Considering Genetic Aspects of MND

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Why is Genetics of MND important?

• Can help answer why MND occurred/better understanding of disease mechanisms and potentially paves the way for better treatment/cure.

• Research

• Significant implications for family members

• Potentially offers family members choice regarding testing for themselves and in a pregnancy
MND - Multifactorial

Genetic susceptibility

Environmental Lifestyle/Occupation/die

Genetic Protective factors

Environmental Lifestyle/Occupation/diet
Genes + environment = effect
Step wise approach

6 Step Hypothesis

Time

1 2 3 4 5 6

MND
Familial MND

Environmental factors

Genetic
Specific gene alteration
What we know

5-10% of all cases of MND are familial
90-95% are sporadic

<table>
<thead>
<tr>
<th>Gene Mutation</th>
<th>% of pw FALs</th>
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</thead>
<tbody>
<tr>
<td>SOD1</td>
<td>15-20%</td>
</tr>
<tr>
<td>FUS</td>
<td>3-5%</td>
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<tr>
<td>TARDBP</td>
<td>3-5%</td>
</tr>
<tr>
<td>C9orf72</td>
<td>30-40%</td>
</tr>
<tr>
<td>NEK1</td>
<td>3%</td>
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</tbody>
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65-70% of cases of FALS will have an identified gene mutation
30-35% of cases do not have an identified gene mutation
Sporadic MND
90-95%

Familial MND
5-10%

- SOD1
- TDP-43
- FUS
- Unknown
- C9orf72
Back to basics
Chromosomes
Genes and DNA

- Chromosome
- DNA
- Gene 1
- Gene 2

The structure of DNA:
- Thymine
- Adenine
- Guanine
- Cytosine
Gene sequence

GGTTTTAGTT CTTCGAGAGT CACACCTCTTT ATTTGGACCA GTATAGACAG
AAGTAAACC ACCTGACTTG TTCTCTGAGA CAGTTTACGT AAAGGGATGCG
TTTCACAGAG CATCACCAGC TGACCTTTCA CGTCCGGGAC CTCTGTAGCC
GCTCTATCTG GCTGGGAAAG AAGATTTTGT CAGACTGAC TGCTCTGACG
GAATCCATAG TAAGTTTCCCT ATTTGTCTGT TA2CTGAAA A CCCCCATXX
XXXXXXXXXX XXCATGGGTA TGACAGAAGA TGTTGCTTTP TCCCTGATOC
TCGCGGAGGT GAAGCATTAG GGGTCTGACG MAACATGAAA CCTGGACTCT
GGGATGGGA TGCCAGTGGG ACAGCAGACT CAGTGACAG A GCCTGACCGA
GCCAGGGCCA CTCAGAGAGA ACCTTCAGGC TTATCTGACC TCCATGTTT
TGTTGGCAGG GCTCTTACGA GACCAGCAGG TGCAATTTAC CACCAGGAAA
GGTGACTTCC ATCAAGCTAT AGACTACCTT CTCTCCAGAC TGCTGCTCTT
TGCTATACAG ATAGAGGTCT TAATGACTT CCTGGAATAC AAGATGGCCG
CCATGAGGC TGAGGGATG GCTATTAAGT TGGAAGATGG TGCTCTCTT
GAGAAGAGGC TGTTGGGCTT AAGGTGCTG CAGAGGTACC CAGTGAGAAC
AGTAAGGTCC ATCCATGACC TTCTTTCAT TTCTCTCTAT CAGACTGGGA
TCGACAGCAG TGAGGGAGAT TAATGAGCT ACGACAGAAAA AAGGTGAGCA
TTAGCGCCTT CTCTCTCCT TGCTTTGCTT TCATAATGAAA TATGGGAGT
DNA - Proteins

... AGG – TTT - ACT – GGA – AGA....

AA    AA    AA    AA    AA    AA

PROTEIN

DNA
RNA (messenger)
Amino Acid
Protein
Mutation

- A gene mutation is a permanent alteration in the DNA sequence that makes up a gene, such that the sequence differs from what is found in most people. Mutations range in size; they can affect anywhere from a single DNA building block (base pair) to a large segment of a chromosome that includes multiple genes.

- Genetics home reference 26 Jul 2016
Mutations

Deletion
CCT-TAG-TCA-GTA-CGC-AGC – CCC
CCT-TAT-CAG-TAC-GC....

