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LETTER TO THE EDITOR

Germline mutations in lung cancer and personalized medicine

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Marafie et al. [1] identified a rare germline *NBN* gene mutation by whole exome sequencing (WES) in a lung cancer survivor from a large family with various types of cancer. Actually, they found 3 siblings, who had lung cancer at age 55, 54 and 49, respectively. The proband, a 59 year-old heavy cigarette smoker female, was diagnosed with lung cancer at age 49, and her histopathologic report revealed an adenocarcinoma (ADCA) of the middle lobe. At genetic analysis, the proband was found to be a heterozygous carrier for a rare variant in *NBN* gene, termed c.93_94delTG, a two bases-deletion disrupting the protein function and considered pathogenic. Moreover, the proband had other variants in *RAD50* and *BRCA1* genes, which are currently considered of uncertain clinical significance. Among the 8 tested subjects, including a yet asymptomatic sister, 6 carried one or more of these variants in different combinations and in an heterozygous state. *NBN* (nibrin) encodes a member of the MRE11/RAD50 double-strand break repair complex, which is an integral component of the BRCA1-associated genome surveillance complex, responsible for double strand DNA damage repair. Heterozygous carriers of *NBN* 657del5 mutation showed an increased risk of developing various tumors.

Lung cancer had been previously reported in mutation carriers from families segregating germline mutations in different genes (*BRCA2, CHECK3, CDKN2, BAP1, EGFR*) and within individuals who had been smokers or non-smokers. Moreover, by performing whole exome or genome sequencing of various patients with lung cancer, different germline alterations were found in other genes. Marafie et al. [1] quoted a paper from our group, documenting an "oligogenic signature" predisposing to lung ADCA in never smokers, discovered by a combination of next generation sequencing with an original "discordant siblings" model [2]. Affected patients showed germline mutations in 5–8 carcinogenic genes, that were not present in the unaffected sib used as a control [2]. After the first 2 couples of discordant sibs, we have collected 5 additional couples (manuscript in preparation). Among them a never smoker with squamous cell lung carcinoma and her normal sib underwent our novel integrative "omic" approach, using a pedigree-based model for discovering genetic factors leading to cancer in the absence of known environmental triggers [3]. A first-step whole-exome sequencing on tumor and normal tissue did not identify mutations in known driver genes. Finally, RNA-sequencing analysis in tumoral and matched non tumoral tissues was carried out, in order to investigate the clonal profile and the pathogenic role of the identified variants. We identified rare/private germline deleterious variants in 11 cancer-associated genes, none of which shared with the healthy sib, pinpointing to a "private" oligogenic germline signature. Two of these genes, namely *ACACA* and *DEPTOR*, turned to be potential targets for therapy, because related to known drivers, such as *BRCA1* and *EGFR*. Interestingly, the "oligogenic signature" of 5–8 germline mutations per patient, that is likely to play a role in cancer occurrence, even if we cannot yet establish its "pathogenic power", is confirmed in all the 8 enrolled patients, i.e. more than 50 mutations in different genes and it never showed the presence of a "common gene" shared with other lung ADCA patients, and possibly acting as a "causative factor".

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Supporting our model, Marafie et al. hypothesized that although variants may be classified of uncertain clinical significance individually, collectively they may increase (in their family) the likelihood of cancer development. They also "encourage family members to join a long-term follow-up program" and suggest to consider functional assays for the variants found in order to confirm/or refute their pathogenicity" [1].

Recent advances in genetic and biomolecular research suggest to look beyond the established classification of genes as "drivers" or "passengers" in cancer genome sequencing data [4]. Innovative analysis of cancer genomic data has led to novel, serendipitous findings. There are many exceptions to the classic model: not all the so called "passenger" mutations are neutral, but many "passenger mutations" are likely deleterious and, although individually weak, the collective burden of "passengers" alters the course of disease progression, leading to observations that are difficult to explain based on a solely "driver-centric" classical model [4]. The current keyword is "complexity". Even if there are a few cancer diseases in which a germline mutation of a single gene (e.g. *APC*) determines cancer occurrence in 100% of Familial adenomatous polyposis (FAP) patients [5], in most frequent cancers a polygenic model should be hypothesized. In particular, in addition to some "shared mutations" that seem to be peculiar of a given cancer, and include both germline and acquired mutations of oncogenes or tumor suppressor genes, our results: (1) confirm as a "proof of concept", the hypothesis of an oligogenic combination for "cancer susceptibility"; (2) further support a model of "private genetic epidemiology" for a better understanding of the genetic effects in families with common cancers; and (3) suggest the possibility that each individual may have his/her personal way to cancer, so determining in every patient a "unique" type of tumor [5]. This "oligogenic signature" could be considered, at least in part, as the biomolecular expression of host "susceptibility" or "resistance" in the complex interaction with inherited factors or environmental deleterious xenobiotics for tumor occurrence or progression. Thanks to a novel integrative "omic" approach, coupling WES and RNA-seq technologies, during the last decade we began to try to detect, from a biomolecular point of view, "which is which", i.e. what could be the "genetic basis for this diversity "in terms of "individual" susceptibility or resistance to tumor occurrence. Our findings could also be of importance in the present era of "personalized medicine" and "targeted" therapy.

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