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Workshop report

AFM/MDA 1st International Myotonic Dystrophy Consortium Conference 30 June–1 July 1997, Paris, France

1. Introduction

Representatives of 28 countries from 43 medical and scientific institutions gathered in Paris on 30th June–1st July 1997 for the 1st AFM/MDA Myotonic Dystrophy International Consortium conference (DMIC), generously sponsored by Association Française contre les Myopathies (AFM), Muscular Dystrophy Association (MDA) and the Denver fund and organised by AFM. This meeting brought together clinicians, clinical scientists and molecular biologists to evaluate current knowledge on clinical, histological, biochemical and molecular genetic aspects of myotonic dystrophy (DM), and to plan international collaborative ventures to resolve some of the most urgent questions regarding this triplet associated disorder. A major part of the meeting was an examination of recent, and as yet unpublished molecular genetic work. The major areas covered were: instability mechanisms, populations genetics, disease mechanisms, diagnosis and treatment.

After a general introduction by A. Roses, B. Wieringa delineated current problems and listed the key questions to be answered: (1) Have all clinical features of DM been described yet? (2) Is the CTG expansion really the only mutation and can the expansion explain the full extent of all features? (3) Is there a developmental timing of the somatic expansion involved and does the extent of the expansion depend on the cell type or on processes such as ageing? (4) Can the complexity in variable clinical phenotypes be explained by the fact that these patients display both in their soma and in their germline mosaicism of the length of the CTG repeat? What determines how the CTG segregates through families and in the different cell lineages? (5) What are the molecular mechanisms by which the CTG expansion causes this disorder? How can we explain the dominant effects?

2. Instability mechanisms

In the sessions on instability mechanisms, data on instability in in vitro models, transgenic animals and human subjects were presented. The data suggested that the stability of the repeat is determined by the repeat size and sequence. However, cis- and trans-acting mechanisms, as well as replication- and transcription-dependent mechanisms also play important roles in the repeat stability.

In *E.coli*, expansions and deletions of CTG/CAG are influenced by the orientation of the insert due to hairpin loop formation during replication and by the length of the CTG repeat. R. Wells proposed a current model to explain the observed expansions and deletions via strand misalignment, incision or excision, followed by DNA synthesis and ligation and DNA polymerase pausing in vitro and in vivo. In vitro, R. Sinden showed that (CTG)n repeats can form slipped strand structures (S-DNA) which may be involved in expansion leading to DM. The interaction of the hMSH2 protein with slipped strand DNA structures (S-DNA) demonstrates that hMSH2 could participate in trinucleotide instability, although hMSH2 alone can not be responsible for massive expansion (J. Griffith).

In humans, CTG expansions are usually larger in muscle compared to peripheral blood. In contrast, the CTG repeat showed limited heterogeneity in non-DM samples (M. Anvret, T. Ansved). Normal length alleles are relatively stable during male germline transmissions and confirm normal Mendelian segregation of the two alleles (D. Monckton). The repeat is apparently stable during the first trimester of pregnancy and increases only after 13 weeks gestational age and before 16 weeks and continues after birth (L. Martorell, M. Baiget).

Therefore two types of CTG repeat instability can be observed, i.e. (1) frequent step-wise mutations resulting in gradual continuous increase of the repeat size and size heterogeneity occurring throughout the life of a DM patient and (2) relatively rare mutations with large changes of the CTG repeat size with a bias toward contraction as seen in expanded CTG repeat tract introduced into prokaryotic and eukaryotic cells in culture, but rarely seen in DM patients (T. Ashizawa).

Recent models in transgenic mice successfully reproduced triplet instability although the size of expansion was not as high as that seen in human patients. The mismatch repair system can be an important modulator but may only affect the rate, not the length, of the mutation. Furthermore, transcription through the region could be a modulator of repeat instability (D. Monckton). In transgenic mice car-

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rying a 45 kb genomic DNA fragment from the DM region and 55 CTG, the somatic instability detected in some tissues increases with age and is more pronounced in pancreas, liver and kidney (G. Gourdon). Transgenic mice containing a DMPK minigene construct with 100 CTG repeats under the control of the CMV promoter and matrix attachment region (MAR) sequences showed also intergenerational trinucleotide repeat instability (R. Korneluk).

3. Population genetics

The rare ancestral DM mutation event may have occurred after the migration from Africa, or in a north-east African population, probably by 'step by step' mutation events (A. Goldman).

