The approach of the patient with a potential neurogenetic disorder

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Disclosure slide

- The speaker has no conflict of interest to disclose

Case report

- History
  - Muscle weakness and pain since childhood
  - Anxiety
  - Burnout syndrome
- Present complains
  - fluctuating tremor
  - panic attacks
  - Worsening of the muscle symptoms
    - Exercise intolerance, myalgia, weakness
- Neurological investigations
- Dystonia fingers right
- Sensory deficits right

Case report

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- Sensory deficits right

Fear of Parkinson, like in her Father

The approach of the patient with a potential neurogenetic disorder

Learning objectives

- To increase awareness about the basic approach to patients with potential neurogenetic disorders
- To know the basic principles involved in neurogenetic counselling
- To understand the place of molecular genetic testing in neurogenetic disorders

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Plan

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Body System	Count
Cardiac disorder	24
Endocrine disorder	34
Eye disorder	44
Gastrointestinal disorder	31
Haematological disorder	353
Mental handicap disorder	22
Metabolic disorder	234
Miscellaneous disorder	69
Neurological & neuromuscular disorder	588
Psychiatric disorder	3
Renal disorder	35
Respiratory disorder	25
Skeletal & craniofacial disorder	72
Skin disorder	46

High probability to encounter a genetic disorder

The neurological history

- Age, sex, handedness, occupation
- Present complain
- Neurological screening questions
- Past medical history
- Drug history

- Social history

The neurological history

- Age, sex, handedness, occupation
- Present complaint
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Family history

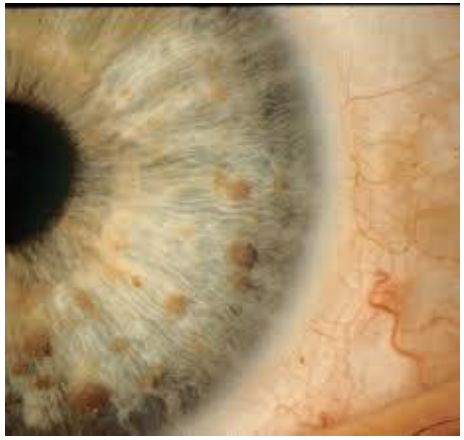
Solve differential diagnosis

Understand aetiology

Avoid unnecessary investigations

Genetics?

- Patients‘ query
- Knowledge
  - Media
  - Internet
- Risk for relatives to have the same disorder?
- Examination delivers genetic diagnosis (not only DNA testing)



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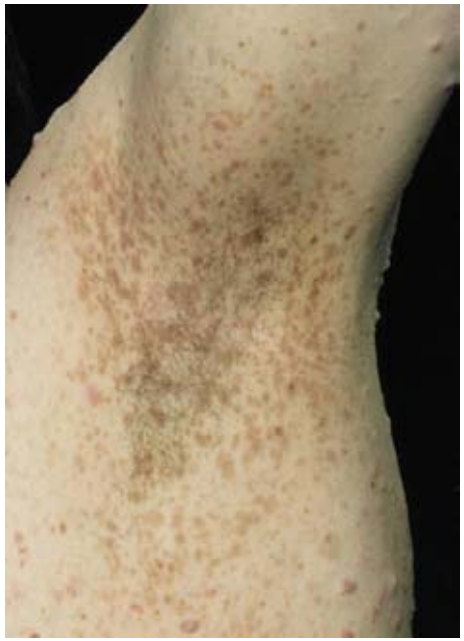

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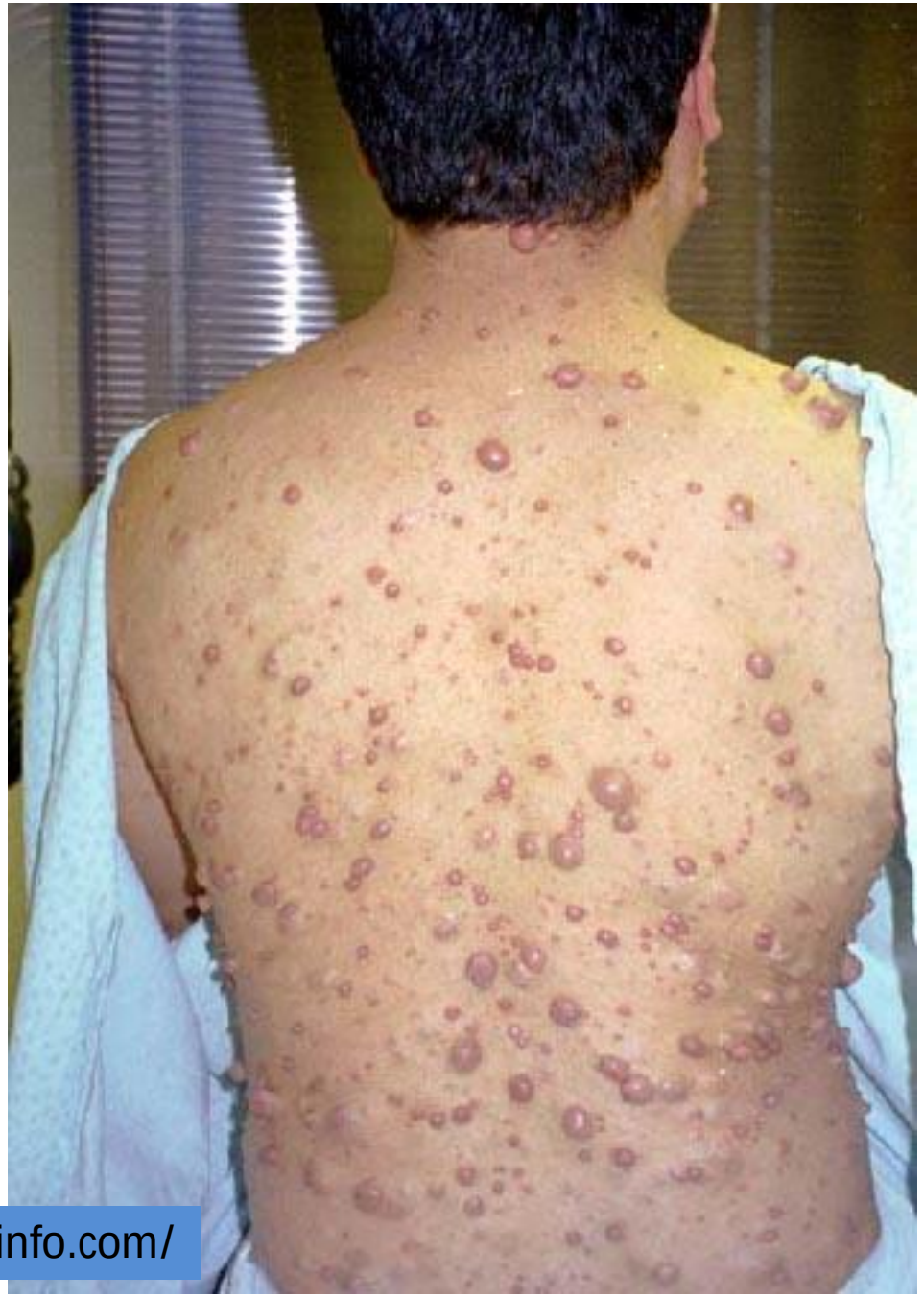

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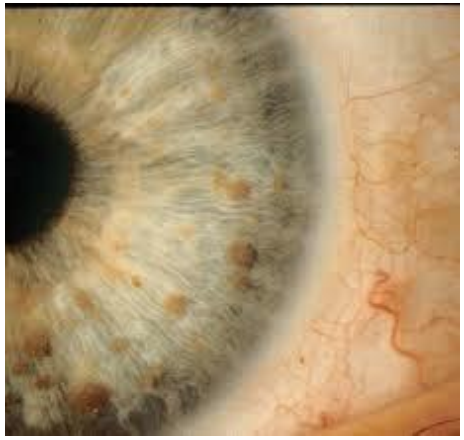

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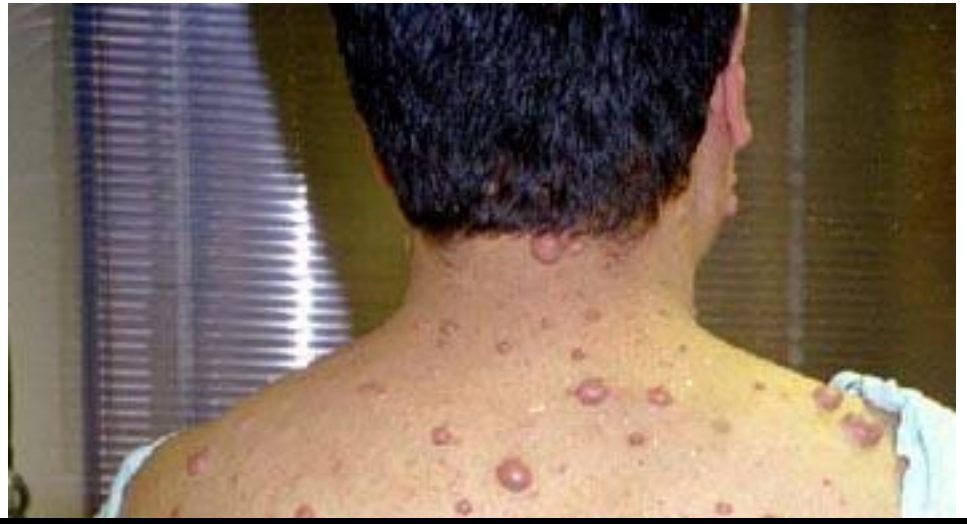

