Genetic Determination of Motor Neuron Disease and Neuropathy

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ABSTRACT

Following the completion of the Human Genome Project, a lot of progress has been made in understanding the genetic basis of motor neuron diseases (MNDs) and neuropathies. Spinal Muscular Atrophies (SMA) are caused by mutations in the SMN1 gene localized on Chromosome 5q11. Amyotrophic Lateral Sclerosis (ALS) has been found to have at least 18 different types, many of them associated to different genetic loci (e.g. SOD1, ALS2, SETX, FUS, VAPB, ANG, TARDBP and others), but many of the forms have still not been associated with a particular gene. Sensomotoric hereditary neuropathies (Charcot-Marie-Tooth) are a large heterogeneous group of various hereditary neuropathies, which have also been associated with a wide spectrum of genetic mutations, such as PMP22, LITAF, EGR2, P0 protein, KIF1B, MFN2, RAB7 and others. It is also apparent that more genes are being implicated, mutations discovered, and phenotypes recognised and broadened. Therefore, a lot of continuing, additional research effort will be required in the coming years to illuminate pathogenic mechanisms that underlie motor neuron diseases and neuropathies and that could lead to new and improved treatments.

Key words: *Human Genome Project, motor neuron diseases, spinal muscular atrophies, amyotrophic lateral sclerosis, Charcot-Marie-Tooth disease*

Introduction

Disorder in the function and structure of the motor unit is called neuromuscular disease[1]. Getting to know the molecular structure of the genome as a hereditary potential located in every cell in the form of the human DNA has been the subject of research for many years. Genomic revolution, which started with the human genome project and the sequencing of the human genome, is now directed toward a personal genome and more personalized medicine[2]. The question is how to apply the above – features, advantages and limitations of this revolution. The genome contains the data of life in the form of the biological code. It should also be recognized that the DNA is a living organism that changes due to lifestyle, environmental factors, by changing and the regulation of the genes. Genes carry the codes for proteins of our organism, so qualitatively and quantitatively altered proteins lead to diseases[2].

If someone is predisposed to a health risk they and their doctor should know it, and start the medical treatment in advance, and in that way affect the creation of offspring[3]. Naturally, this raises significant ethical issues and laws must have strict guidelines in order not to abuse but take good advantage of this confidential material[4]. Most neuromuscular diseases that are genetically determined are expressed already in childhood, but some of them show the real clinical picture and are determined in adulthood. If the latter is the case, consultation on further genetic information may be difficult or impossible[5].

Anterior Horn Cell Disease of Spinal Cord and Motor Nuclei Cranial Nerves

These are the progressive degenerating motor neuron diseases of the spinal cord, brainstem and cortical motor neurone. The frequency is 1–2 patients per 100,000 persons[2,6].

Spinal muscular atrophies

Spinal Muscular Atrophies (SMA) are caused by mutations in the SMN1 gene localized on Chromosome 5q11. SMN gene is necessary for the creation of small nuclear ribonucleins which are involved in the process of the creation of mRNA. SMA is the second most frequent autoso-

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mal recessive disease with the frequency of 1 in 10,000 live newborns; the frequency carrier is (1/40–1/60[3])[2,6]. SMA region is very unstable due to frequent deletions and gene conversion, and the number of gene copies can vary from 0–4 per chromosome. For the majority of Caucasian population the most frequent number of copies of genes is 2. SMN1 gene determines the status of SMA carriers as well as SMA patients. In 95% of the cases of SMA the patients are homozygotes for the lack of axon 7 on SMN1 gene, while the 3.6% are complex heterozygotes with a point mutation on the second allele[1,2,6].

There is an opinion that the number of SMN2 gene copies and gene Naipi can determine the severity of the disease. SMA carriers are in most cases heterozygotes, with no signs of disease, with one copy of axon 7 of SMN1 gene and 0 or more copies of axon 8 of SMN1 gene. SMN2 without mRNA in 80% of the cases are pre-Mrna attached in the SMN without exon 7. SMN without exon 7 is unstable and it quickly disintegrates[7].

