Teaching Course 3

Genetic counselling in neurogenetic disorders - Level 1

Counselling in neurogenetic disorders with autosomal dominant or recessive inheritance

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COUNSELLING IN NEUROGENETIC DISORDERS WITH AUTOSOMAL DOMINANT OR RECESSIVE INHERITANCE

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Genetic counselling is an information-giving process “by which patients or relatives at risk of a disorder that may be hereditary are advised of the consequences of the disorder, the probability of transmitting it and the ways it can be prevented, avoided or ameliorated” (Harper P. “Practical Genetic counselling”-1998).

Genetic counselling also includes investigative and diagnostic elements.

STEPS IN GENETIC COUNSELLING:

- **Establishing the diagnosis**: based on taking personal and family history, perform detailed examination and undertake appropriate investigations (referral to specialists; order appropriate genetic (chromosome-molecular) tests.
- **Pedigree charting and defining mode of inheritance**: if constructed with proper and complete information, the pedigree offers in a concise manner the state of the disorder in the family.
- **Estimating the risk**: based on the diagnosis and mode of inheritance, evaluating the risk of developing and/or transmitting the disorder.
- **Communicating the risk**: quantify and qualify the risk, discuss the choices or options available for dealing with it. Provide consultants with all information needed to arrive at their own informed decision, detail reproductive options, alternative approaches to conception, review of techniques, limitations and risks associated with methods available for prenatal diagnosis.
- **Ensure long-term contact and support**.

1) AUTOSOMAL DOMINANT AND RECESSIVE INHERITANCE: THE BASICS

All “autosomal genes” (i.e. genes not on the X or Y chromosomes) are present in pairs (termed “alleles”). One is inherited from the mother and one from the father.

Conflict of interest:
The author has no conflict of interest in relation to this manuscript
If the two alleles at a specific locus in a chromosome are different in sequence, the individual has an heterozygous genotype for this gene. If the allele is the same in the two chromosomes, the genotype at this locus is homozygous.

In the case of an HETEROZYGOUS GENOTYPE for a DOMINANT mutation, the mutation will be passed to 50% of offsprings on average:

In the case of AUTOSOMAL DOMINANT INHERITANCE, heterozygotes (with one copy of the abnormal gene) are affected (phenotype).

In the case of AUTOSOMAL RECESSIVE INHERITANCE, homozygotes (with two copies of the altered gene) are affected (phenotype).
In case of an HETEROZYGOUS GENOTYPE for a RECESSIVE mutation, the individual will be a carrier (generally healthy). Each child of two parents who are carriers for the same autosomal recessive disorder has a :

- 1/4 (25%) chance of neither being affected nor a carrier of the disease
- 1/2 (50%) chance of being a carrier of the mutation but unaffected
- 1/4 (25%) chance of inheriting both copies of mutated genes and thus the disease

For an individual that is known to be a carrier but whose partner is of unknown carrier status, the risk of affected offspring depends on the carrier rate in the population at large. For example, the carrier frequency for SMN gene deletion (causing in homozygosity the Spinal Muscular Atrophy (SMA) phenotype) in about 1 in 50. A couple who have had a child with SMA diagnosis have a 1 in 4 chance of having another affected child. However, if either parent (both carriers) decide to have children with an alternative unrelated partner, the risk of SMA recurrence will be 1 in 200.
2) AUTOSOMAL DOMINANT AND RECESSIVE INHERITANCE: INFORMATION FROM THE PEDIGREES

AUTOSOMAL DOMINANT INHERITANCE

- Females and males exhibit the trait in approximately equal proportions
- Males and females are equally likely to transmit trait to their offspring
- No skipping of generations: if an individual has the disease, one parent must also have it
- Vertical transmission pattern - disease phenotype is usually seen in one generation after another
- If neither parent has the trait, none of the children has it
- Father to son transmission may be observed

AUTOSOMAL RECESSIVE INHERITANCE

- Autosomal recessive diseases are usually seen in one or more siblings or as an isolated case but not in earlier generations (no vertical transmission)
- Parents of an affected subject are healthy
- Females and males are affected in equal proportions
- 1/4 of the offspring of two heterozygous carriers will be affected with the disorder
• Consanguinity is present more often in pedigrees involving AR inheritance than with other types of inheritance

3) FACTORS THAT MAY COMPLICATE THE DEFINITION OF INHERITANCE PATTERNS AND THE ESTIMATION OF RECURRENCE RISK:

- New mutation
- Germline Mosaicism
- Delayed age of onset
- Reduced penetrance
- Variable expression
- Locus Heterogeneity

I) NEW MUTATION VS INHERITED MUTATION

new mutation is a frequent cause of appearance of a dominant genetic disease in individual with no prior family history of the disorder; differently from an inherited mutation, recurrence risk for individual’s siblings is very low. May be substantially elevated for individual’s offspring.

