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Workshop report

214th ENMC International Workshop: Establishing an international consortium for gene discovery and clinical research for Congenital Muscle Disease, Heemskerk, the Netherlands, 6–18 October 2015

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1. Introduction

At this ENMC meeting, a multidisciplinary group of 26 participants, including 22 clinical and basic science researchers from 11 different countries and 4 patient advocacy representatives convened to discuss the formation of a formal consortium to improve diagnosis and gene discovery for congenital myopathy (CM) and congenital muscular dystrophy (CMD). The mission statement of the consortium is that "every individual with a congenital muscle disease deserves a genetic diagnosis". The workshop consisted of three sessions: (1) identifying existing diagnostic and gene discovery infrastructure (databases, analysis platforms, phenotyping tools, cohorts, validation work and registries), (2) exploring current gene discoveries models and tools in the CM/CMD cohort and other disease cohorts, and (3) formalizing next steps towards the establishment of a consortium.

Pediatric neuromuscular disorders encompass a spectrum of diseases with great genetic and phenotypic heterogeneity, varying in age of onset, rates of clinical progression, disease severity, systems involved, and underlying genetic and physiological mechanisms [1–6]. Congenital or early onset muscle disorders are particularly diverse. Included in this group are congenital myopathies, congenital muscular dystrophies, and congenital myasthenic syndromes (CMS). Individual conditions within these groups are rare, but collectively they represent a major subset of neuromuscular disease across the lifespan [7]. Diagnostic challenges arise from the rapidly expanding genetic heterogeneity underlying seemingly distinct clinical phenotypes, and from the frequently striking phenotypic heterogeneity arising from mutations in single genes. There also remains an important subset of patients with the clinical and/or biopsy features of congenital muscle disease within whom a genetic diagnosis has yet to be reached.

The much broader availability of next generation based sequencing (NGS), including particularly multi gene panels, whole exome sequencing (WES), whole genome sequencing (WGS) and RNA sequencing (RNA-seq) has come with enormous opportunities, as well as unique challenges for our field [8]. While there likely are many more genes underlying early onset muscle disorders that remain to be discovered, it is equally likely that each of them will be rare and perhaps not immediately obvious in single cases or small families. Going forward, it will be essential to harness the potential of comparing datasets of genotypes as well as phenotypes, to recognize or confirm emerging novel disease genes, phenotypes and molecular mechanisms. This is currently done on an informal basis with good success, but there are several recent models for other cohorts that may aid in establishing a structure to formally link datasets and collaborators in order to significantly increase the chances for gene and mutation

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discovery by enhancing synergies, formalizing the process of cross-cohort interrogation of genotypes and phenotypes, and laying the foundation to enlarge the network.

2. Examples of existing cohorts and approaches

Currently there are several successful diagnostic and gene discovery CM/CMD cohorts studied independently yet also through partnerships and informal collaborations. Such established and working cohorts may be national CM/CMD referral cohorts, or ones with targeted clinical or histopathological based recruitment. Even though diverse in size and focus, they provide a good foundation through which a consortium may be established.

2.1. National & clinical network based referral cohorts

The Dubowitz Neuromuscular Centre at the Institute of Child Health, UCL and Great Ormond Street Hospital is the major national referral center for CMD in the UK. Currently, the Centre is a member and coordinating center for CMD on a multicenter collaborative grant (NeurOmics), funded by the European Commission. **Irina Zaharieva** from the Centre reported that WES was performed in 100 clinically well characterized patients with CM/CMD, resulting in the identification of several new causative genes [9,10]. Overall, 58% of the CMD cases have been resolved by mutations in well-established neuromuscular genes [11]; 5% carried mutations in a known gene but associated with unusual features; in another 5% of cases a new phenotype associated with known genes was described, and in 19% a plausible novel candidate genes were identified.

