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Perspective

Germline Genetics Designs and Somatic mutations in Cancer Pharmacogenomics

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DESCRIPTION

The way a person reacts to medication is influenced by genetic diversity. By choosing the right treatments and administering them at the right doses for each patient, knowledge of this variance may make therapy safer and more effective. While a patient's germline genetic variation will also affect treatment response (both efficacy and toxicity), and here we focus on how to research this variation, tumours in the context of cancer may have particular disease-defining mutations. Clinical trial designs, statistical genetics analytic techniques, and sequencing technology advancements have all showed promise for finding variations linked to treatment response. With an emphasis on the unique study design issues, we talk about how germline genetics analytic methodologies can be applied to pharmacogenomics research on cancer.

Pharmacogenomics seeks to comprehend how genetic variations affect the effectiveness and toxicity of medications. These investigations can show how genetic variation among people influences the pharmacokinetics and pharmacodynamics of a medicine. For the benefit of patients, practical use of such information can be adopted if the relationships between genotypes and drug-induced phenotypes are repeatable and have substantial effect sizes. This is crucial in oncology since cancer is a prominent cause of morbidity and mortality in developed countries and because unsuccessful therapy frequently poses a serious threat to life. The ambitious goal of personalized oncology is to be able to predict how a cancer patient will respond to a certain treatment plan.

Somatic mutations in cancer pharmacogenomics

Somatic mutations may act as either the primary or secondary determinant of the cancer subtype. When identifying somatic mutations in DNA-sequencing investigations, it is important to take into account the fact that tumour samples contain both cancerous and normal cells. Considering that DNA is partially damaged in small biopsies taken from tumours that have been Formalin-Fixed and Paraffin-Embedded (FFPE), it is very important to check whether a sample is suitable for genomic research. The mutations inside the cancer cells may also be heterogeneous, meaning that various tumor-related components may result from various clonal expansions. Although research on the branching structure of tumour evolution is still in its early stages, the current advice for treating this heterogeneity is to focus therapy efforts on universal changes in the phylogenetic tree's trunk, if such medications are available. Some of the proteins that are triggered by somatic mutations (typically tyrosine kinases) have become the target of targeted therapy.

Designs

In cancer pharmacogenomics, the candidate gene approach is frequently employed; variations in well-known drug-metabolizing enzymes and drug targets are investigated for associations with relevant phenotypes. Pharmacogenomic candidate gene studies can benefit from the use of genotyping arrays with hundreds of SNPs in known drug absorption, distribution, metabolism, and elimination (ADME) genes. However, the candidate gene technique may still be useful in cancer pharmacogenomics when patient sample sizes are small, especially if pharmacokinetic data are also available. Of course, the candidate gene approach requires a priori biological knowledge and will miss unknown regions of connection. To conduct out thorough genome-wide analysis, however, every effort should be made as genotyping and sequencing costs continue to decrease.

Due to its standardized medication dose and phenotypic collection, clinical trials provide the appropriate framework for pharmacogenomic investigations. A novel medicine's maximum acceptable dose is established in phase I trials, and the effectiveness of the treatment is assessed in phase II trials to determine whether it should move on to phase III. Phase I and II oncology trials frequently have sample sizes of less than 100 patients, making them unsuitable for genome-wide pharmacogenomic discovery investigations. However, they might be valuable for candidate gene research. Comparative Phase III

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trials frequently enroll hundreds of patients to tens of thousands of patients, making them valuable data sources for Genome-Wide Association Analyses (GWASs). It is also possible to design prospective cancer pharmacogenomic research independently from clinical trials, although caution should be exercised to ensure that uniform dose regimens, phenotypic collection protocols, and covariate collection methods are used. Retrospective investigations are feasible and might provide a larger sample size, but uneven data collection and treatment may skew the findings.

DNA source

Normal DNA is simple to extract from blood or, in the case of individuals with blood malignancies, saliva for germline cancer pharmacogenomic research. Formalin-Fixed and Paraffin-Embedded (FFPE) biopsy samples should normally be avoided as a source of DNA for germline investigations because tumour samples are a mixture of malignant and healthy cells. In a recent big investigation, the correlations between phenotypes associated to tamoxifen use and variations in *CYP2D6* (which encodes a cytochrome *P450* enzyme) were sought to be replicated. FFPE blocks of tumour tissue were used to extract DNA, and SNPs in *CYP2D6* displayed dramatic departures from the Hardy-Weinberg Equilibrium (HWE). The deviation from HWE in this instance was consistent with the high percentage of hemizygous *CYP2D6* deletions found in the tumour tissue from which the DNA was taken. As a result, the interpretation of this data set was severely constrained because the tumour tissue did not consistently match the germline genotype.