II) GERMLINE MOSAICISM

mosaic is an individual who has more than one genetically distinct cell lines in his or her body, germline mosaicism occurs when all or part of a parent’s germline is affected by a disease mutation but somatic cells are NOT affected. Two or more offspring will present with an autosomal dominant disease when there is no family history of disease. Because mutation is rare
event, it is unlikely that this would be due to multiple mutations in the same family. This event elevates recurrence risk for future offspring of mosaic parent.

An example of **PATERNAL GERMLINE MOSAICISM: COLLAGEN VI RELATED MYOPATHIES**

A case of recurrence of Ullrich congenital muscular dystrophy in two girls, half-sibs from healthy parents. In both affected subjects genotyping revealed the presence of the COL6A1 (one of the three genes encoding for Collagen type VI, an important component of extracellular matrix) p.Gly299Glu mutation in exon 10 apparently arising *de novo* (not present in parents). Mutation segregation in the family strongly suggested the presence of mosaicism in father’s gonadal cell lines (germline mosaicism).

![Family tree showing segregation in half-sibs of COL6A1 gene variation causing Collagen VI-related myopathy.](image)

The occurrence of mosaicism in gonads has important implications in pre-natal genetic counselling. In fact, in case of an apparently *de novo* dominant mutation, the recurrence risk for future pregnancies is empirically estimated in about 1%, and the application of invasive pre-natal procedure, implying a risk of miscarriage, is questionable. A different scenario arise when, for a specific disease, the actual possibility of gonadal mutations has been demonstrated. In these cases, even if a precise risk figure is lacking, invasive prenatal diagnosis could be justified as an option for future pregnancies.

**III) DELAYED AGE OF ONSET AND REDUCED PENETRANCE**

Delayed onset in autosomal dominant diseases can cause difficulty in deducing mode of inheritance because it is not possible until later in life to determine whether an individual carries a
mutation. Examples are Huntington Disease; Familial Alzheimer disease; Polycystic kidney disease).

Reduced (or incomplete) penetrance means that some individuals with a particular disease-causing mutation or genotype fail to express most if not all features of the disease in question, even though they can transmit the disease gene to the next generation.

IV) VARIABLE EXPRESSION

Penetrance may be complete, but severity of autosomal dominant disease can vary greatly. An example is neurofibromatosis type 1 (NF1) Parent with mild expression of disease (so mild they may not know they carry gene), can transmit gene to child who can have severe expression. Variable expression provides a mechanism for disease genes to survive at higher frequencies in populations.

V) LOCUS HETEROGENEITY

Disease that can be caused by mutations at different loci in different families is said to exhibit locus heterogeneity; disease states are often indistinguishable.

In case of marriage of two individual affected by the same autosomal recessive all offspring are expected to be affected, considering that both parents will transmit the mutated gene (a) with 100% probability.

In case of genetic heterogeneity, the disease being due to different genes in the parents, all offspring will be unaffected and carriers of both mutated genes (a and b)
4) OBLIGATE CARRIERS IN AUTOSOMAL DOMINANT AND RECESSIVE INHERITANCE

Autosomal dominant inheritance: any individual who has an unaffected parent and an affected child is obligate carrier of the disease mutation (even if can be unaffected due to incomplete disease penetrance.

Autosomal Recessive inheritance: both parents and all offspring of an affected individual are obligate carrier of the disease mutation.

5) EMERGING CONCEPTS

In the recent years, the wide application of next generation sequencing technologies (gene panels, exomes, genomes) has provided new insights into the molecular mechanisms underlying complex scenarios in autosomal dominant and recessive inheritance models.

I) MOLECULAR MECHANISMS OF REDUCED PENETRANCE:

Large scale sequencing and genotyping studies in the general population (as is the 1000 Genomes Project) have shown that a typically healthy individual harbors a quite large number (80-100) of potentially disadvantageous variants without suffering any obvious ill effects. Thus “reduced penetrance” came out to be much more common among described disease-causing mutations that originally thought. This is particularly frequent for dominant mutations, but apply also to some autosomal recessive disorders.

Many and varied mechanisms underlie the phenomenon of incomplete clinical penetrance:

• the mutation itself for a given disease, some causal mutation may exhibit complete penetrance, whereas other mutations in the same gene show incomplete or even very low penetrance. Clinical penetrance may vary with the mutation type (i.e in dominant negative effect, missense mutations are more detrimental than truncating mutations) or with the
location of the mutation in the gene/protein. Triplet repeat expansion mutations show reduced penetrance of allele of intermediate size.