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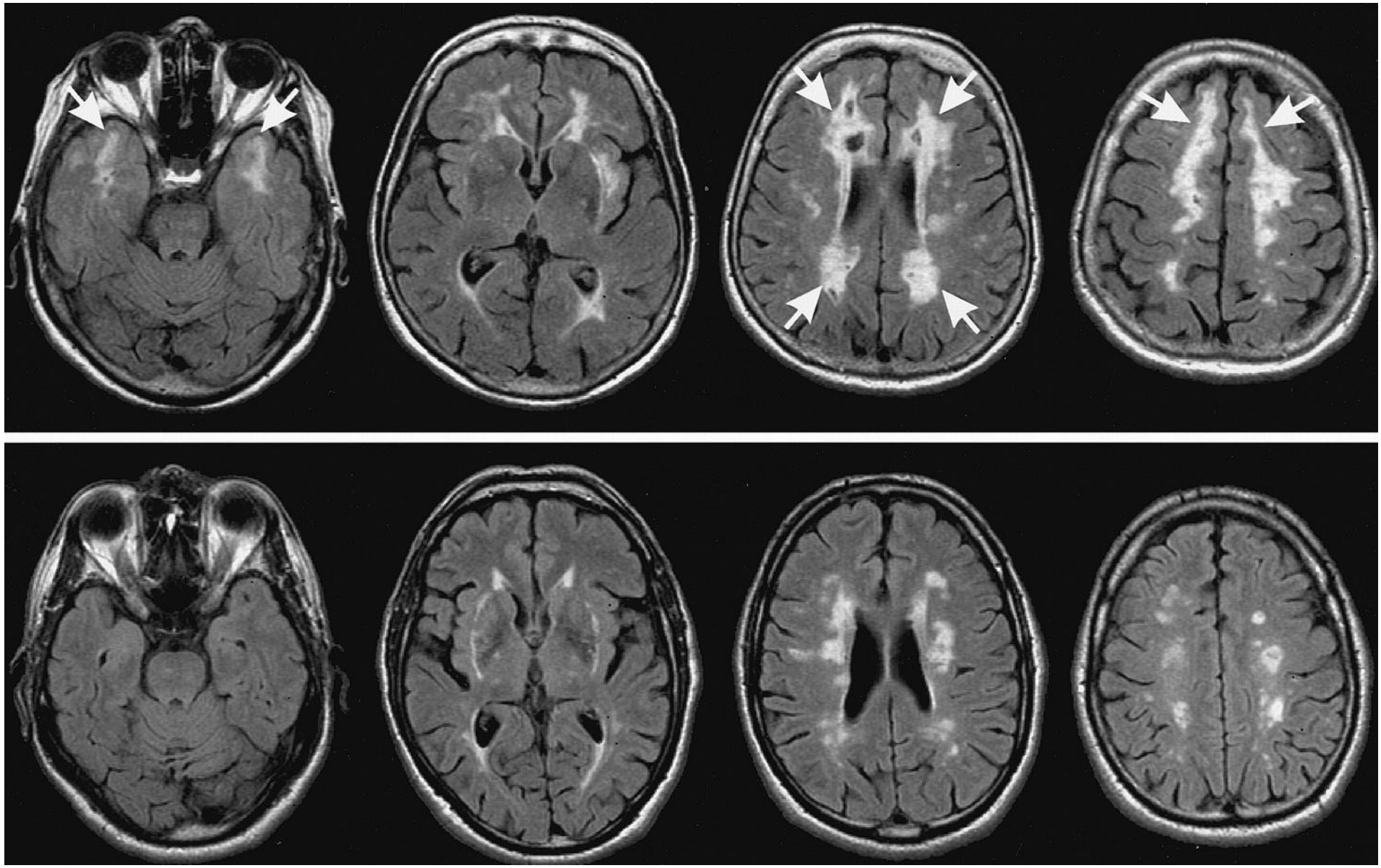
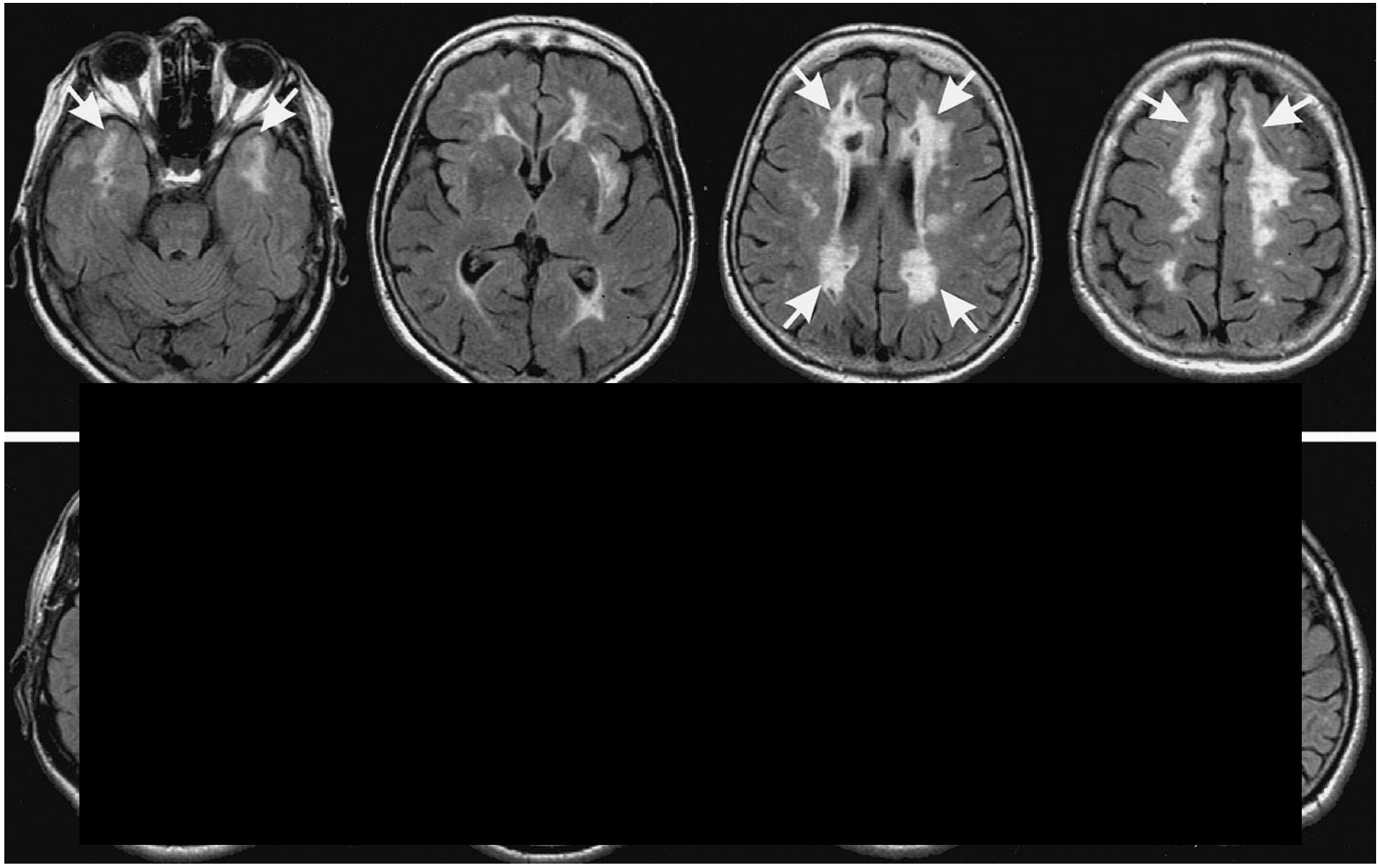


http://radiology.rsna.org



http://radiology.rsna.org

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Aims of genetic counselling (EuroGentest Network of Excellence)