Amyotrophic lateral sclerosis

Until now, a number of genetic mutations have been found to be associated with different types of ALS[1,2,6,7]. (Table 1)

Acquired motor neuron diseases occur due to the disorder on chromosome 21 which converts superoxide (O_2) into hydrogen (H_2O_2). It is a defect of superoxide dismutase, which leads to a defect of converting Cu/Zn, the increase in the number of free radicals that could lead to oxidative stress[7,8]. The glutamate is not ejected from the synapses field. The same changes can (more rarely) be caused by the disorder of chromosome 5q. It is inherited as an X-recessive forms, or X – dominant forms[7,8].

Distal, scapuloperoneal, facioscapular amiotrophy

Distal, scapuloperoneal, facioscapular amiotrophy is characterized by a specific abstraction of muscle atrophies and gradual development of deformities, slow disease progression, shutting down of myotic reflexes and atony. According to the characteristic EMNG findings, the differential diagnosis is made according to dystrophies. All are caused by a genetic mutation in the SMN1 gene localized on Chromosome 5q11, with a different penetration of genes (fewer repetitions of nucleotides)[1,2,8,9].

Parents who have a child affected by SMA are recommended to perform a prenatal diagnosis for every following pregnancy because there is a 25% risk to have a child affected by this disease. This way, we can determine the point mutations. In 4% of patients with 2 copies of SMN1 exon 7 is the carrier, as both copies are on the same chromosome, which can also be determined by this method[8,9].

Sensomotoric hereditary neuropathies

Sensomotoric hereditary neuropathies (Charcot-Marie-Tooth) are a large heterogeneous group of various hereditary neuropathies[1,10].

As this is a group of heterogenic diseases, the inheritance of HMSN can be different[9,10]. Type 1 (1A) in which demyelination is created as well as creation of bulbs, is inherited autosomal dominant recessively. These patients

TABLE 1
GENETIC MUTATIONS ASSOCIATED WITH DIFFERENT TYPES OF ALS

Type	OMIM	Gene	Locus	Clinical codes
ALS1	105400	SOD1	21q22.1	Most frequent forms of ALS
ALS2	205100	ALS2	2q33.1	
ALS3	606640	?	18q21	
ALS4	602433	SETX	9q34.13	
ALS5	602099	?	15q15.1–q21.1	Juvenile start
ALS6	608030	FUS	16p11.2	
ALS7	608031	?	20p13	
ALS8	608627	VAPB	20q13.3	
ALS9	611895	ANG	14q11.2	
ALS10	612069	TARDBP	1p36.2	
ALS11	612577	Fig4	6q21	
ALS12	613435	OPTN	10p13	
ALS13	183090	ATXN2	12q24.12	
ALS14	613954	VCP	9p13.3	Rare, described in only one family described in one family
ALS15	300857	UBQLN2	Xp11.23–p11.1	
ALS16	614373	SIGMAR1	9p13.3	Juvenile start, very rare, described in only one family
ALS17	614696	CHMP2B	3p11	Very rare, described only in a few patients
ALS18	614808	PFN1	17p13.3	Very rare, described only in a few Chinese families