- Presence of a second pathogenic mutation on the same allele (in cis) can enhance the effect of the phenotype of a low-penetrance missense mutation.

- In disease exhibiting locus heterogeneity, clinical penetrance may vary between mutations in different genes.

- Some allelic variants may influence the expression of their host gene so as to alter the penetrance of a potential pathological mutation in the same gene (functional polymorphisms with modulatory effect).

- Allele dosage: for most “dominant” disorders in which homozygous have been reported, their clinical symptoms tend to be significantly more severe than in the heterozygotes (i.e. patients homozygous for sodium channel mutations causing autosomal dominant myotonia and paramyotonia congenital (SCN4A, CLCN1) display much more severe clinical features than heterozygous for the same mutations).

- Copy number variations (CNVs). A mutant gene can be functionally “compensated” by the existence of duplicated sequences providing a back-up wild-type copy of the gene. (i.e. increased copy number of SMN2 gene, partially able to functionally compensate the loss of SMN1 gene, can greatly reduce the severity of Spinal muscular atrophy).

- Modifier genes: rare and common variants in unlinked genes serve to modulate the clinical penetrance of specific disease.

- Digenic mutations: the interaction of mutations in two different genes is required for expression of the clinical phenotype (digenic inheritance sensu stricto) or is responsible for a more severe phenotype, each single mutation alone being associated with a milder form of the disease (digenic inheritance sensu lato).

- Sex dependence: sex specific genomic architecture can influence the expression of human phenotypes, including disease traits. It is likely that the underlying mechanism is differential gene regulation in males and females, mainly in relation to sex steroid-responsive genes.

- Epigenetic influences: epigenetic modifications can account for incomplete penetrance (i.e monozygotic twins discordant for disease phenotype)
• **Gene environment interaction:** the environment will often influence clinical penetrance, either ameliorating or exacerbating the impact of heritable genetic variants (i.e. cancer susceptibility; Parkinson disease; psychological disorders).

![Diagram showing factors affecting penetrance](image)

*from: Cooper DN et al., Hum Genet 2013; 132:1077-1130*

II) **MUTATION LOAD AND PHENOTYPIC VARIABILITY: the example of neuropathies**

Charcot Marie Tooth (CMT) disease is a common hereditary peripheral neuropathy with an estimated prevalence of 1 in 1200 individuals. Most patients present with an apparently sporadic disease, attributable partially to the extreme clinical variability and age dependent penetrance of the phenotype. More than 40 genes are known to be causative. In a recent study, whole exome sequencing (the sequence analysis of all exons of known coding genes) was performed in patients with peripheral neuropathies: in most patients the primary causative variant in a known gene was identified but potential contributing or modifying variants in other neuropathy associated genes also emerged as far more frequent in patients in respect to healthy controls.

![Graph showing mutation load](image)

*The “mutation load” (i.e., the contemporary presence of multiple nonsynonymous rare variants in the same patient) in CMT genes is significantly greater than the background load in unaffected control.*

*from: Gonzaga-Jauregui C et al., Cell Rep., 12(7):1169-1183*
This mutation load probably influences the phenotype contributing to the clinical heterogeneity and the spectrum of severity observed in neuropathies. The combinatorial effects of rare variants in genes that interact genetically in the same biological pathway can modulate the penetrance and/or the expressivity of the overall phenotype.

III) RANDOM MONOALECILIC EXPRESSION OF AUTOSOMAL GENES

Genes are generally expressed from their two alleles, except in case of random inactivation of one of the two X chromosomes in female mammals or imprinted genes which are expressed only from the maternal or paternal allele.

A phenomenon only partially unraveled is Random Monoallelic Expression (RME) of autosomal genes: genes located on autosomes that are stably expressed in a random and clonal (differently in different cells and cell types) fashion from either the paternal or maternal allele.

Several genes for which a RME has been established experimentally are associated to autosomal dominant diseases, and this evidence might have major implication in diseases expressivity and age-related penetrance.

Two examples of genes for which protein dosage is critical in vivo and have been reported to show RME in vitro are APP (amyloid beta precursor protein) and SNCA (alpha-synuclein) implicated respectively in Alzheimer’s and Parkinson’s diseases. In case of the occurrence of a RME of these genes in relevant brain region (currently unexplored in vivo), effects could be important. In both cases, excess protein levels are known to be detrimental, leading to formation of amyloid plaques in the case of APP in Alzheimer’s disease and Lewy’s bodies in the case of SCNA and Parkinson disease. Therefore if such genes are frequently monoallelic in the brain, epigenetic alterations, for example during aging, might lead to a dysregulation of RME mechanisms and an increase of gene dosage which could potentially trigger the disease (age-related penetrance).