The "Myocapture" project in France (516 exomes completed at the time of presentation out of 1000 planned) analyzed patients with congenital muscle disease who had been extensively pretested (i.e. not diagnosis naïve). This network relied on collaborations with clinicians from the national neuromuscular network Filnemus, DNA banks, histopathologists, research teams and the Genome Institute in Evry. **Jocelyn Laporte** discussed that for this project, novel analytic pipelines and tools were created, including programs for variant ranking and gene prioritization [12]. To identify causative mutations, an integrated approach to diagnosis was build, comparing the generated genetic data with clinical, histopathological, biochemical and imaging investigations [13]. The underlying genetic cause in this myopathy patient cohort was confirmed in about 36% of families and tentatively identified in about 24%. This success rate is highly dependent on the number of individuals that can be tested per family; analysis is ongoing for the remaining cases.

The Institute for Neuroscience and Muscle Research (INMR) in Sydney, Australia is a referral center with sample contributions from across Australia as well as a more local clinical cohort. **Emily Oates** discussed the analysis workflow in the Institute. Patients were screened through clinical history, images, neurophysiology, array CGH, DM1-DM2 exclusion, single gene Sanger sequencing and analysis through the Perth SuperCapture NM gene chip (>200 genes). WES sequencing was then combined with SNP-based homozygosity mapping and linkage studies. The diagnostic rate for using this entire approach in diagnosis naïve patients was approximately 72% overall, and was 75%, 43% and 55% for CNM, LGMD and CMD respectively.

The Neuromuscular and Neurogenetic Disorders of Childhood Section at the NIH uses thorough clinical (either on site or via traveling clinics), histological and imaging characterization as an entry point into the cohort. **Sandra Donkervoort** from the NIH discussed the integration of the WES data with this clinical phenotyping approach in conjunction with national and international data sharing. This has led to the successful establishment of unique deeply characterized and extensively pretested cohorts in which to elucidate novel disease mechanisms and genes [10,14,15]. Approximately 60% of patients remain undiagnosed after WES analysis.

Marina Mora reported that the neuromuscular centers in Italy have recently received funding from The Italian Telethon to form a network for CMs and CMDs, currently encompassing some 700 patients, two thirds of which have an established molecular diagnosis.

2.2. Biopsy based cohorts and gene specific efforts

Several cohorts were discussed that were developed out of muscle biopsy referral centers. Taking the entry point to gene identification from the "histotype" is a particularly valid approach for congenital muscle disease, since much of the classic classifications in this group are based on histological, histochemical and ultrastructural criteria. The availability of well-characterized muscle biopsy tissue, linked to accurate phenotypic data, also becomes a powerful resource for gene and mutation identification when combined with next generation sequencing approaches. Muscle morphological studies and histochemical findings, such as nemaline rods, allow for disease categorization and direction of the genetic testing process. Moreover, the availability of banked muscle tissue is extremely valuable for the validation of novel variants and for emerging technologies such as RNA-seq. Experienced morphologist and biopsy-based cohorts are therefore an integral part of the collaborative diagnostic and discovery gene studies. Various biopsy cohorts currently exist, which include national and international networks (Italian Telethon network of Genetic Biobanks (TNGB), EuroBioBank (EBB), that also house other biomaterials such as fibroblast lines and serum (as discussed by **Marina Mora**). The EBB is merging with RD-Connect to become the reference biobank aimed at linking databases, registries, biobanks and clinical bioinformatics data into a central resource for worldwide research in rare diseases. EBB is composed of 25 members from 11 countries and consists of 22 biobanks, of which 11 are neuromuscular disease dedicated biobanks.

The biopsy cohort at the Muscle Morphology Lab of the Myology Institute in Paris was discussed by

Edoardo Malfatti. Biopsies were classified based on various histochemical diagnoses and independently collected DNA samples used for NGS diagnostics for the undiagnosed patients. As an example, the application of exome sequencing in nemaline and core-rod myopathy groups ($n = 54$) revealed the presence of *NEB* mutations in approximately 50% of cases, while a new gene *MYO18B* was identified in collaboration with the Laporte lab in the *NEB* negative group [16]. The opportunity for a careful morphological re-characterization after identification of the causative gene is a strength of this repository, for instance identifying features overlapping congenital myopathies and congenital muscle dystrophy in patients harbouring *TTN* variants.