TABLE 2
A SUMMARY OF KNOWLEDGE ON GENETICS AND THE INHERITANCE OF HEREDITARY NEUROPATHIES

Gene	Inheritance	Locus	
HMSN1-CMT1			
CMT1A:	PMP-22	Dominant/sporadic	17p11
CMT1B:	P0 protein	Dominant	LQ22
CMT1C:	LITAF	Dominant	16pl3
CMT1D:	EGR2	Dominant	10q21
CMT1E:	P0 protein	Dominant	LQ22
CMT1F:	Neurofilament light chain	Dominant/sporadic	8p21
HMSN2-CMT2			
CMT2A1:	KIF1B	Dominant	lp36
CMT2A2:	MFN2	Dominant	lp36
CMT2B:	RAB7	Dominant	3ql3–q22
CMT2C:	TRPV4	Dominant	12q23–Q24
CMT2D:	Gars	Dominant	7pl5
CMT2E:	Neurofilament light chain	Dominant	8p21
CMT2F:	HSPB1	Dominant/recessive	7q11–q21
CMT2G:	Dominant	12ql2	
CMT2I:	PO	Dominant	LQ22
CMT2J:	PO	Dominant	LQ22
CMT2L:	HSPB	Dominant	12q24
AR-CMT2A	Lam in A/C	Recessive	lq21.2
AR-CMT2E	Med25	Recessive	19ql3.3
CMT2K:	GDAP1	Dominant/recessive	8q21
HMSN3DSN/CHN			
DSNA	PMP-22	Dominant/recessive	17p11–2
DSNB	MP2	Dominant/recessive	LQ22
DSNC	EGRP2	Dominant	10q21/EGR2
DSND	Dominant	Sq23–24	
DSN	PRX	Recessive	19ql3.1–13.2
DSN	GDAP1	Recessive	8ql3–21.1
Congenital hypomyelination			
CHA	22 PMO	Dominant	17p11.2
CHB	MP2	Dominant	LQ22
CHC	EGRP2	Dominant/recessive	10q21
HMSN4-CMT4			
CMT4A:	GDAP1	Recessive	8q21
CMT4B1:	MTMR2	Recessive	11q23
CMT4B2:	SBF2	Recessive	11p15
CMT4C:	SH3TC2 (KLAA1985)	Recessive	5q32
CMT4D:	NDRG1	Recessive	8q24
CMT4E:	EGR2	Dominant/recessive	10q21
CMT4F:	Periaxin	Recessive	19ql3
CMT4H:	FGD4	Recessive	12ql2
CMT4J	Fig4	Recessive	6q21
HSMN5			
Silver syndrome	Seipin/BSCL2	Dominant	11ql3
Troyer syndrome	SPG20	Recessive	13ql2.3

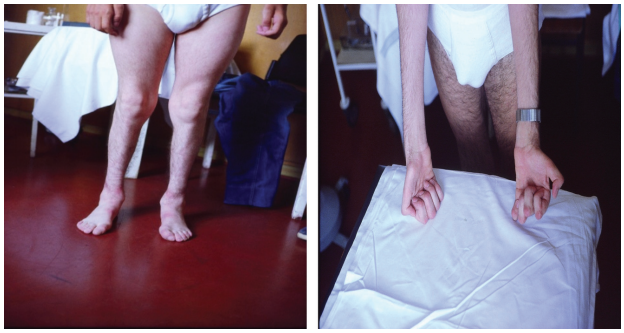

Fig. 1. Charcot-Marie-Tooth disease (hereditary sensory neuropathies Type A).

revealed the duplication of peripheral myelin protein, located on the gene 22 (PMP22) on chromosome 17q11.2. Type 2 or axonal form (according to EMNG findings) is inherited autosomal dominant or recessively (the gene responsible for this form is gene1 and gene 22). CMT-3, 4 CMT, CMT X are inherited recessively and the gene responsible is gene one, but sometimes the changes have been found in the gene PMP22 as well[1,10]. It was found that a mutation in exon 21 and exon 22 on the gene SCN9A are responsible for the loss of sensitivity and the autonomic nervous system disorders[1,2,8–10].

Hereditary neuralgic amiotrophy

Hereditary neuralgic amiotrophy is caused by mutations on the gene SEPT9 (17q25). The same is idiopathic brachial neuralgic amiotrophy (plexopathy)-Personage-Turner syndrome[1].

Compressive neuropathies

Hereditary compression neuropathies with a penchant paralysis can be found in 2 to 5 people per 100,000 inhabitants. The mutation on the PMP 22 gene causes neuropathies with a penchant on the pressure palsy. The loss of one copy of on the PMP 22 gene or its alteration leads to instability of the myelin sheath. The disease is inherited autosomal dominantly[10].