In both Caucasian and Japanese populations, haplotype analysis of DNA markers close to the DMPK gene suggested that a few common ancestral mutations have originated from a common haplotype (T. Miki). In 69 Brazilian DM affected families, the mutant allele appears to be preferentially transmitted to male offsprings through males which could give a biological explanation for the significant excess of affected males as compared to affected females (M.-R. Passos-Bueno). In unaffected individuals of 16 diverse populations, larger CTG-repeat alleles (for size ≥29 repeats) are preferentially transmitted during female meiosis while no segregation distortion occurs during male meiosis. A mutation-selection-drift equilibrium may lead to a stable frequency of DM in populations (R. Chakraborty).

4. Disease mechanisms

This large session on disease mechanisms focused on the DM region including three genes (59, DMPK and DMAHP), a CpG island, a hypersensitive site and on the role of the CTG repeat. All plausible disease mechanisms were discussed. Studies of the DMPK gene suggested multiple mechanisms at DNA, RNA and protein levels. Experimental data suggested that 59 and DMAHP may also play important pathophysiological roles.

4.1. DMPK DNA/RNA

In alleles with large repeat expansions the region is converted in a more condensed chromatin on at least 10 kb around the repeat (J. Tapscott). This was also observed in somatic cell hybrids where there were reduced levels of DMPK and an inverse correlation between the number of repeats and chromatin sensitivity (V.L. Funanage). Thus, the repeat expansion could have a long range effect on chromatin structure. In young and severely affected patients (congenital), complete methylation of restriction sites *Sac* II, *Hha* I and *Hpa* II in exons 11–15 and a large CpG island was found on the mutated chromosome. There was also a significant reduction of the interaction of the transcription factor SP1 at a CAGGGCGG binding site upstream of the CTG repeat in this methylated region (P. Steinbach). R. Korneluck reported that SP1 binds to a GC box within the basal promoter of DMPK. Myoblast specific gene expression may also be controlled by a MyoD responsive enhancer located in the first intron.

Approximately 50% of polymerases transiently adopted an elongation incompetent configuration at the entrance of the first two CTG repeats and the elongation rate within the CTG repeat was inherently slow. This slowed-down rate of transcription may affect the rate of processing which could also depend on the cell type (R.R. Sinden). D. Brook and B.M. Davies reported independently that transcripts from expanded DMPK alleles are retained within the nucleus, forming nuclear foci, and are absent from the cytoplasm of DM cell lines. Formation of nuclear foci is a novel mechanism for preventing transcript export and effecting a loss of gene function.

A model to explain the genetic dominance of this disease proposes that the DMPK (CUG)*n* expansion exerts its effect at the RNA level by modulating the binding of a (CUG)*n*-binding protein (CUG-BP/hNab5), characterized as a novel human heterogeneous nuclear ribonucleoprotein (hnRNP) (M.S. Swanson). In addition, DMPK phosphorylates CUG-BP in vitro suggesting that phosphorylation by DMPK could regulate the subcellular distribution of CUG-BP. Thus, CUG-BP and DMPK might regulate each other (L.T. Timchenko). Acrylamide gel experiments showed that CUG tract transcript formed secondary structure. Duplex structures formed by CUG repeat RNA may also bind and activate PKR, a dsRNA dependent protein kinase and potent regulator of translation, and thus may contribute to reduced muscle protein synthesis and muscle wasting in DM (C. Thornton). In agreement with the hypothesis that DM could be a generalised RNA metabolism disorder, significant reductions in insulin receptor RNA in DM muscle were found, thus providing a possible molecular mechanism for the increased insulin resistance observed in many DM patients (C. Milcarek).

4.2. DMPK protein

DMPK contains, from the amino to the carboxyl terminal, an L motif, a kinase catalytic domain, a coiled-coil region, and a tail region. A 54-kDa protein kinase (a DMPK family member?) was immunoprecipitated from human heart and skeletal muscle. This protein kinase was phosphorylated in vivo on serine residues (mostly in heart) and tyrosine residues (mostly in muscle) (J. Puymirat). Using antibodies, the DMPK protein was localised to the endoplasmic reticulum in epithelial cells in human lenses and in the B3 human lens epithelial cell line. This observation suggests that DMPK may regulate membrane transactions of the microtubule-associated endoplasmic reticulum complex. In DM, the

recycling of membrane from the Golgi complex to the endoplasmic reticulum could be specifically affected leading to inclusion bodies and cataracts (H.F. Epstein). In muscle tissues, triads and sarcoplasmic reticulum (SR) terminal cisternae are also immunoreactive for two DMPK proteins of different molecular weight (85 and 54 kDa). In addition, immunofluorescence studies of cardiac muscle reveal a heavy concentration of DMPK localised to the intercalated discs, as well as a weaker reaction in the sarcoplasm (S. Salvatori).