The Muscle Sample Repository in Japan was discussed by **Ichizo Nishino**. This collection started as a muscle sample repository that now receives approximately 70% of muscle biopsies from Japan. Even after extensive immunohistochemistry staining, approximately 63% of biopsies remain without a diagnosis. NGS, including targeted panels, and WES had now been performed on over 750 samples. These Japan based cohorts have made important contributions to novel gene discovery as well as to careful histo- and phenotyping of novel genetic entities after they emerged.

Some cohorts have been set up from the beginning as including both DNA as well as muscle biopsy samples (such as is the case in the congenital myopathy cohort presented by **Alan Beggs** from Boston Children's Hospital/Harvard Medical School). This registry was established in 1992, and now includes over 1000 affected individuals from approximately 850 families. The majority (80%) of patients are referred by their provider based on specific histochemical findings on biopsy, while 20% of patients are self-referred. A systematic mutation and gene identification effort is in progress in this cohort and has yielded and contributed to a number of recent gene discoveries, such as mutations in *SPEG*, also resulting in the recognition of a novel phenotype of centronuclear myopathy with transient neonatal cardiomyopathy [17].

One of the considerations pointed out by the discussants pertaining to collections that have been stored over a longer period of time is that for the older muscle samples there may only be limited clinical information available, genomic DNA samples may not be available from the proband or family members (which will then have to be extracted from the muscle directly), and re-consenting for next generation sequencing may be difficult. **Alan Beggs** confirmed that in his experience one of the key elements for successful genetic diagnostics therefore is an IRB protocol that allows for the ability to re-contact families and to share data with external collaborators. Current independent cohorts are tied to their own Institutional Review Boards, with every group having their own regulations for data sharing, patient follow up and consenting.

Finally, taking her clues for a carefully assembled national cohort of patients found to have *RYR1* mutations with national reach in the Netherlands, **Nicol Voermans** discussed the unexpectedly broad clinical spectrum emerging for *RYR1*-related myopathy in both the pediatric and, importantly, adult population. Extrapolating from these findings with *RYR1*, it is thus deemed critical that, when establishing a CM/CMD consortium for the purpose of novel gene discovery, the entire potential phenotypic and age related spectrum should be considered [18].

2.3. Applicable available infrastructures and consortia that can be adapted

Care 4 Rare (C4R), discussed by **Jodi Warman Chardon**, is a multicenter gene discovery pipeline of researchers, clinicians, informaticians, and scientists working across Canada. Tools used include PhenomeCentral (https://phenomecentral.org), a database portal where clinicians can enter clinical phenotypic information (Phenotips) using Human Phenotype Ontology (HPO) terminology. PhenomeCentral also enables integration with relevant genetic information, and functions as a matchmaker program to assist in the discovery of similar patients around the world. C4R also establishes connections between clinicians and basic scientists with laboratory based and functional expertise to explore disease pathways (via the RDMM, or Rare Disease Models and Mechanisms pathway).

2.4. Challenges in large countries with less established gene testing infra-structures

A number of countries with large populations have unique genetic makeup and also sophisticated clinical and histological resources to assemble important cohorts for gene discovery, but are lacking the infrastructure for widespread and efficient genetic testing for the known and more frequent genetic conditions. **Edmar Zanoteli** (Brazil), **Hui Xiong** (China) and **Mert Karakaya** (Turkey) discussed unique challenges in establishing a genetic testing infrastructure for each of their patient populations. Since reimbursement of genetic testing is either non-existent or very limited, and their programs rely on international collaborations to pursue research based diagnostic testing. Additionally, government restrictions may pose limitations on sending patient biological material abroad for research-based testing.

2.5. Countries and regions that are not represented and have no ready infrastructure

Genetic diagnostic confirmation has to be considered the gold standard for diagnosis in genetic muscle disease [19], while negative genetic testing for established genetic conditions defines the patient cohorts most relevant for gene discovery. Moving forward, it will thus be essential to include clinicians from all regions and countries to establish a platform for genetic testing. This will also require provisions for consenting, phenotyping and follow up.