Discussion

Genetic background and pathogenesis of motor neuron diseases (MNDs) have been increasingly elucidated over recent years[2]. Phenotypic manifestations of MNDs include spinal muscular atrophies (SMA), familial or sporadic amyotrophic lateral sclerosis (fALS, sALS), bulbospinal muscular atrophy (BSMA), and unclassified MNDs[2]. An increasing number of mutated genes is recently recognised in fALS, but also sALS patients. Genes mutated in sALS include C9orf72, SOD1, TARDBP, FUS, UBQL2, SQSTM1, DCTN1, and UNC13A. Juvenile fALS is most frequently caused by mutations in ALS2, SETX, spatacsin, or Sigmar1, and adult fALS by mutations in C9orf72, SOD1, TARDBP, and FUS. There are differences between geographic regions, mutations and genes that affect the onset, phenotype, progression, and outcome of ALS[2].

Renton et al.[11] also reviewed genes implicated in the pathogenesis of motor neuron degeneration, namely ALS, SOD1, TARDBP, FUS, OPTN, VCP, UBQLN2, C9ORF72 and PFN1. They also outlined next-generation sequencing approaches to identify de novo mutations, the genetic convergence of familial and sporadic ALS, and how each new genetic discovery is broadening the phenotype associated with the clinical entity we know as ALS[11].

Recently, Scotton et al.[3] recognised that clinical trials of new therapies are difficult due to lack of reliable and monitorable clinical outcome measures. They proposed biomarkers as a way to speed up research, providing an insight into the pathophysiological mechanisms behind such diseases[3]. Biomarkers, which could include genetic profiling of each patient, may provide invaluable tools for monitoring the progression, prognosis and individualised treatment[3]. They summarized the types, applications, characteristics and best strategies for biomarker discovery[3].

Conclusion

We can conclude that a considerable progress has been made over the past several year in the clarification and understanding of the etiology and pathogenesis of MNDs, particularly due to research technologies that were made available after the human genome was sequenced more than a decade ago[2]. However, it is also apparent that more genes are being implicated, mutations discovered, and phenotypes recognised and broadened. Therefore, a lot of additional effort will be required in the coming years to illuminate pathogenic mechanisms that underlie motor neuron diseases and neuropathies and that could lead to new and improved treatments[2,11].

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GENETSKE OSNOVE BOLESTI MOTONEURONA I NEUROPATIJE

S A Ž E T A K

Nakon završetka Projekta ljudskog genoma, dosta je napretka postignuto u razumijevanju genetske osnove bolesti motoneurona (MNDS) i neuropatija. Spinalne mišićne atrofije (SMA) su uzrokovane mutacijama u genu SMN1 lokaliziranih na kromosomu 5q11. Za amiotrofične lateralne skleroze (ALS) utvrđeno je da imaju najmanje 18 različitih vrsta, a mnoge od njih su povezane za različite genetske lokuse (npr SOD1, ALS2, SETX, FUS, VAPB, Ang, TARDBP i drugi), ali za mnoge od oblika još nije nađena povezanost sa određenim genom. Senzomotorne nasljedne neuropatije (Charcot-Marie-Tooth) su velika heterogena skupina raznih nasljednih neuropatija, koje su povezane sa širokim spektrom genetskih mutacija, kao što su PMP22, LITAF, EGR2, P0 proteina, KIF1B, MFN2, RAB7 i drugi. Također je jasno da se sve više gena implicira, mutacija otkriva i fenotipa tih bolesti prepoznaje i širi. Dakle, puno dodatnih istraživanja i truda će biti potrebno u narednim godinama za osvjetljavanje patogenetskih mehanizama na kojima se zasnivaju bolesti motoneurona i neuropatije i koji bi mogli dovesti do novih i poboljšanih načina liječenja.