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COMMENT

The simplest explanation does not have to be preferred: co-occurrence of pathogenic variants in cancer-predisposing genes

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Occam's razor or the principle of parsimony states that in front of a problem, the simplest explanation is to be preferred. This law is attributed to English Franciscan friar William of Ockham, a philosopher and theologian of the 13th century, and it is used for instance in the scientific method or when facing a clinical diagnosis.

Mendelian inheritance follows the principles originally proposed in 1865 by Gregor Mendel, another friar, Augustinian in this case, and considered one of the founders of modern genetics. A Mendelian trait is one that is controlled by a single locus in an inheritance pattern. In such cases, a mutation in a single gene can cause a disease that is inherited according to Mendel's principles. Dominant diseases manifest in heterozygous individuals. Recessive ones are sometimes inherited unnoticeably by genetic carriers. Indeed, Mendelian inheritance has been the Occam's razor for many years in the field of germline predisposition to disease. The Online Mendelian Inheritance in Man (OMIM, https://omim.org/) database contains information on all known Mendelian disorders and over 16,000 genes.

Next generation sequencing (NGS) technologies emerged and gained momentum in the first years of the current century [1]. Over that time, there was a fundamental shift away from the application of automated Sanger sequencing to genome analysis. Prior to this departure, the automated Sanger sequencing method had dominated gene characterization for two decades and led to a number of monumental accomplishments, including the completion of the first human genome sequence. This technological paradigm shift implied that molecular genetics diagnostics and research laboratories trying to unravel germline predisposition moved from testing inherited genes sequentially until a pathogenic mutation was detected in a patient to NGS approaches performing simultaneous parallel testing of large numbers of inherited cancer genes.

Departing classical monogenic inheritance is a path that is proving to be difficult to walk for many clinicians and researchers. However, in the advent of the previous shift, traditional wisdom can be more easily challenged and other inheritance forms can be considered such as digenic or more complex inheritance [2]. In this particular direction, McGuigan et al. [3] revisit and update in this issue of EJHG the Multi-locus Inherited Neoplasia Allele Syndrome (MINAS), which refers to cancer patients with germline pathogenic mutations in two or more cancer susceptibility genes (CSG). Indeed, this term was first proposed by the same research group [4].

McGuigan et al. [3] report in their article the frequency and cancer phenotypes associated with MINAS by reviewing the recent literature and by checking the UK 10,000 Genomes Project data from participants with a phenotype of tumor predisposition syndromes or multiple primary tumors. A list of 94 CSGs was used to identify 2 or more potentially pathogenic genetic variants. Pathogenicity of the genetic variants in these genes was assessed to identify pathogenic or likely pathogenic (P/LP) variants according to the classification criteria of ClinVar or the American College of Clinical Genetics guidelines. They identified a total number of 385 cases of MINAS with a clear exponential increase over time, most likely due to the generalization of NGS in molecular diagnostics in the last years.

Among the 385 MINAS, 430 unique P/LP variants were identified in 63 CSGs, being *BRCA1* and *BRCA2* combinations present in a majority of cases (78.5%). Other relevant CSGs included combinations with *MEN2*, *MLH1*, *MSH2*, *APC*, *RET*, and also with *CHECK2*, *ATM*, *FANCM*, *PALB2*, *BLM*, the latter combinations almost exclusively detected in more recent studies. Regarding phenotypic presentation associated in MINAS cases, it could be of interest to know if they are additive reflecting each CSG independently or synergistic resulting in more severe phenotypes. All in all, 108/385 MINAS cases (28%) had multiple primary tumors at presentation, being breat–ovarian the most common combination. Due to its high prevalence in their cohort, they also explored this matter by dividing their cohort between *BRCA1/BRCA2* or non-*BRCA1/BRCA2* MINAS. In this sense, atypical tumor phenotypes not previously linked to the affected CSGs were identified in about 15% of non-*BRCA1/BRCA2* MINAS. On the other hand, the mean age of cancer diagnosis was in *BRCA1/BRCA2* MINAS was similar as in *BRCA1* carriers. As highlighted by the authors, tumor studies using loss of heterozygosity (LOH) in tumors could pinpoint the importance of one of the CSG involved in each MINAS case and be helpful in providing prognostic information for patients. Finally, all data generated by the authors is gathered in a MINAS database (https://databases.lovd.nl/shared/diseases/04296), which corresponds to a very useful resource to advance in the study of these patients.

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This study and those to follow could be improved by a more open reporting of MINAS cases in the field, by taking into account additional CSGs still not considered, by incorporating data generated by exome or genome sequencing, or by further characterizing MINAS tumors more precisely with LOH or mutational signature profiling. Indeed, tumor mutational signatures are a reflection of the natural history of the tumor including endogenous factors such germline predisposition or exogenous exposures such as smoking or diet [5], and they could be useful to progress on MINAS delineation.

In summary, the article by McGuigan et al. sends the clear message to the scientific community that co-occurrence of pathogenic variants in cancer-predisposing genes is an explanation to be considered in some patients and that the systematic reporting of MINAS and its throughout characterization is the necessary strategy to follow in order to advance further in the study of these specific tumor patients in order to be able to offer them the more adequate and personalized surveillance and therapeutic options in the near future.

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COMPETING INTERESTS

The author declares no competing interests.

ADDITIONAL INFORMATION

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