2.6. Patient database and available registries

Patient registries, medical record repositories and disease specific foundations play an integral part in identifying and registering patients, including those still in need of a genetic diagnosis. They are instrumental in helping to bridge the gap between researchers, clinician and the patient community. Patient initiated foundations play an important role in advocacy, family outreach, fundraising, clinical trial recruitment, data repository, and advancing research and genetic testing when feasible, which in turn lay the foundation for the advancement of clinical trial readiness and implementation. Foundations may be gene/disease specific, such as the *RYR-1* Foundation (www.ryr1.org), represented at the workshop by **Michael Goldberg,** and the Myotubular Trust (mtmcnmregistry.org), represented by **Anne Lennox**, or focused on the entire group of disorders such as the Congenital Muscle Disease International Registry (CMDIR; www.cmdir.org) represented by **Anne Rutkowski**. Registries such as the CMDIR provide essential platforms for identification and registration of undiagnosed patients and for advocating wide access to baseline genetic testing.

3. Available genetic approaches

3.1. Current use of next generation tools in the various cohorts

The overall approach to genetic analyses was very comparable amongst the cohorts discussed. Given the genetic heterogeneity of the target disease population (which in addition to all typical CMD and CM genes also includes various LGMD genes, all the alpha-dystroglycanopathies, and CMS genes), initial NGS-based testing using large panels that include all genes previously linked to muscle diseases was recognized as a cost-effective first diagnostic approach for congenital muscle disease cohorts. It was interesting to note that at the time of the workshop, diagnostic rates in the CM/CMD population using gene panels or whole exome sequencing was 40–60%. Highest yields were seen in well-characterized pheno- and histo-typed cohorts, families with multiple affected or those ran as trios or quartets. This consistent number of about 50% undiagnosed patients, even after the application of WES, emphasizes the need for a broad and consistently applied platform for data sharing to appropriately recognize rare variants in a given gene that are seen in more than one family with a similar phenotype across the cohorts, and to select families and phenotypes for higher level genomic investigations including whole genome sequencing (WGS) and RNA-seq.

3.2. Analysis of genome data – variant calling

Daniel MacArthur from the Broad Institute discussed the use of large-scale genomic approaches for the diagnosis of rare neuromuscular diseases. Important tools in this effort are large population reference panels, such as the Exome Aggregation Consortium (ExAC) data set, a publicly available reference data set which spanned 60,706 exomes at the time of the workshop. There are various informatics tools for the analysis of exome data, such as the in-house pipeline at Broad (*Seqr)*. Additionally, the international Matchmaker Exchange network (www.matchmakerexchange.org) is an essential tool in identifying rare disease families with mutations in novel candidate genes.

3.3. Validation approaches available

Next generation sequencing projects are generating a large number of variants with unknown significance that require validation studies. **Tobias Willer** (University of Iowa) highlighted the use of patient fibroblast collections for complementation grouping and gene validation as a possible blueprint to assist in discriminating pathologic changes from polymorphic variations [20]. **Yann Herault** from the Mouse Clinical Institute of the French National infrastructure PHENOMIN, discussed that mouse models can provide invaluable insights in candidate gene validation, disease mechanisms, and potential drug discovery. Potentially cheaper and more rapid alternative models can be generated in non-mammalian organisms such as zebrafish. Zebrafish models may be germline mutation based (e.g. *caf* model of MDC1A and *neb* model of nemaline myopathy) and/or morpholino based (spanning several examples). **James Dowling (**Hospital for Sick Children, Toronto) highlighted the strengths (ease of creating knockouts, availability of large numbers of mutants, robust assays for defining myopathy) and weaknesses (difficulty generating knock-ins and tissue specific knockouts, gene duplications) of the zebrafish model for testing novel gene mutations.

4. Summary and future plans – development of a congenital muscle disease consortium

The formation of a consortium devoted to mutation and gene identification in the CM/CMDs is to build on the described existing efforts and individual strengths to create and expand an interactive platform with the potential of adding complexity, functionality and depth to the analysis, while also expanding it globally.