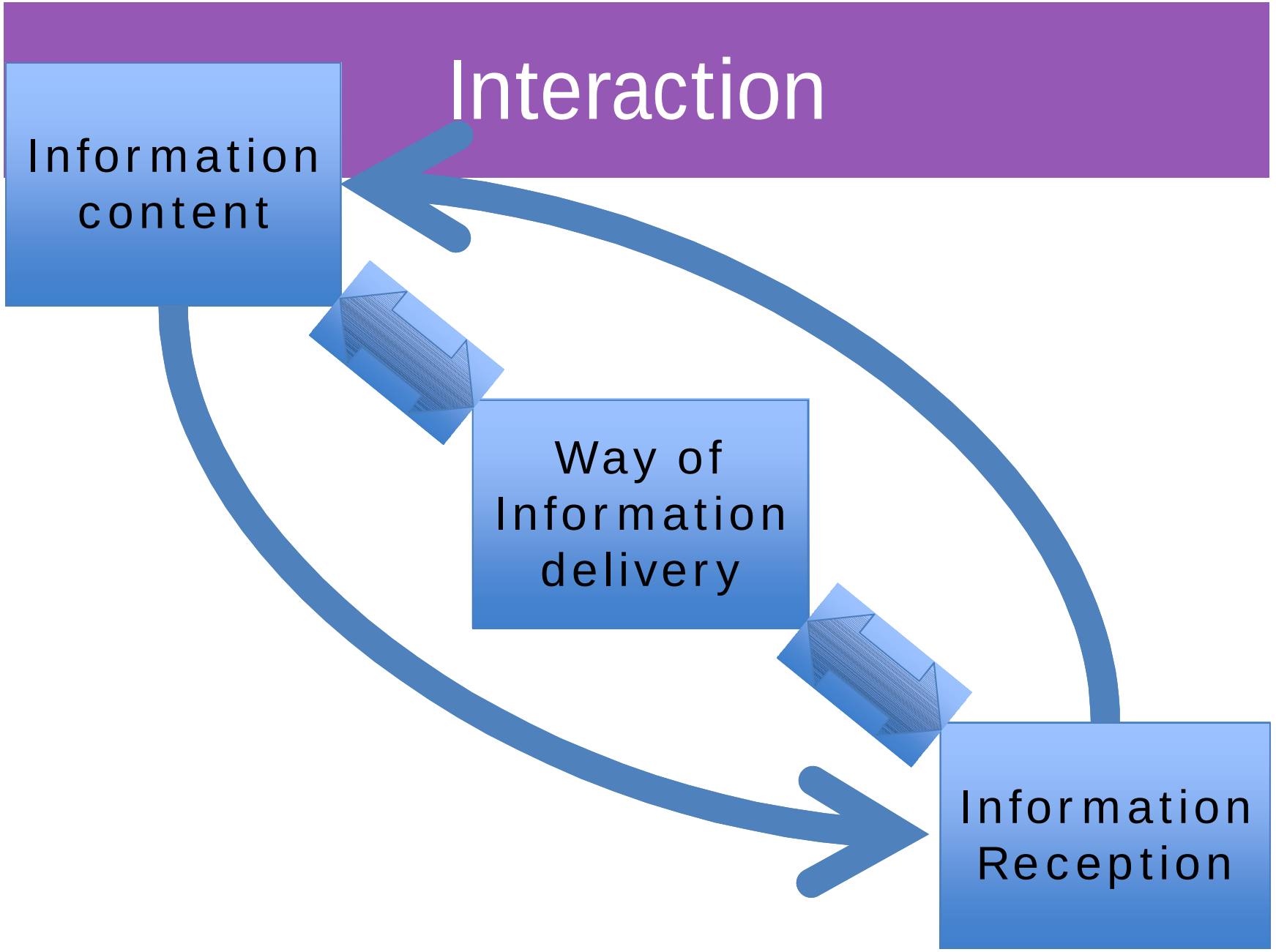
- Understand the medical facts of the disorder
- Appreciate how heredity contributes to the disorder and the risk of recurrence in specified relatives
- Understand the options for dealing with the risk of recurrence
- Use this information to make choices in adjustments

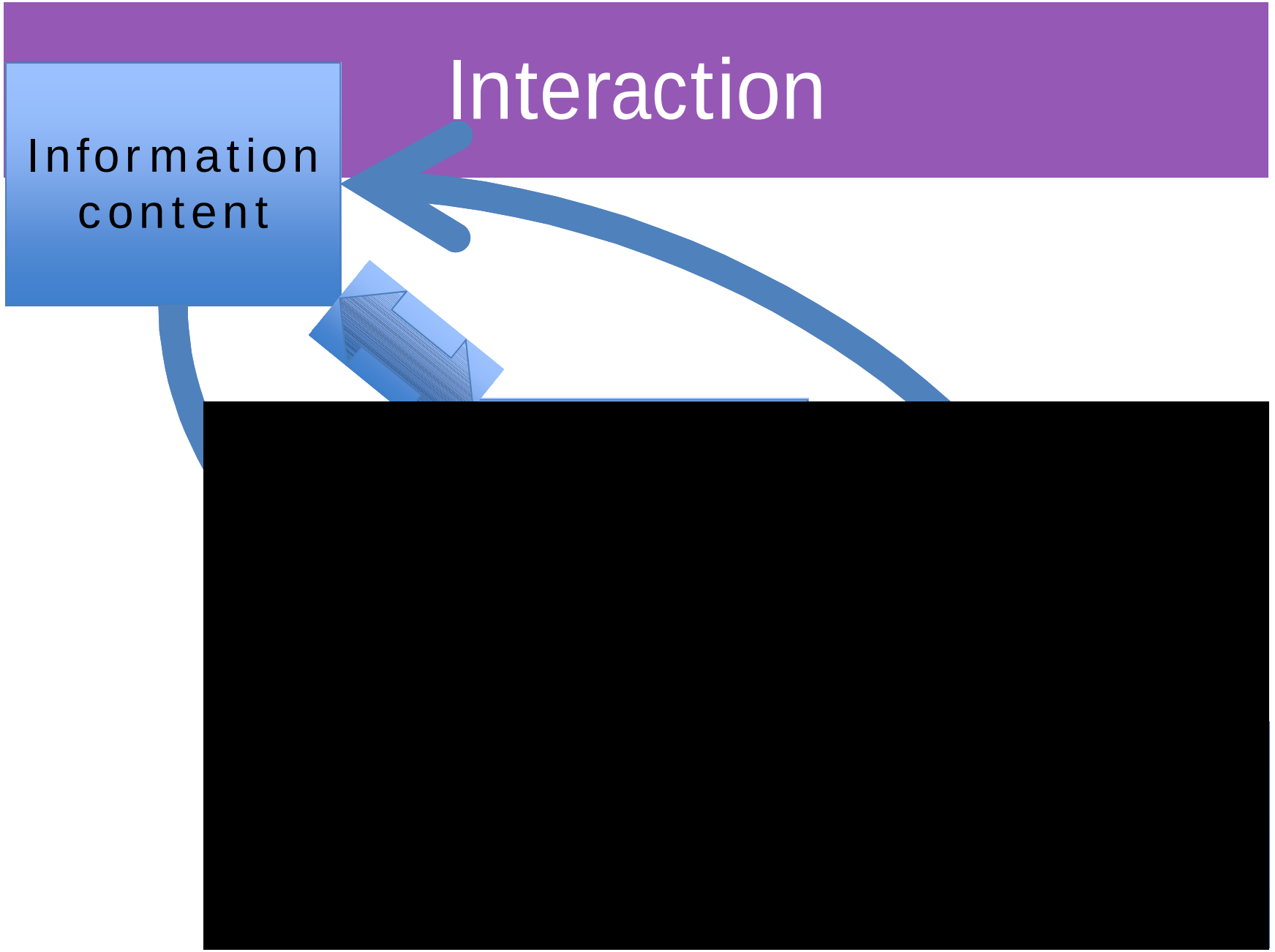
Counsellor

- Appropriate training and knowledge
  - genetic aspects of the disease
  - mode of inheritance
  - epidemiological aspects
  - specific features (neurological and general)
    - age at onset
    - course
    - phenotypical presentation
    - possibilities of treatment

Counselee

- Autonomy
  - decision taking
  - searching information
  - other aspects of the interaction
  - decision to know or not to know
  - Respected also by relatives


Interaction
Information content
Way of Information delivery
Information Reception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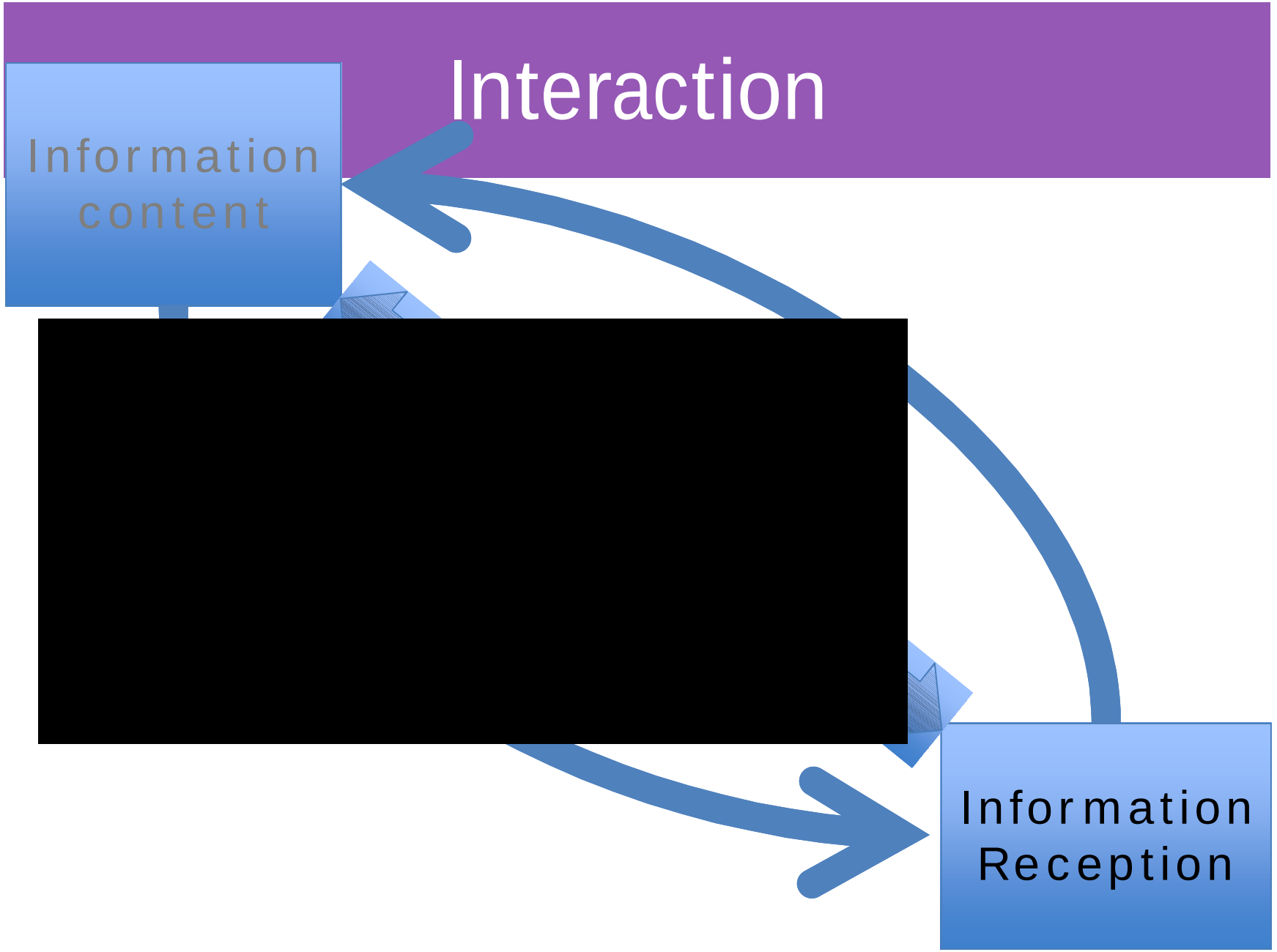
Interaction
Information content
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Information Reception