Myotonia in DM shows a slight warm-up phenomenon and the EMG reveals bursts of intermediate or long duration lasting several seconds. These charges can be caused by a reduced muscle chloride conductance as well as a destabilisation of the inactivated state of the muscle Na+ channel (F. Lehmann-Horn). In RNA injected *Xenopus* oocytes, the reduction of Na + current amplitude by DM kinase coexpression results from a decreased probability of channel opening without a change in other single channel properties (J.R. Moorman). In homozygous DMPK (–/–) mice, mutant myotubes cultured in vitro exhibit also an altered open probability of the voltage gated L type Na+ channel and of the voltage gated Ca^{2+} channel (P. Groenen).

4.3. DMAHP/59 (N9)

Around DMPK, there are six different genes that map within an interval of 200 kb of the expanded repeat. Three of the genes, 59, DMPK and DMAHP map in a very short interval. Other transcripts, including the 5C2C gene (containing exons identical to the gene symplekin), the 20D7 gene (expressed in testis), and the GIPR gene (gastric inhibitory peptide receptor) may be involved in DM-associated testis problems and diabetes (K. Johnson, D. Brook).

DMAHP contains three exons and the first exon A contains a homeobox encoding domain and the SIX domain. Two alternative splicing forms have been identified. In exon C the reading frame is altered by alternative splicing in exon B (K. Johnson). Binding targets of DMHAP genes remain to be identified. However, it has been shown that, in vitro, the Six2 and DMAHP genes bind to the same target. In the promoter region of DMPK there is a sequence which could bind DMAHP (S. Harris). C. Thornton also observed that an in vitro translation homeobox domain of DMAHP does bind to sequence element of the ATPase alpha1A promoter.

Using RNAse protection assays, DMAHP has been shown to be expressed at low levels in myoblasts and muscle and the full length transcript is predominant with a reduced expression of the DM-linked allele in DM patients (C. Thornton). A decrease of 80% of DMAHP was also observed in cerebellum and frontal cortex of two DM patients with 300–350 CTG repeats (P. Ammicucci). The hypersensitive site positioned near the CTG repeat contains enhancer elements located between DMPK and DMAHP, including two E box suggesting that it could be regulated by MYOD. The CTG expansion could alter transcription of the DMAHP gene by a change in chromatin structure precluding transcription factor access to the regulatory regions (S.J. Tapscott). In somatic cell hybrid cell lines, in contrast with other observations, the triplet repeat expansion in DM and CDM patients did not affect transcription of either DMAHP or 59. Therefore the situation may be different in skeletal muscle and in hybrid cell lines (V.L. Funanage).

The 59 gene is positioned immediately upstream of the DMPK gene with only a 1.1 kb spacing between the poly(A) addition signals in the 59 gene and the actual transcription starts site(s) in DMPK. The gene contains five exons of which exon 4 is alternatively spliced. The 59 gene product is a cytosolic WD-repeat protein with unknown function which is ubiquitously expressed at a low level in all tissues, but is particularly abundant in brain and testis. This gene may have a role in the fertility problem observed in male DM patients (B. Wieringa).

4.4. Transgenic animal models

We still do not have a clear understanding of how the repeat expansion leads to the complex multisystemic DM phenotype. Moreover, neither transgenic mice overexpressing human DMPK nor knockout mice completely deficient for DMPK display many of the features of the DM phenotype (like myotonia and CDM features). As such, much attention has shifted to the potential involvement of other genes, such as DMAHP and 59. Animal models can give some information on some DM pathological features but it has to be considered that muscle differentiation is different in mouse and human (R. Korneluk, B. Wieringa).

The DMPK KO model presented by P. Groenen shows only minor abnormalities with myopathy in some muscles including neck muscle. However in older males (over 18 months), a tubular atrophy can be observed in the testis with absence of spermatogenesis. This feature could be due to the loss of DMPK expression or to a possible decrease of the N9 gene in this model. In the second KO model presented by S. Reddy, testicular atrophy is observed although not as dramatic. These mice also develop distinct cardiac electrophysiological abnormalities of atrioventricular conduction.