A significant barrier to the formation of cohorts with a high yield for novel gene discovery is the lack of standard genetic diagnosis for a large number of CM/CMD patients globally. This lack of genetic diagnosis at the same time also poses a hindrance to appropriate clinical care and therapy development for this group of patients. This is due in part by inadequate access to testing of known CM/CMD genes. There is therefore a great need for better access to, and application of, clinical testing of the known CM/CMD genes, which will then facilitate the concerted gene discovery efforts aimed at identifying the remaining genetic causes of CM/CMD, which is the core mission of this consortium.

Thus, three steps were deemed to be essential for the consortium to be successful:

1) development of a clinical genetic testing platform for individuals without current access to testing,
2) creation of a large-scale data sharing platform for existing and new cohorts, and
3) development of a common phenotype and validation platform.

4.1. Providing a global genetic testing platform

The consortium will aim to increase access to genetic testing for patients with CM/CMD, which may be accomplished in part through collaboration with pharmaceutical or non-for profits organizations and advocacy. Available gene panel testing for LGMD initiated by the Jain Foundation was cited as a model. An increase in confirmatory genetic diagnoses will aid in appropriately directing clinical care, determine accurate recurrence risk counseling and facilitate establishment of well-defined cohorts for phenotype and genotype correlation studies, natural history studies and clinical trial readiness for the CM/CMD patient population. Patients, for whom the genetic diagnosis remains unknown, will then be offered referral to a research-based gene discovery platform as represented in the consortium. A working group within the consortium was created to discuss patient entry criteria, to identify available genetic testing platforms and to develop an algorithm for screening, consenting and follow-up.

On the research level the consortium will then work on optimal use and access to genome wide sequencing technology and approaches, including WES (now more widely available, and covered as a clinical diagnostic in some countries), WGS as well as RNA sequencing. An additional point and potentially rich resource the consortium will need to address is the wealth of sequence data stored in commercial testing labs after diagnostic WES was completed in a patient but did not result in a clear genetic diagnosis. This data could be extremely valuable to include the gene discovery efforts across the consortium.

Update on progress since the ENMC workshop: Since the ENMC workshop, advances in access to clinical testing have largely mirrored the dropping price globally and expanded insurance coverage of gene panels and whole exome sequencing. In Canada and the United States, for example, most individuals with congenital muscle disease are able to obtain testing through commercial laboratories. In addition, continued efforts through large research-based sequencing projects (such as MyoCapture in France, Care4Rare in Canada, and broad-based sequencing initiatives in Australia) plus funded individual studies from several investigators have led to diagnoses for many patients and the identification of new genetic causes. Furthermore, new initiatives incorporating "multi –omics", and particularly RNA sequencing, have been successful in identifying disease causing variants in a subset of "exome negative" cases. These approaches are not yet available as clinical/commercial tests. Of note, however, the continues to be a gap in the availability of testing in many countries and regions and will require continued efforts to consider how best to provide testing in those circumstances.

4.2. Establish a large-scale data-sharing platform

Most "low hanging fruits", i.e. genes where mutations represent a relative common cause of congenital muscle disease, have been discovered. Therefore, every new gene will probably be found in a limited number of patients, and thus collaborators will need algorithms to facilitate targeted analysis of phenotypically comparable cases in order to identify variants in candidate genes that are shared by the patients. Also, groups of new candidate genes can be defined by shared pathways or interactomes and then be interrogated across the entire sequence dataset. As well, function-based screening platforms are available to support such in silico data. The consortium identified various existing platforms and mechanisms that can be used for confidential data sharing, including sharing of novel candidate genes and variants, the development of a CM/CMD specific infrastructure to be implemented in Matchmaker and phenotype integration for CM/CMD in Phenome Central. As the crucial next step, the consortium recognized the importance of working toward a functional initial level of data sharing, allowing collaborators to access and analyze exomes reprocessed through a mutual agreed upon platform, such as the Broad Institute. A working group within the consortium will establish a mutual strategy for candidate gene interrogation approaches, and for interpretation and validations of gene variants. The consortium agreed that collaborators would benefit from a consensus to establish pathogenicity and to prevent any mis-assignment of pathogenicity of patient variants and of potential new disease genes.