Consent

- Expression of the autonomy in taking decision
- Continuously assessed
- Informal way
- Observe knowledge reception
- Finally (before blood sampling for genetic test) in written form

Genetic Counselling

- Non directive, patient-family oriented approach
- Take time to explain
- Confidentiality
- Pitfalls!

„Genetic testing“
Issues and concerns

- Psychological distress
- Problems with disclosure to the relatives
  - Their own risk
  - Proof of carrier status in an AD disorder
  - Paternity?
- Confidentiality
  - information about genetic result is privileged
  - Disclosure only upon specific consent
- Potential of discrimination

Types of genetic testing situations

- Diagnostic testing
- Pre-symptomatic testing
- Gene carrier testing
- Prenatal testing
- Preimplantation genetic diagnosis
- Research tests
- Genetic association/Susceptibility testing
- Pharmacogenetic testing

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„Genetic testing“
Legal aspects

810.12

Bundesgesetz
über genetische Untersuchungen beim Menschen
(GUMG)

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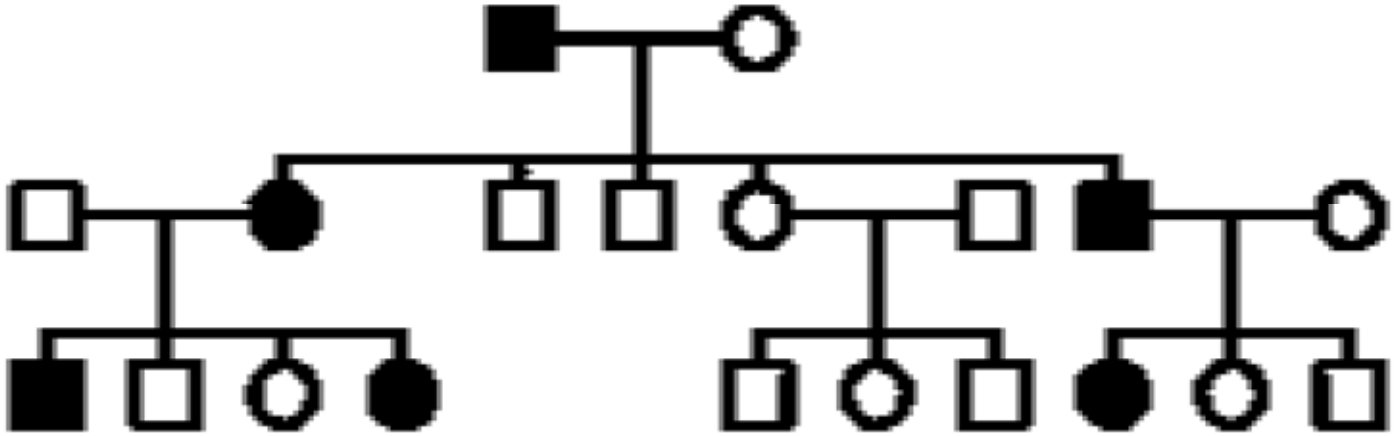
General approach in a case of possible neurogenetic disorder

- Thorough clinical assessment
  - History
  - Family history
    - If possible also taken directly from family members
  - Examination
    - neurological
    - cognitive testing
    - psychiatric evaluation
    - internal

Interpreting a pedigree



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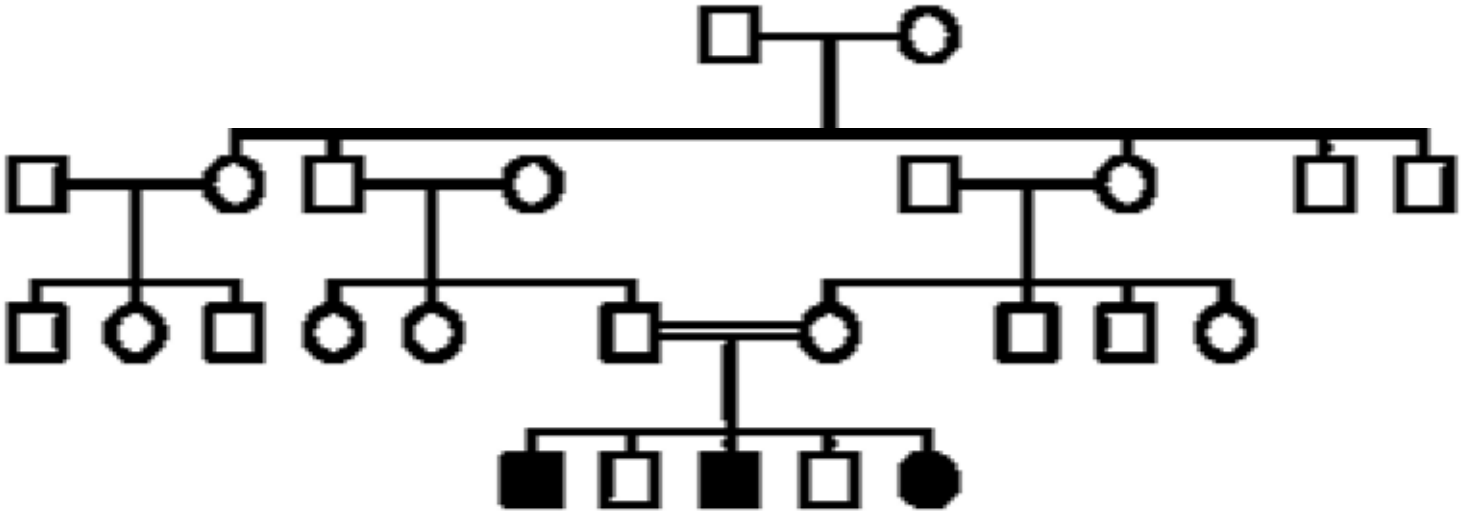

