME Nodes

Name	**Location**	**Patients/Cases Total**	**In MME Patients/Cases**	**In MME Contributors/Submitters**	**In I Uni**
DECIPHER	United Kingdom	80,000	40,624	570	8,98
GeneMatcher	United States	62,718	62,492	11,031	13,5
IRUD	Japan	3,578	62	1	55
MyGene2	United States	4,492	1,600	304	1,31
PatientMatcher	Sweden	10,060	18	4	25
PhenomeCentral	Canada	12,775	8,974	444	3,02
RD-Connect GPAP	Europe	13,929	5,847	77	902
seqr	United States	7,929	1,193	84	1,24
Total	**Total**	195,481	120,810	12,515	>13

*The gene overlap across nodes has not been determined so the total genes is conservatively estimated using the largest single node.

TABLE 2 Opportunities to improve the efficiency of the MME

Add additional details to submissions and information going across the MME (e.g., phenotypic features, variant details, zyg
Remove or suspend submissions that are solved or add tags that a case is solved, but looking for additional cases for second
Remove or suspend submissions with candidates with very limited evidence
Generate collaboration templates for tracking cases, collaborators, and publications

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