Update on progress since the ENMC workshop: While there is currently not a congenital muscle disease specific platform that has emerged since the workshop, Matchmaker programs have been broadly implemented across the entire spectrum of rare disease, resulting in new gene discoveries as well as new phenotypic associations with existing genes. The same is true related to data sharing. There have also been important efforts (including by consortium members) to address questions of variant interpretation and classification for specific genes, such as for *TTN* and *RYR1*. Based on experiences since the consortium meeting, it seems likely that such studies may need to be focused on individual genes, as the difficulties regarding variant interpretation and functional validation present unique challenges that require specialized strategies.

4.3. Development of a common phenotyping and validation platforms

Deep pheno/histo-typing and clinical recognition is essential for establishment of specific cohorts to facilitate appropriate genetic testing, both on the clinical and the research level. As many of these patients may have rare or unusual clinical presentations, there is a critical need

for a platform that allows for clinical case matching and then integration with the sequence databases. The consortium identified Phenotips as the primary choice and will establish a working group to develop a minimal, but maximally useful dataset that includes clinical phenotype, imaging and pathology data points. The application of Matchmaker will be explored as a platform on which to share such phenotype and histotype standardized elements. Additionally, there is a critical need to establish a platform that allows clinical case and variant matching, with matching of human gene discovery findings with pre-exiting but perhaps unpublished animal modeling data. A general consensus is needed based on available literature and expert opinion regarding in silico molecular modeling, protein based functional studies, and animal models best suited for validation work for CM/CMD. Lastly, careful consideration is needed regarding appropriate use of ever-diminishing muscle biopsy resources, to ensure tissue availability for additional histopathological and protein analysis in undiagnosed cases, for validation studies and biomarker development, and future diagnostic testing such as RNA sequencing analysis.

Update on progress since the ENMC workshop: Progress related to establishing gene specific natural history and genotype-phenotype correlations has been evident for several CM/CMD subtypes, including *MTM1*, *LAMA2*, *LMNA* and *COLA1/2/3*. There remains a great need for such data for several of CM/CMD subtypes, and efforts by consortium members are underway to address the existing gaps in this knowledge. Importantly, it appears that the most effective strategy for obtaining these data is to focus on specific genotypic subtypes, and to use knowledge gained from completed to studies to continually inform on the data points that are relevant to consider and collect. Lastly, there is an evolving consideration of "histo-type" versus genotype, and ongoing discussion on how best to characterize and describe the various CM/CMD subtypes. Given that the initial diagnostic care standards for both CM and CMD were established prior to the widespread application of exome sequencing, we view it important to consider revisiting these recommendations in the near future.

Workshop participants

The workshop was attended by: Alan Beggs (Boston, USA), Gisele Bonne (Paris, FR), Carsten Bönnemann (Bethesda, USA), Sandra Donkervoort (Bethesda, USA), James Dowling (Toronto, CAN), Victor Dubowitz (London, UK), Michael Goldberg (RYR1 Foundation, USA), Morton Goldberg (RYR1 Foundation, USA), Yann Herault (Paris, FR), Mert Karakaya (Koln, GER), Jocelyn Laporte (Strasbourg, FR), Anne Lennox (MTM Trust, UK), Daniel MacArthur (Boston, USA), Eduardo Malfatti (Paris, FR), Katherine Mathews (Iowa City, USA), Marina Mora (Milan, IT), Ichizo Nishino (Tokyo, JP), Emily Oates (via WebEx) (Sydney, AU), Anne Rutkowski (CureCMD, USA), Melanie Spring (MTM Trust, UK), Nicol Voermans (Nijmegen, NL), Jodi Warman (Ottawa, CAN), Tobias Willer (Regeneron, USA), Hui Xiong (Beijing, CH), Irina Zaharieva (London, UK), Edmar Zanoteli (Sao Paolo, BR).

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Supplementary materials

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