Some aspects of the DM phenotype seen in patients could be associated with a gain of function of the RNA messenger carrying CUG repeats. Transgenic mice containing a noncoding sequence with 160 CTG under the control of the ubiquitous EF1a promoter displays also male sterility and reduced fertility in females. However, muscle weakness and myotonia are not observed (D. Monckton). Other transgenic model containing 45 kb of the human genomic DM region with the N9, DMPK and DMAHP genes and either 20, 55 or 320 CTG repeat have been generated. They are used to study mechanisms by which the CTG repeat influences the expression of the three genes and to verify if the expression of a 3′UTR carrying an expanded CTG could lead to DM phenotype features (G. Gourdon). A third type of trans-

genic mice was also presented. Mice containing MAR sequences over-expressing the human DMPK gene show profound loss of photoreceptors but no cataracts. Diagnostic hallmarks of DM including sarcoplasmic masses, increased centronucleation and type I fiber atrophy were also observed (R. Korneluk).

An alternative approach has been developed by the transplantation of DM myoblasts into the skeletal muscles of immunodeficient mice (SCID). One month following transplantation, EMG search showed, in DM myoblasts, typical myotonic. The DM myoblasts grafted into the skeletal muscle of SCID mice could be a useful muscle model for DM (J. Puymirat).

After completing these sessions, B. Wieringa led a review of the covered materials to reach consensus. The DM pathophysiology may involve multiple complex mechanisms resulting from the CTG expansion. Several lines of evidence now suggest that part of the autosomal dominant DM phenotype might be associated with a direct gain of function of the repeat with a role for the DMPK message from the mutant chromosome containing an expanded CUG tract.

4.5. Clinical studies of the disease mechanisms

After a clinical introduction on DM and CDM by C. Thornton, G. Butler-Brown, in view of the developing mouse models, compared muscle development between man and rodent. In the two species, the development of skeletal muscle is characterized by the progressive transformation of undifferentiated fibres into mature slow and fast contracting fibres but the chronology of muscle maturation differs: in man, most muscle fibers are mature at birth whereas in rats and mice, all this muscle maturation occurs after birth. The establishment of the mature phenotype depends upon the development of a mature motor innervation and of other epigenetic factors (G. Butler-Brown).

In affected CDM foetuses, the skeletal muscles show essentially an arrested or delayed maturation, with abnormalities ranging from the presence of myotubes to incomplete fibre type differentiation, and a general smallness of fibres. Central nuclei, nuclear chains, ring fibres and inflammatory changes associated with the adult form are not found. Among the different markers which are important, the delayed expression of the slow MHC is a useful marker especially in terms of morphological diagnosis (J.P. Barbet). A new case of paternal transmission of CDM by a 40 year old man with DM has been reported. Surprisingly the intergenerational expansion between the father and the CDM daughter, although associated with obvious anticipation, was very small, contrasting with previous reports of paternally transmitted CDM (B. Eymard).

Analysis of 23 patients, with age ranging from 18 to 56 years and CTG expansions ranging from 100 to 1500 repeats, by brain magnetic resonance imaging (MRI) suggests the role of age in the pathogenesis of the encephalic alterations generally detected in DM. (M. Giacanelli).

In 12 DM patients the observed reductions in myocardial metabolic rate for glucose (MMRGlu) measured by positron emission tomography (PET) and in phosphorylation of glucose are inversely linked to the length of the mutation. Thus myocardial hexokinase activation could be abnormal because of impaired phosphorylation by DMPK. A pacemaker study which enabled recording of cardiac rhythms showed complete atrioventricular block in 15 patients. Moreover while ventilatory functions were normal, without pathologic involvement of the ventilatory muscles, many episodes of desaturation of haemoglobin with central apnoea were observed suggesting a possible cause for sudden death (D. Duboc).

4.6. Proximal myotonic myopathy (PROMM)

Proximal myotonic myopathy (PROMM) is a newly (1994) described autosomal dominantly inherited multisystem disorder distinct but similar to DM. Extensive clinical experience confirms the earlier described phenotype: predominantly proximal muscle weakness without atrophy, muscle pain, cataracts, occasional mild or lacking clinical myotonia, elevated gamma-GT in the absence of other symptoms like gallbladder stones, elevated CK and lacking of CTG expansion. Until the identification of the mutation underlying the DM phenotype, many of these patients were classified as atypical DM patients. Once the DM mutation had been identified it was shown that they were indeed negative for the unstable (CTG)n repeat (and any other mutations in the DMPK gene) indicating that this is a different genetic disease entity. Because of genetic heterogeneity there is a need for a strict classification for Promm phenotype for molecular studies to be properly conducted (M.C. Koch, F. Lehmann-Horn).

