FMRP, a multifunctional RNA-binding protein in quest of a new identity

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Introduction

In the early days of gene discoveries, the denominations in initial reports were often imprecise, restrictive or uninformative. Indeed, genes were usually originally named in reference to the context of their discovery, according to the specific tissue, cell type, cellular function, disease or phenotypic outcome under scrutiny. As a result, it was not uncommon that the same gene would have several names, simply because different researchers were working on the same gene, albeit in distinct contexts. Consequently, despite gene names harmonization, which coincided with the adoption of official gene symbols used in databases, most genes still exhibit a handful of aliases. Also, the official alias was generally chosen on historical grounds rather than as a reflection of the actual functions of the gene. More recently, several genes were renamed as their historical name was either imprecise and/or vector of negative connotations. Renaming the FMR1 gene has recently been the object of such debate in the community (Herring et al., 2020).

The specific case of renaming the FMR1 gene involved in fragile X syndrome

Since its cloning in 1991 (Verkerk et al., 1991), the official name of the gene mutated in Fragile X Syndrome (FXS) has been Fragile X Mental Retardation 1 (official gene symbol FMR1), as it was the first of a long series of X-linked genes associated with intellectual deficiency, termed at that time mental retardation. FXS is a leading cause of developmental delay, inherited intellectual disability, and the most frequent monogenic cause of autism spectrum disorder (ASD) (Kaufmann et al., 2017). FXS is caused by abnormal expansions of CGG triplets (n > 200 repeats) in the untranslated region (5’-UTR) of the X-linked FMR1 gene, which turn off its expression (Verkerk et al., 1991). Over the past two decades, while the general population exhibit in average 30 CGG repeats, premutations between 50 and 200 repeats in the FMR1 gene have been associated with Fragile X Premutation Associated Conditions (FXPAC), a set of conditions with no
intellectual disability (Hagerman and Hagerman, 2016; Johnson et al., 2020). Also, it is important to note that mutations in the \textit{FMR1} gene are incompletely penetrant, and some individuals, in particular females bearing abnormal CGG repeat expansions will exhibit no signs of FXS or FXPAC (Johnson et al., 2020). As our society becomes more inclusive and recommends not to stigmatize individuals with intellectual deficiency, the term “mental retardation” has been progressively banned from scientific or clinical reports. Also, since \textit{FMR1} mutations are not necessarily accompanied by intellectual deficiency, the term mental retardation has been progressively banned from database nomenclature issues. However, we wish to point that the new name “Fragile X Messenger Ribonucleoprotein” does not reflect the pleiotropic functions of \textit{FMR1} gene that three decades of research have contributed to unravel. The letter M now standing for “messenger” and the R for “ribonucleoprotein. First, the choice of “messenger” for M does not reflect the fact that FMRP, the \textit{FMR1} encoded protein, not only binds messenger RNA in the translation machinery to modulate translation (Corbin et al., 1997; Khandjian et al., 2022).

**Discussion**

We agree that removing “mental retardation” was necessary and keeping the original acronym \textit{FMR1} was essential for database nomenclature issues. However, we wish to point that the new name “Fragile X Messenger Ribonucleoprotein” does not reflect the pleiotropic functions of \textit{FMR1} gene that three decades of research have contributed to unravel. The letter M now standing for “messenger” and the R for “ribonucleoprotein. First, the choice of “messenger” for M does not reflect the fact that FMRP, the \textit{FMR1} encoded protein, not only binds messenger RNA in the translation machinery to modulate translation (Corbin et al., 1997; Khandjian et al., 2022).
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