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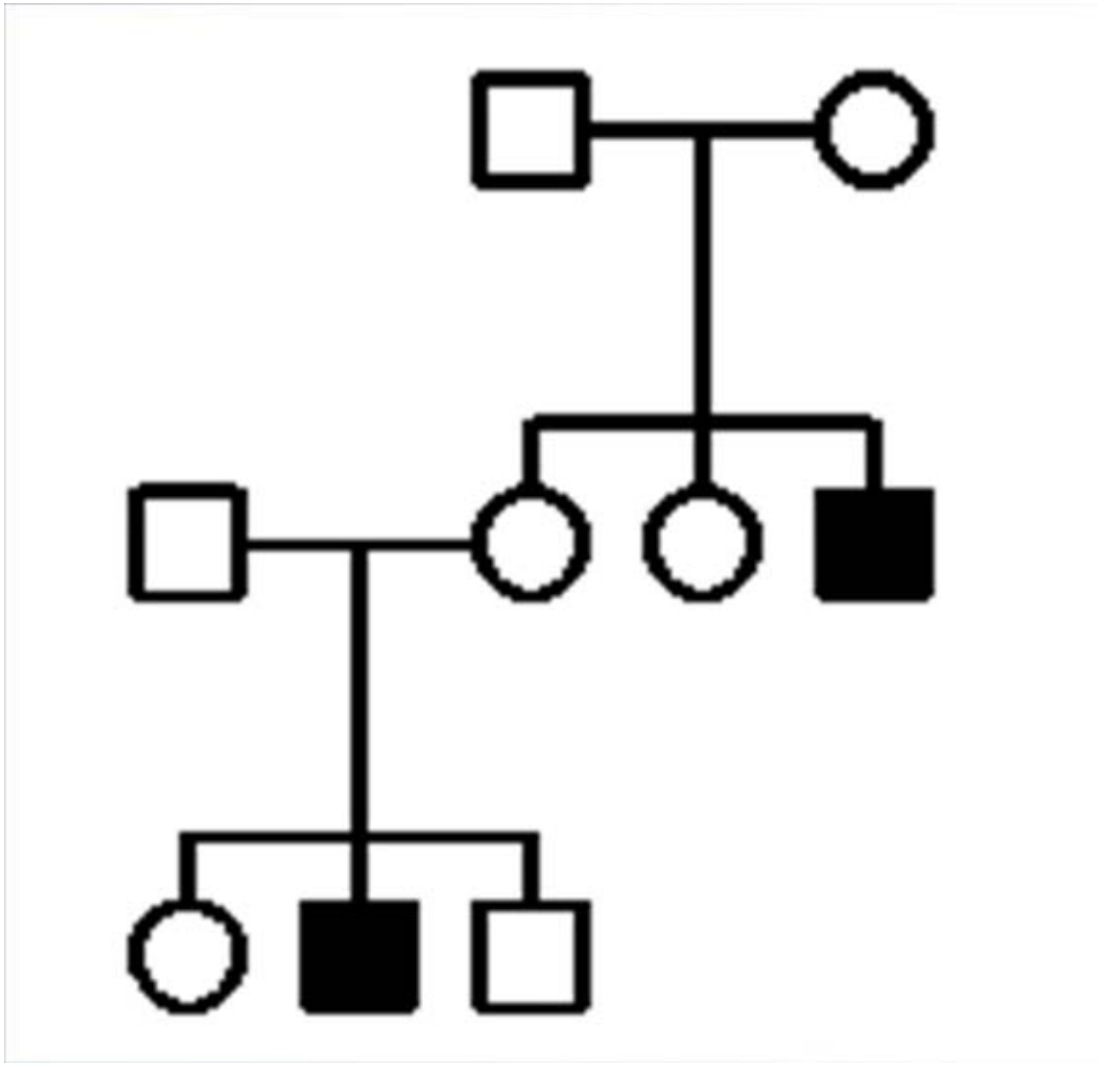

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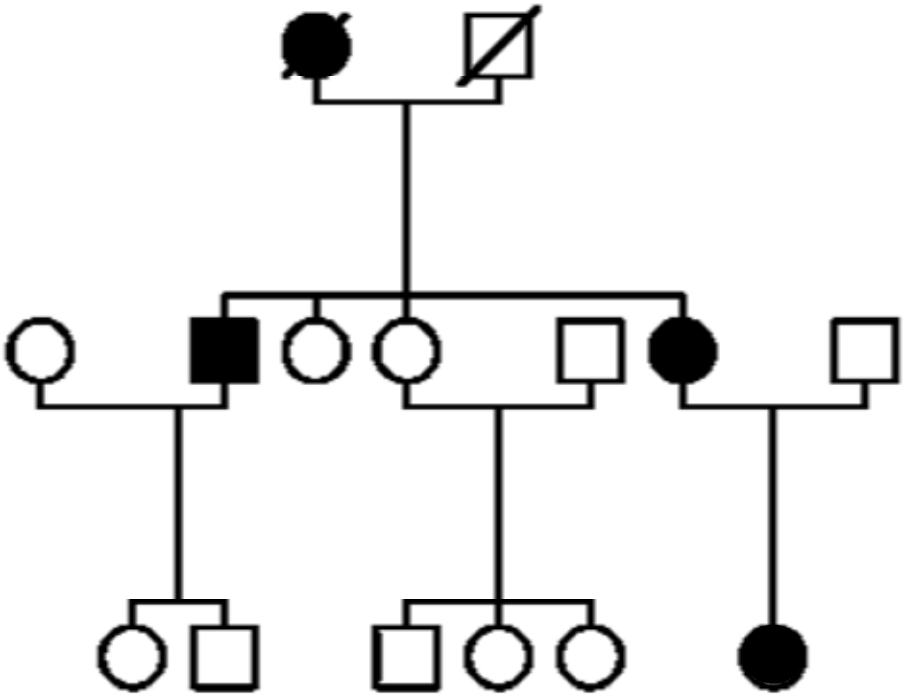