5. Scientific aspects: conclusion

The key questions listed at the beginning of the workshop were re-examined and updated in the light of unpublished data presented by each participant. The first question was whether all clinical features of DM have been described and well-enough. With the discovery of the mutation in 1992, the natural history of the disease obviously needs to be redefined. Even the reference textbooks should be re-explored in view of the newly described PROMM. Brain pathology is certainly a new area of research. Brain features include formation of inclusion bodies, atrophy or tangles. DM patients are prone to develop tumours such as parotid tumours or gastrointestinal tumours. Have tissues like kidney, liver, or heart been well-described? The second question was whether the expansion is really the only mutation? How can one be sure it is DM when the patient did not have a repeat expansion. About 15 cases that were unequivocally diagnosed as DM, have definitely been sequenced and still come up with no mutation. The third question was whether

there is a developmental timing of the somatic expansion involved and whether the extent of the expansion depends on the cell type or on processes such as ageing. These questions can not be answered, yet.

It is important to define precisely the material and resources used in experiments to be able to compare results from different groups. The background of the strains of mice used for transgenic models should be described. The other questions concerning the CTG instability mechanisms and its implication in the complexity of variable clinical phenotypes are surely in progress but remain unresolved. However development of models such as *E.coli*, yeast, cell cultures and mice should soon give at least some of the answers. Establishing a data bank for clinical and experimental information/materials was proposed. AFM announced that it would help establishing the data bank and a website for DM to exchange information on resources and on expertise (B. Wieringa, R. Korneluk, K. Johnson, H. Epstein, T. Ashizawa, C. Junien).

6. Treatment, diagnosis and genetic counselling

R. Moxley and T. Ashizawa reviewed the clinical trials of treatments and underlined a unified clinical rating scale for DM both for establishing the natural history of DM and for future therapeutic trials (R. Moxley, T. Ashizawa). Patients may have a severe heart disorder and a high risk of sudden death even in the absence of muscle weakness. Therefore they have to be convinced to come for consultations. Cardiac guidelines for pacemaker therapy have to be better defined. M.T. Rogers presented a rating scale developed in Cardiff, UK. These protocols are to be used in a routine assessment with the aim that they can be transferred from doctor to doctor with reasonable reproducibility in quantitative data which will be suitable for long term longitudinal studies (M.T. Rogers). At the present time it is too early to formulate treatment strategies based on pathophysiology, since exact disease mechanisms have not been elucidated. However, R. Moxley and N. Ohsawa studied two endocrinologically derived drugs, troglitazone and dehydroepiandrosterone-sulphate DHEA-S, respectively. Unlike DHEA, DHEA-S has no hormonal activity, is a weak androgen, and has a much longer plasma half life. The drug has been in the market for several years in Japan with a good safety record. In a trial involving 11 patients for 8 weeks, improvements of Activity of Daily Living (ADL), muscle strength, clinical and electrical myotonia and cardiac conduction defects were documented. A multicenter trial is ongoing in Japan (N. Ohsawa).

One of the major achievements in DM in these recent years has been the powerful diagnostic tools now available for genetic counselling. A new long PCR-formatted protocol that allows the simultaneous identification of wild-type and large alleles (up to 4000 CTG) with a single amplification step was presented. Measurement of triplet expansion in chorionic villi sampling (CVS) is valuable and accurate for DM prognostic assessment during the first trimester of gestation and relevant for genetic counselling of this disease (M. Gennarelli). The invention of DNA diagnosis has brought forth various psychosocial and ethical issues. Many such problems in DM are unique and can not allow a simple application of guidelines established for other genetic disorders. With the leadership of M. Baiget, the consortium will draft the guidelines (M. Baiget). Ethical problems and financial issues concerning testing such as asymptomatic children and over-protective attitudes were also discussed.

The workshop achieved its intended goals by updating investigators with the current research status, generating new ideas, facilitating collaborations and establishing communications between basic and clinical scientists and, at last, proposing an AFM website to deal with data concerning the collection of resources, information on patients, material and guidelines for protocols.

7. List of participants

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