Insertion
CCT-TAG-TCA-GTA-CGC-AGC – CCC
CCT-TTA-GTC-AGT-ACG....
C9orf72

Repeats
normal
AGA...GGGGCCCGGGGCCC..(-30)..GGGGGCCC..TTC

mutated
AGA ...GGGGGCCGGGGCCC............(+30)...............GGGGGCCC..TTC
SOD1
Autosomal dominant inheritance

- mother
  - unaffected
- father
  - affected

50:50 chance the child will inherit the disease from the father
Genotype and Phenotype

• Genotype - the genetic makeup of an individual.

• Phenotype - the set of observable characteristics of an individual (appearance, development, and behaviour)
Penetrance - what is it? why is it important

Pedigree 2. An idealized pedigree demonstrating the effects of incomplete penetrance.
Penetrance

_Penetrance_ refers to the proportion of people with a particular _genetic_ change (such as a mutation in a specific _gene_) who exhibit signs and symptoms of a _genetic_ disorder. If some people with the mutation do not develop features of the disorder, the condition is said to have reduced (or incomplete) _penetrance_.

SOD 1-depends on mutation C9orf72 – almost full at age 80yrs
*(Chio 2016)*
What families need/want to know?

‘Role of genetic factors should be discussed with all patients with ALS’ (Talbot, 2014)

Often explored from the question ‘what causes MND?’ – multi-factorial answer including Genetics.

? preconceived ideas do family have
Is it Familial? - Family History

Does anyone else in the family have MND?
Parents – whether they have any muscle problems, problems with thinking/behaviour.
What they died of
Uncles and aunts/ sibs – any problems as above, any early dementia.
Also remember diagnosis difficult going back in time so M/S, PD, ‘in a wheelchair’
If it looks Familial -

What do we say?

Depends if they ask the question

Often they will have worked it out

What do we need to think about?

Managing anxiety/uncertainty in a situation where they may be already overwhelmed/information to give

What do we do?

Encourage discussion with Neurologist or refer to Genetics Department
Options for patient with MND with family history

- Choose not to look at genetic issues
- DNA testing
  - test positive for known MND mutation
  - test negative for known MND mutation

Patient needs to be aware of implications

?refer for Genetic Counselling

- DNA storage

Research/sporadic cases
Genetic testing – where does it sit?

• Genetic testing of those affected – what are benefits for patient/family?

• Genetic testing of those at risk (other family members) (Predictive testing)

  disclosing to the family
  (psychological/social/ethical/legal considerations)

MND clinic

Genetic Counselling
Genetic testing for family members at risk

Only if you have identified a gene mutation in an affected individual in the family

Refer to Regional Genetics Centre

- International Guidelines for Predictive testing in neurodegenerative conditions
- Penetrance
- Genetic counselling
Genetic counselling is the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease. This process integrates the following: Interpretation of family and medical histories to assess the chance of disease occurrence or recurrence. Education about inheritance, testing, management, prevention, resources and research. Counselling to promote informed choices and adaptation to the risk or condition.

National Society of Genetic Counselors
Options for family planning

• Normal pregnancy
• Decide not to have children
• Egg/sperm donation
• Adoption?
• Prenatal testing
• Pre-implantation genetic diagnosis (PGD)
Pre-natal testing

• Generally only offered where parent (with family history) has confirmed mutation.

• Counselling regarding outcome and action couple will take if result positive.

Psychological/ethical implications
Pre-implantation Genetic Diagnosis (PGD)?

• Combination of
  – In Vitro Fertilisation (IVF) techniques
  – Genetic diagnosis techniques
• 1 or 2 cells are removed from an 8 cell embryo
• These cells are then tested
• Only embryos that do not have the genetic condition are placed into the womb
Take home message

• It is complicated
• For pwMND and relatives - uncertainty
• Always make sure those affected individuals that your Consultant may be testing in your clinics are aware of the implications
• For those at risk who want genetic testing (where there is a known mutation in an affected relative) – refer to local Regional Genetics Department.
Project MinE (2014)

- Patient driven
- Global initiative (19 countries)
- Whole genome sequencing
  - Cost per genome $1,850
- Target 22,500 genomes worldwide
- MND Association target 2,200 (completion 2018/19)
Any Questions?