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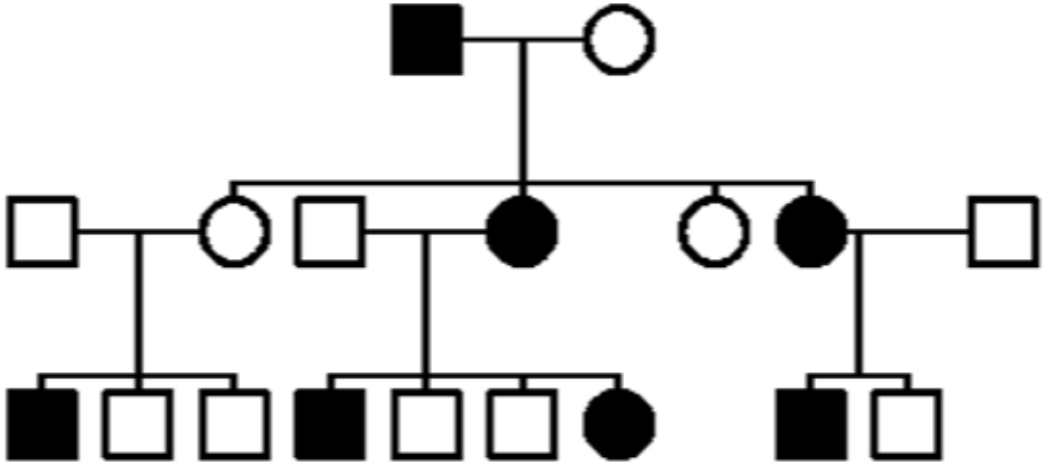
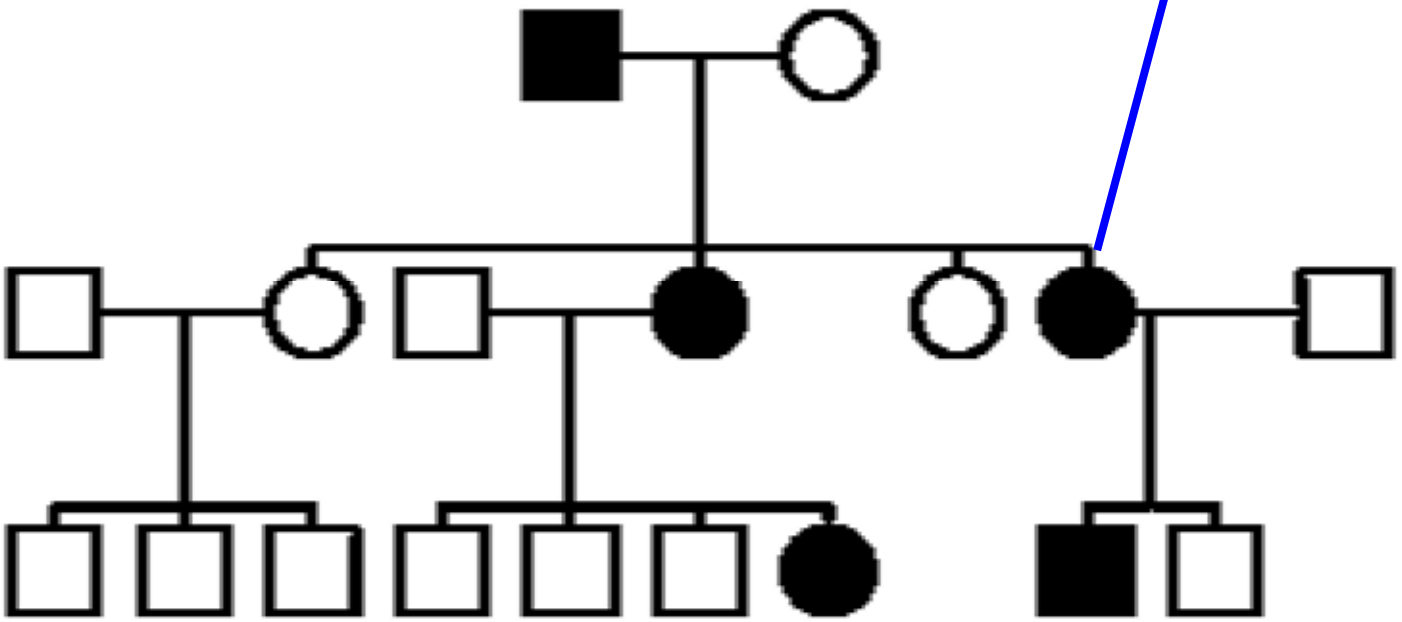
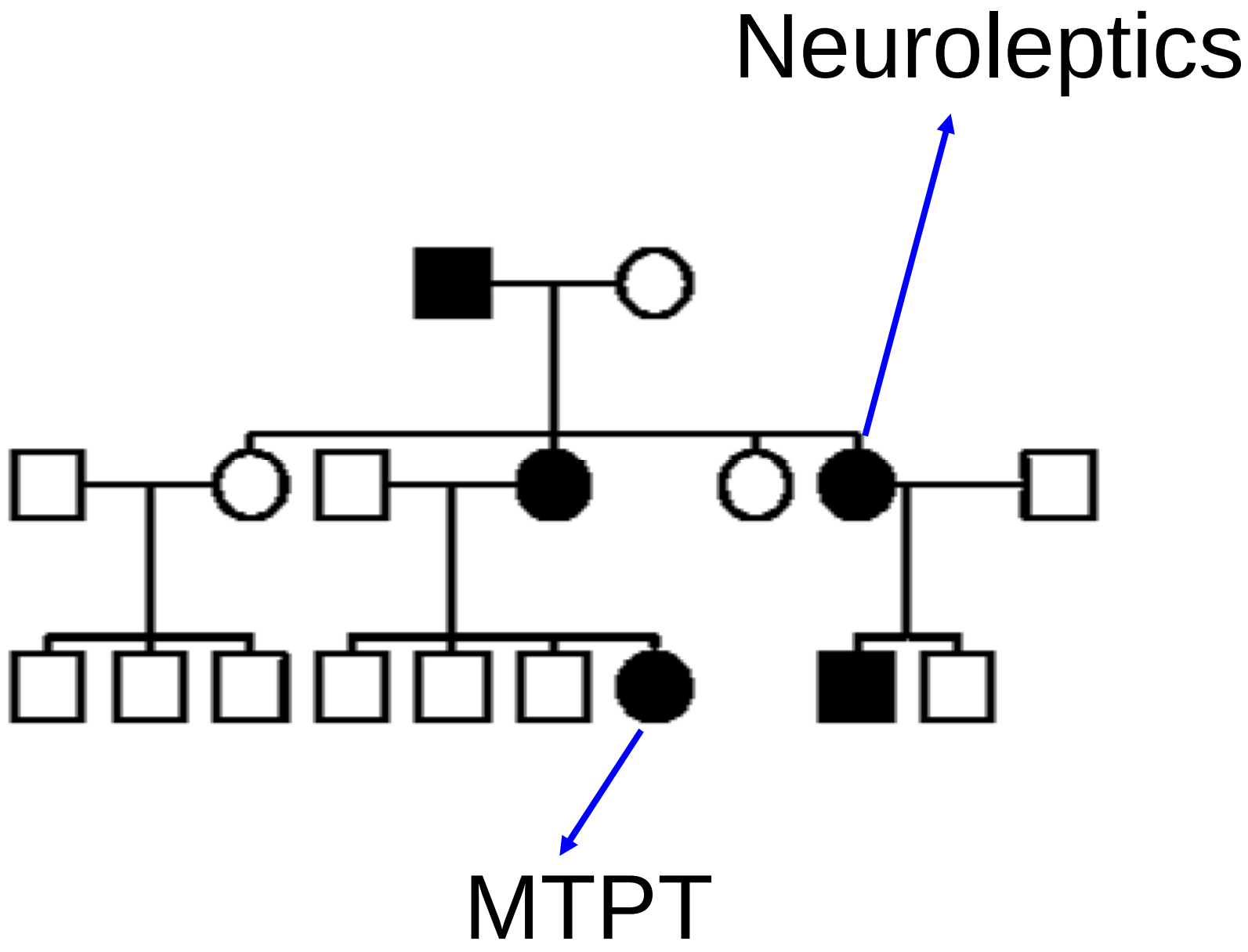
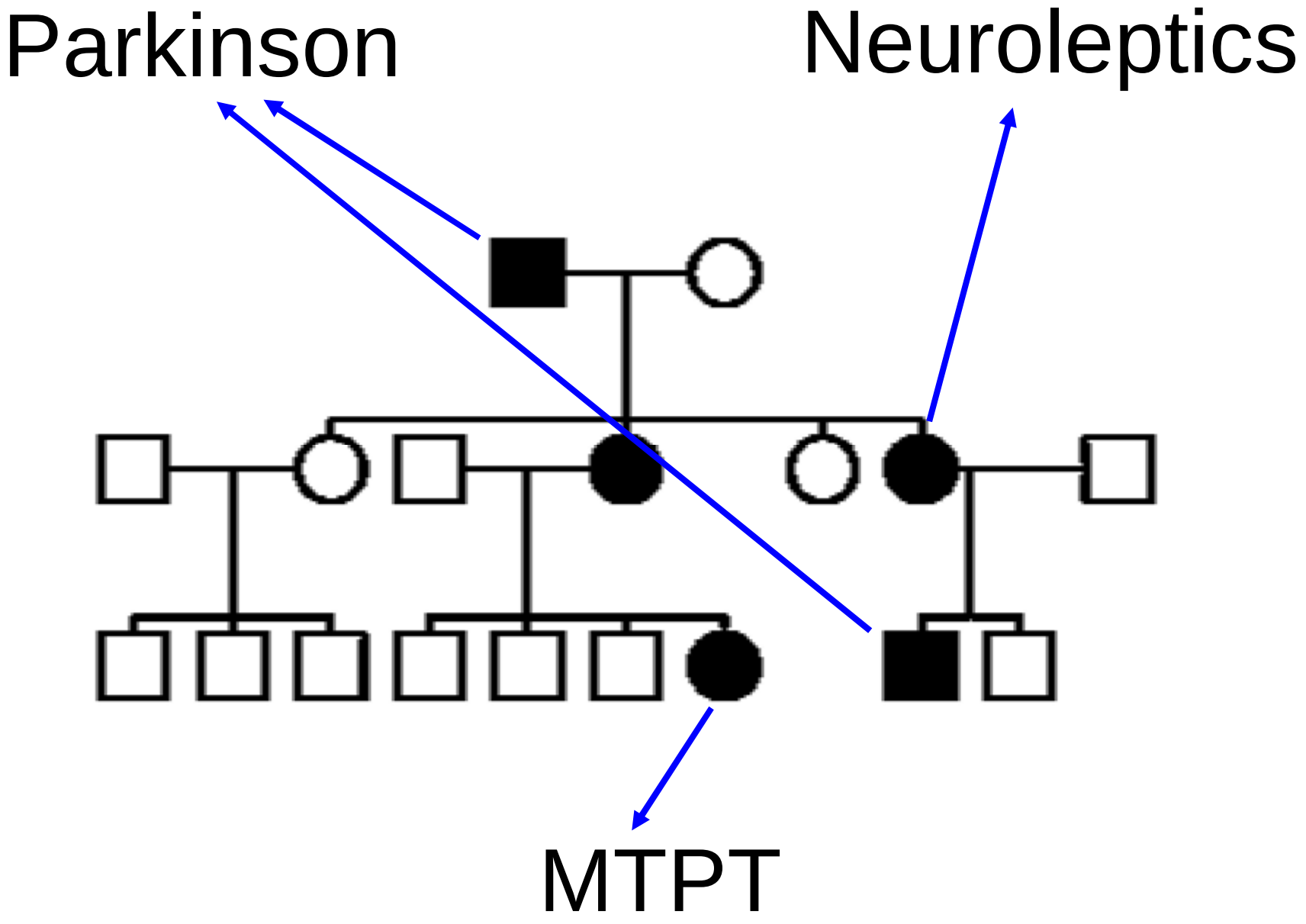


Neuroleptics




Neuroleptics
MTPT


Parkinson
Neuroleptics
MTPT

Difficulties in the interpretation of a pedigree

- Phenocopies
- Variable penetrance
- Phenotypical variation
- Wrong paternity
- Inheritance from both parents

General approach in a case of possible neurogenetic disorder

- Thorough clinical assessment
  - History
  - Family history
    - If possible also taken directly from family members
  - Examination
    - neurological
    - cognitive testing
    - psychiatric evaluation
    - internal

General approach in a case of possible neurogenetic disorder

- Targeted laboratory evaluation
  - According to differential diagnostic equation
- Imaging
- Neurophysiological investigations

- Evaluation of genetic testing
  - Clear hypothesis
  - Availability
  - costs
  - Consequences for management

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The choice of a genetic test

Analyse information

- Phenotype
  - Age at onset
  - Course
  - Symptoms
  - Signs
  - Additional investigations
- Family history
  - Pedigree
  - Phenotype
- Prevalence
  - Disorder
  - Gene mutation
  - Regional – Ethnic differences
- Test resources
  - Cost
  - Availability

European Journal of Neurology 2009, **16:** 777–785 doi:10.1111/j.1468-1331.2009.02646.x

EFNS GUIDELINES/CME ARTICLE

EFNS guidelines on the molecular diagnosis of neurogenetic disorders: general issues, Huntington's disease, Parkinson's disease and dystonias

European Journal of Neurology 2010, **17:** 179–188 doi:10.1111/j.1468-1331.2009.02873.x

EFNS GUIDELINES/CME ARTICLE

EFNS guidelines on the molecular diagnosis of ataxias and spastic paraplegias

European Journal of Neurology 2010 doi:10.1111/j.1468-1331.2010.02985.x

EFNS GUIDELINES

EFNS guidelines on the molecular diagnosis of channelopathies, epilepsies, migraine, stroke, and dementias

European Journal of Neurology 2009, **16:** 1255–1264 doi:10.1111/j.1468-1331.2009.02811.x

EFNS GUIDELINES/CME ARTICLE

EFNS guidelines on the molecular diagnosis of mitochondrial disorders

European Journal of Neurology 2010 doi:10.1111/j.1468-1331.2010.03069.x

EFNS GUIDELINES

EFNS guidelines for the molecular diagnosis of neurogenetic disorders: motoneuron, peripheral nerve and muscle disorders

