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RESEARCH ARTICLE (Open Access)

The Aetiology of Genetic, Acquired and Sporadic Prion Diseases

NEILA BAJRAMI[1*], ZYRI BAJRAMI[2]

[1]University of Medicine, Faculty of Technical Medical Sciences, Department of Diagnostic and Health Rehabilitation

[2]University of Tirana, Faculty of Natural Sciences, Department of Biology

Abstract

Based on the protein X or the chaperone protein hypothesis which enables the reaction of conversion from PrP^{c} to PrP^{Sc} and the gene interaction of this protein with prion protein gene (PRNP gene) we do propose the genotypes involved and give possible explanations of genetic, sporadic and acquired forms of prion diseases. In this context, the genetic forms of prion diseases like fCJD, fGSS and FFi have A-B genotypes. In these genotypes, PRNP gene and Xchap have been subject to a dominant mutation. In the sporadic forms of prion diseases like sCJD and sFI, the Xchap gene has been subject to dominant mutation but in the acquired forms of prion diseases (kuru, iCJD and VCJD) the PRNP gene has been subject to a dominant mutation.

Keywords: prion diseases, PRNP, Protein X chaperone, gene interaction, gene module

1. Introduction

Prion diseases are fatal neurodegenerative disorders like Creutzfeld- Jacob, Gerstmann-Sträusler-Scheinker (GSS), fatal isomnia (FFI), Kuru and the new variant of CJD named uCJD in humans. The main characteristic of prion diseases is post translaational conversion of cell prion protein PrP^{c} to her isoform named PrP^{Sc}. Prion diseases are biologically unique [2]. Their distinct nature is due to the fact of their transmission through mutational gene of prion protein (PRNP) and their infectous behavior when in contact with PrP^{Sc}. Additionally, prion diseases are sporadic and generates PrP^{Sc}.

The main purpose of our study is to build a model wich must be able to explain the aetiology of prion diseases. The building of such a model it is based in two main assumptions reached so far by scientific community: First, is a well known fact that cell prion protein and its gene are present in all prion disease. Secondly, another hypothesis states that an unidentified cell protein (X protein) make possible the conversion of PrP^{c} to PrP^{Sc} [9] [5]. Which is the role of PRNP gene and X protein in genetic, sporadic and acquiredethiology of prion diseases? Why does prion diseases have a genetic nature?

2. PRNP gene as a genetic module

The concept of gene as a deposit of information regarding a certain requirement that needs to be fulfilled and according to which this information, a product must be formed in order to fulfill the needed requirement, it is shown on the picture below (Figure 1).

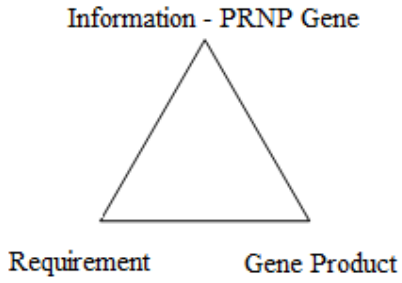

Figure 1. PRNP gene as a genetic module.

Gene concept can also be explained in a metaphoric way. If information can be equated with the knowledge on how to open a lock, a genetic product is the key formed according to this knowledge and thus, the gene function is to open the lock with the proper key [1]. In Figure 1 the gene module of PRNP is shown. A gene module is a module of which information carried in a gene serves to fulfill a certain function. The PRNP gene functions and its products, PrP^{Sc} are not known. Besides that, the interest on PRNP gene is linked to his functions in aormal

*Corresponding author: Neila Bajrami; E-mail: neilabajrami@gmail.com
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conditions. The non normal function of PrP^{c} begins with the conversion to PrP^{Sc}.

3. The bimodular module of individuals without prion diseases

According to Fig. 1.1 everything with go normally if PRNP gene has not been subject to mutations and if PrP^{c} protein assures the three dimensional functional conformation. Therefore, the functional unit of normal individuals (individuals without prion diseases) will have a bimodular structure (Figure 2).

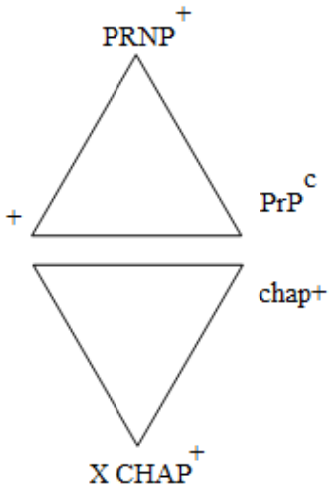

Figure 2. The bimodular model of PRNP normal gene.

In the Fig. 2 it is shown that individuals do not have prion diseases when PRNP gene and X Chap (the gene responsible for chaperones) have not been subject to mutational effect. This model is acknowledged by the idea that if there does exists a protein (a chaperone) that make possible the conversion from PrP^{c} to PrP^{sc} [9] does exist even a normal protein formed by a gene who has not been subject to a mutational effect. For this reason, PRNP gene and Xchap are non-mutational and therefore the PrP^{c} protein performs its functions.

4. The bimodular model of individuals with prion diseases

From a modular perspective, the forms of prion diseases as genetic, sporadic and acquired can be explained as interactions between PRNP genes and X CHAP.

a) Genetic (familial) prion diseases

Individuals which have mutations in the gene responsible for prion protein (PrP^{c-}) and in the gene responsible for chaperone protein (Xchap-) will be affected by prion diseases that are hereditary. In the figure 1.3 it is shown the bimodular model of these genetic prion diseases like for example (fCJD, fGSS and (f) FFI).