Information sources

- http://www.genetests.org/
- http://www.omim.org/
- http://www.orpha.net/consor/cgi-bin/index.php
- http://www.journalofneurogenetics.org

Myotonic dystrophy

- Prevalence: 1 / 8000
- Progressive weakness atrophy
- Myotonia
- AV block
- Cardiomyopathy
- Cataract
- Testicular failure
- Sleep disorder- Fatigue
- Neuropsychological changes

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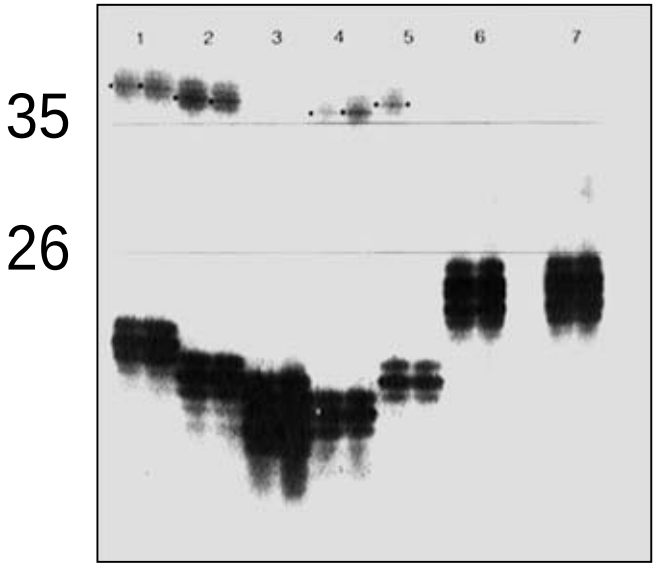
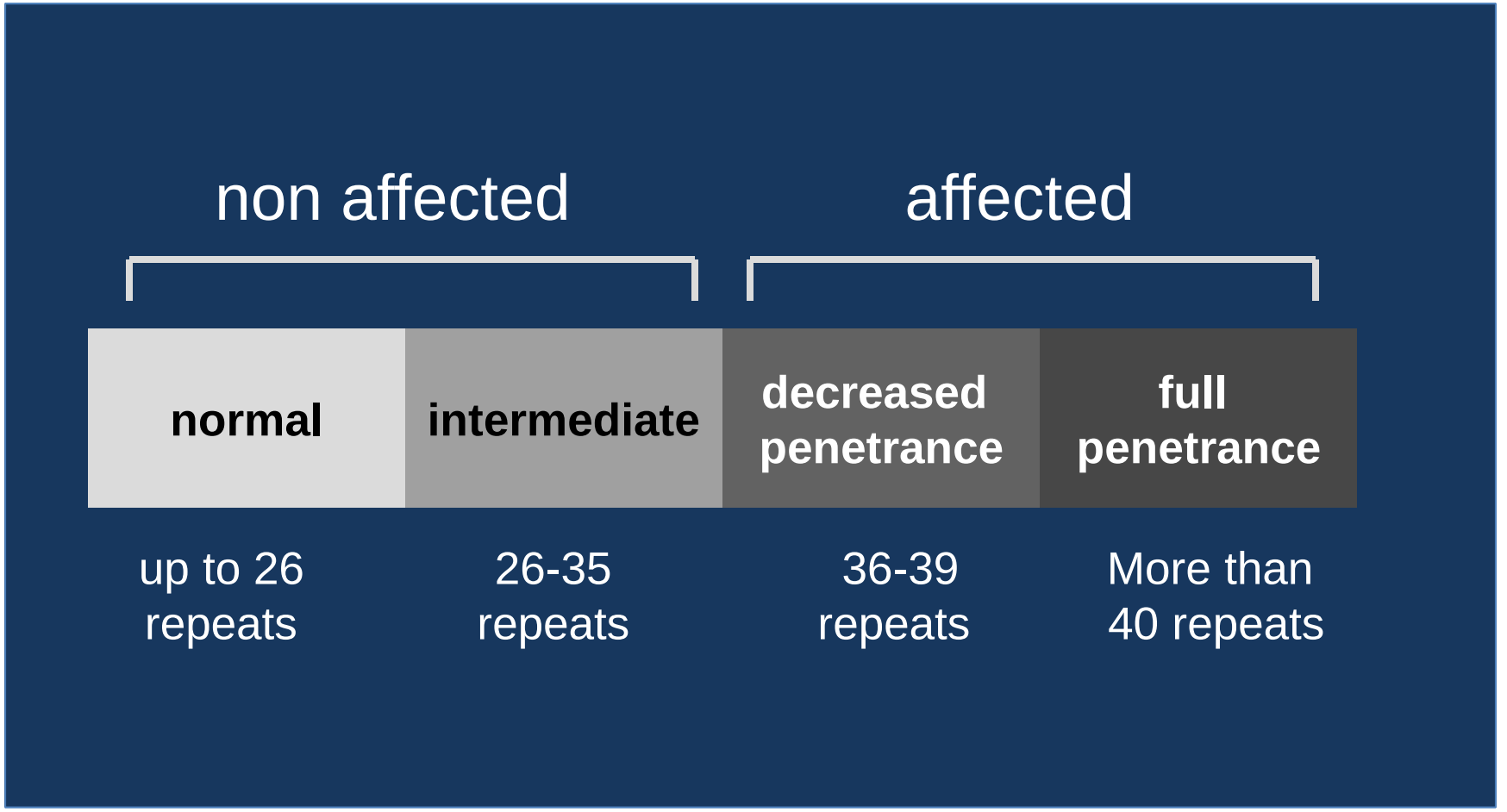
CGT repeat expansion in the myotonin protein kinase gene *DMPK*

Simple diagnostic (not psychological) situation

- Patient with chorea, cognitive impairment, psychiatric disturbances
- Positive family history with AD inheritence
- Test HD: count CAG repeats on HD gene



CAG repeat numbers



PD: more complicated

Table 2 Molecular diagnosis of Parkinson's disease

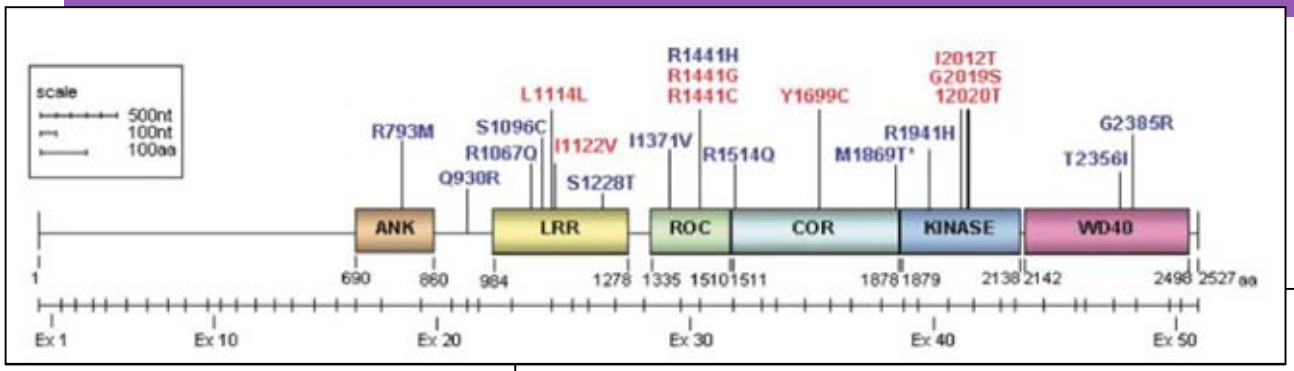
Disease	Locus	Inheritance	Position	Gene product
Familial Parkinson disease, dominant	PARK1/4	AD	4q21	alpha-Synuclein
	PARK8	AD	12p12	LRRK2, Dardarin
Familial Parkinson disease, recessive	PARK2	AR	6q25–27	Parkin
	PARK6	AR	1p33	PINK1
	PARK7	AD	1p34	DJ-1
Familial parkinsonism, other	PARK9	AR	1p36	ATP13A2
	GBA	AD	1q21	Glucocerebrosidase

PD: EFNS guidelines

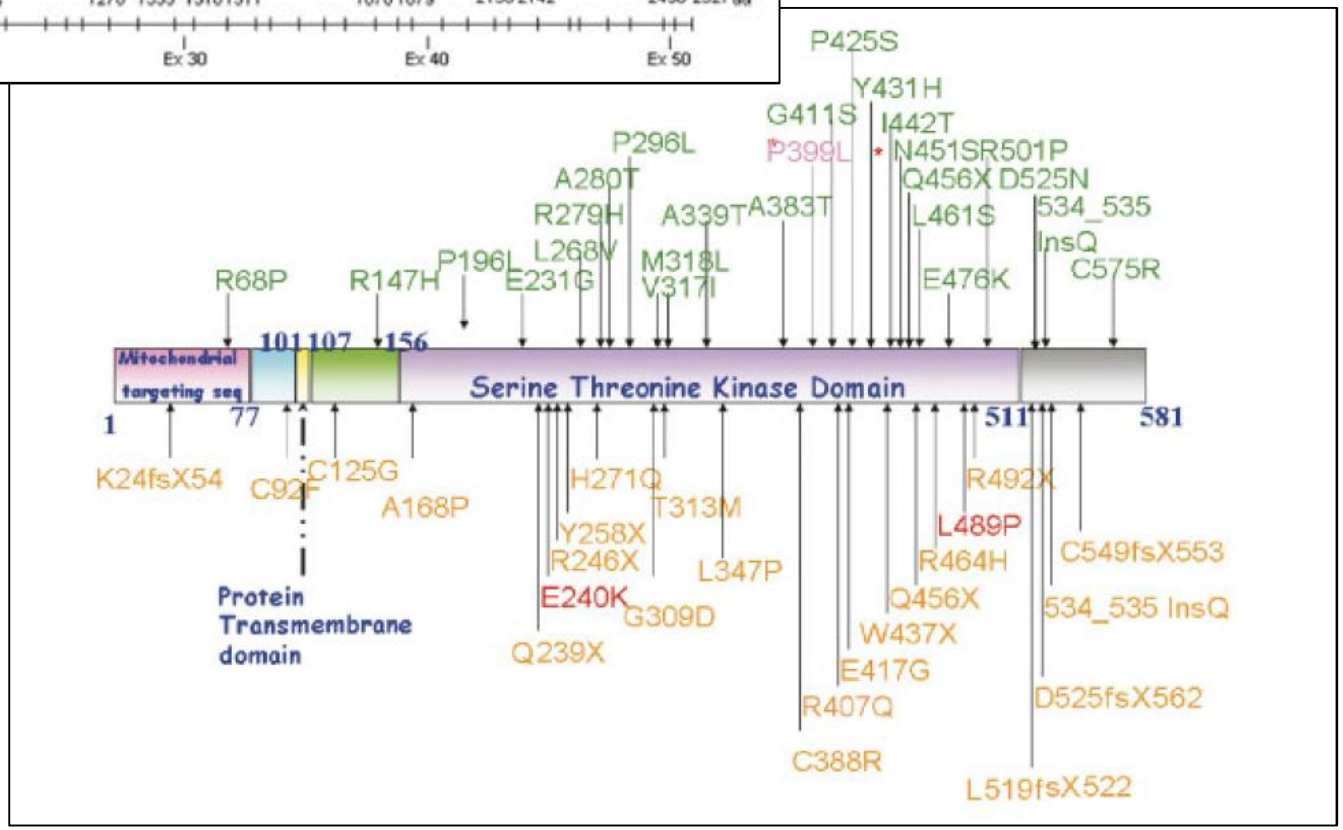
- In Europeans, PD with AD inheritance:
  - Test LRRK2
- Ashkenazim or North African Arabs
  - Test LRRK2 G2019S
- PD with AR inheritance:
  - Test parkin, PINK1, DJ-1
- Sporadic PD with very early onset (<35 years)
  - Test parkin, PINK1, DJ-1

PD: Mutations in 2 genes

PINK1



LRRK2



Tan EK 2007

Hereditary spastic paraplegia

- 56 genetically distinct forms
- some with many of mutations at different locations

Hereditary spastic paraplegia

- 56 genetically distinct forms
- some of many of mutations at different locations

    - Inheritance?
    - additional signs?
    - Pure HSP
    - Neuropathy?
    - X-linked, early onset, with matter changes
    - AR
    - sporadic progressive no other cause

Hereditary spastic paraplegia

Pure HSP — point mutations in the SPAST gene (SPG4), in 50%
multiplex ligation-dependent probe amplification assay (MLPA
sequencing of atlastin (SPG3)

Neuropathy? — REEP1 and KIF5A

X-linked, early onset, with matter changes
L1-CAM (SPG1) and PLP (SPG2)

AR — SPG11
thin corpus callosum SPG15
cerebellar features SPG7

sporadic progressive with no other cause
SPG4 mutations by MLPA
Sequencing of SPG7

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Gene and phenotype correlation

- Mutations in single gene causing one defined known disease
- Mutations causing newly recognised complex phenotypes
- Similar phenotypes in mutations of several genes
- Mutations associated with several disorders
- Phenotypic variability
- Environmental and genetic modifiers

Gene and phenotype correlation

- Mutations in single gene causing one defined known disease
- Mutations causing newly recognised complex phenotypes
- Similar ph
- Mutations
- Phenotyp
- Environm

DNA methyltransferase gene mutations

- sensory neuropathy, dementia,and hearing loss

ABHD7 gene mutations:

- PHARC (peripheral neuropathy, hearing loss, ataxia, retinitis pigmentosa,cataract)

repeat in the C90RF72 gene

- frontotemporaldementia/amyotrophic lateral sclerosis

Gene and phenotype correlation

- Mutations in sing
known disease
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phenotypes
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- Phenotypic variab
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spastic paraplegia
56 genetically defined forms
Present in other complex disorders

ataxia
36 genetically defined forms
Present in other complex disorders

Gene and phenotype correlation

- Mutations in s
  known disease
- Lamin A/C is cau
  phenotypes
- Similar pheno

Cardiomyopathy, dilated, 1A	115200
Charcot-Marie-Tooth disease, type 2B1	605588
Emery-Dreifuss muscular dystrophy 2, AD	181350
Emery-Dreifuss muscular dystrophy 3, AR	181350
Heart-hand syndrome, Slovenian type	610140
Hutchinson-Gilford progeria	176670
Lipodystrophy, familial partial, 2	151660
Malouf syndrome	212112
Mandibuloacral dysplasia	248370
Muscular dystrophy, congenital	613205
Muscular dystrophy, limb-girdle, type 1B	159001

- Mutations associated with several disorders

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Alzheimer genes

- Monogenetic causation
  - Beta amyloid
  - Preselinin 1 and 2
  - Tau

Young onset
Clear family history

- Association with specific genetic polymorphisms

Linkage /// Association

- Linkage study
  - Physical gene localisation
  - Examination of informative families
- Genetic association study
  - Statistical occurence of a particular allele with a disease
  - Comparison of a group of patient with a control group

The APOE gene

3 common sequence variants

ε3	112 Cys	158Arg	75% Caucasians
ε4	112 Arg	158Arg	15% Caucasians
ε2	112 Cys	158Cys	10% Caucasians

APOE polymorphisms in AD

ε4 40% of patients with AD (C: 15%)

ε2 2% of patients with AD (C: 10%)

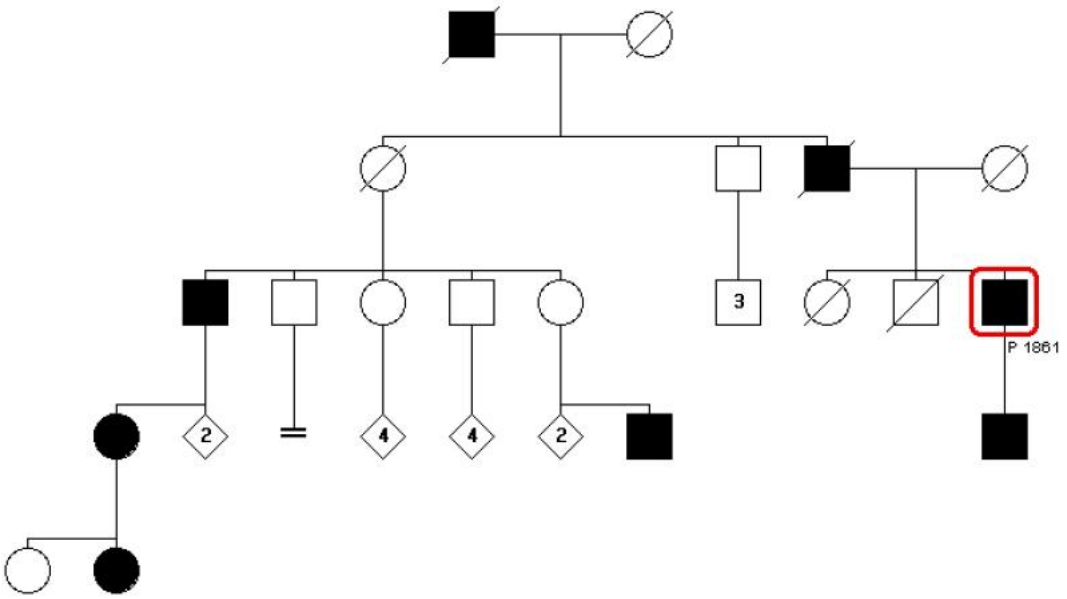
ε4/ ε4 age at onset: <70 years

ε2/ ε3 age at onset: >90 years

Case report

- History
  - Muscle weakness and pain since childhood
  - Anxiety
  - Burnout syndrome
- Present complains
  - fluctuating tremor
  - panic attacks
  - Worsening of the muscle symptoms
    - Exercise intolerance, myalgia, weakness
- Neurological investigations
- Dystonia fingers right
- Sensory deficits right

Case report



- Family History
  - Parkinson
  - Tremor
  - Dementia
  - Sudden death due to cardiac arrhythmia
  - Epilepsy
  - Myalgia
  - Anxiety disorder
  - Depressions

Case report

- Genetics
- Mitochondrial genome
  - Uncle
    - 3-6 kpb deletion
    - 24-50%
  - Father
    - 5-10 kpb deletion
    - 78-95%

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