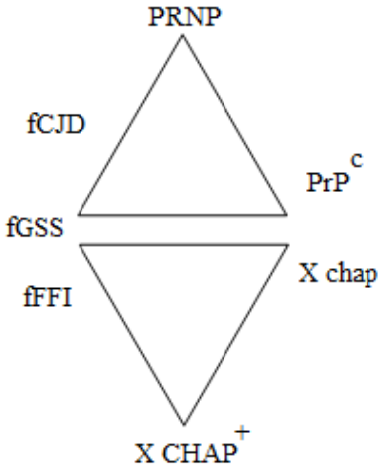

Figure 3. The bimodular model of genetic prion diseases.

Approximately 15 percent of prion diseases in humans are connected with dominnat autosomic mutations in PRNP [3]. There has been described over 30 mutations connected to different categories of prion diseases [8]. In our model the mutations of PRNP gene are not enough. In the reaction of conversion PrP^{c} to PrP^{Sc} are necessary the mutations on XChap gene and the formation of mutational chaperone XChap. It is a well known fact that the newly formed polipeptidic chains need molecular chaperone help not only to achieve as fast they can their final tridimensional form but also to correct misfolded protein [4]. Moreover in the manifestation of prion diseases other gene take place [6] and this counts for the idea that maybe these gene take part in chaperone formation.

b) Acquired and sporadic prion diseases

In the table below (Table 1) it is shown the classification of prion diseases in humans according to [3] and the genotypes of these diseases according to the hypothesis of the interaction between PRNP gene and XCHAP.

Table 1. The classification of prion diseases in humans and their genotypes according to interaction of PRNP gene and XCHAP hypothesis. (PRNP gene: A- dominant mutation and a- normal. XCHAP gene: B- dominant mutation and b-normal).

Aetiology	*Phenotype*	*Genotype*		*%*
		PRNP A-mutant a-normal	XCHAP B-mutant b- normal	
1) Familial (inherited)	f CJD f GSS FFI	AABB, AaBb,AaBB,AaBb		10 - 15
2) Sporadic	s CJD s FI	aaBB,aaBb		85 - 90
3) Acquired	Kuru iCJD vCJD	AAbb, Aabb		~ 1

If genetic prion diseases manifest themselves when individuals have the dominant alleles of PRNP gene and XCHAP then sporadic and acquired prion diseases have only one dominant allele of PRNP gene or XCHAP gene (Table 1). Our hypothesis states that prion diseases of sporadic form are characterized by the presence of mutant allele of XCHAP gene. The mutant proteinic chaperone does not recognize the cell prion protein PrP^{c} and as a consequence, this misfolded protein turn into its isoform PrP^{Sc}. But could be another two explanations. First, PRNP gene could be a carrier of some genetic polimorphisms which grow the possibility of conversion reaction from PrP^{c} to PrP^{Sc}. Secondly, the PRNP gene can be subject to somatic mutations. The three explanation regarding sporadic prion diseases manifestations are possible. Perhaps a reciprocal support can be found in the explanation of sporadic prion diseases along with acquired prion diseases. It is supposed that the acquired prion diseases manifestations are present in the individuals which carries the mutant alelle of PRNP gene. These individuals manifests prion diseases only in if they are in physical contact with surgical tools or contaminated foods which carry PrP^{Sc} isophorm. In this case, mutated prion protein cell PrPc get by contamination the seed of cristalization. So on, a molecular selection begin. The initially PrP^{Sc} in organism becomes a catalisator for the reaction of conversion from PrP^{c} to PrP^{Sc}. Because of cell prion protein PrP^{c} is mutant, it slightly tends with proteinic normal chaperone. The joint between PrP^{c}- PrP^{Sc} leads to higher conversion reaction of PrP^{c} to PrP^{Sc} and it is highly favorized in contrast to PrP^{c}- normal chaperone. Our hypothesis states that the genetic, sporadic and acquired forms of prion diseases manifests because of the interactions of PRNP gene and XCHAP and their nature is genetic. In figure 4 we depict the bimodular models of sporadic and acquired prion diseases.

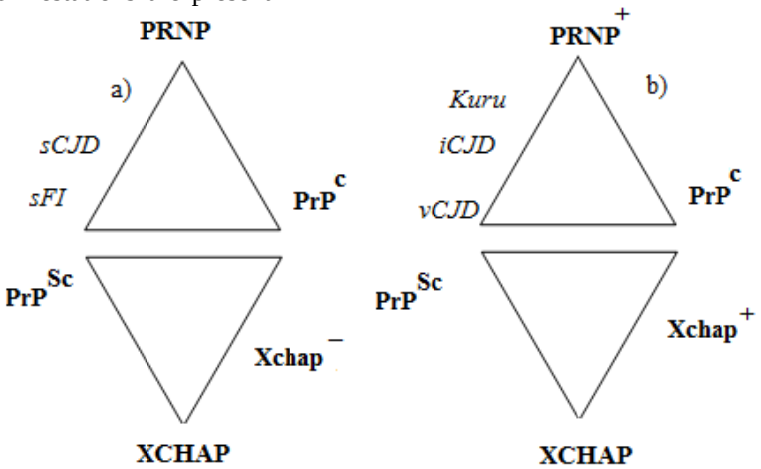

Figure 4. The bimodular model of sporadic (a) and acquired (b) prion diseases.

Table 1.1 and the bimodular models proposed in this paper of genetic, sporadic and acquired forms of prion diseases are consistent with another study like the article by J. A. Mastrianni [7]. The two modules are genetic because the information according to which a function is performed is itself a gene. But which is the function? In the individuals with prion diseases does function the reaction of conversion from PrP^{c} to PrP^{Sc} and this mechanism is bimodular. For example, prion disease is considered as acquired because its manifestation is conditioned by infected food intake. From a genetic point view, as it is presented in gene modular concept, the manifestation of e phenotype will initially depend from the deposited information and then, by the accuracy of the way this information has created the product.

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