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Review Article

Impact of Genotype-Drug Interaction on Effectiveness of Therapeutic Response

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Abstract

When different Genotypes respond to different drugs in different ways, new technique under well designed experiment should be investigated. Genomic profile should be investigated through DNA extraction from each person of the genotype drug combination groups suggested in this article. Biopsy specimens should be collected for histopathological and immunohistochemistry and pharmaceutical characteristics. Diversity of molecular markers at the DNA level within and among individuals within genotype drugs combination groups would be used to detect genetic markers and consequently early prediction of effectiveness of therapeutic response to drugs at early stage of life.

Keywords: *Genotype; Drug Interaction; Therapeutic Response*

Introduction

The knowledge of the statistical term "genotype-drug interaction, GD interaction" is a vital issue to many researchers in medical sciences for the investigation of effectiveness of therapeutic response to many diseases. The definition of the term GD interaction is when two (or more) different genotypes respond to different drugs in different ways. The reason for discussion GD interaction is the desire to find an effective way to overcome the traditional techniques of therapy of many serious diseases. As the variations in genetic makeup, drugs and their interaction is likely to play role in effectiveness of therapeutic response to many diseases. The GD interaction also indicates the different effective therapy response of different genotypes varies to different drugs (Figures 1-8).

This article will deal and focus on the role of GD interactions on many biological and pathological features and their integration and interactions in the therapy of some serious diseases (mainly: cancer and coronary heart disease (CHD). This would also be a significant task through using genomic information that can help tailor the output of a drug interaction program for a patient. This would reduce drug interactions by tailoring the presentation of drug interaction information based on genetic differences that affect drug metabolism and interactions. This is to combine specifics patient's genome with genomic information in the drug interactions to increase the accuracy and details of a drug interaction program and this would be a significant step toward providing personalized drug that would improve therapy. This would also help warn clinicians of the adverse drug interactions.

The genetic variations can contribute to individual variability in drug response and safety, including drug-drug interactions. Moreover, research result indicated that gene-drug interaction chart provides information to guide patient medication selection. The chart shows the enzyme involved in the metabolism of the associated medication. Variation was found in the patient's genotype that may impact their response to that medication. Also the chart indicates the gene that associated with medication response, but the patient's genotype is normal. Finally, in the future, identifying GD interaction may lead to a more comprehensive method of identifying individuals who are at risk for adverse drug reactions. Several gene-drug interactions are identified, where the copy number of a gene is associated to survival of a patient exposed to a certain drug [1-3].

Objectives of the Study

To discuss GD interaction through investigation the relation between of various genotypes effectiveness of therapeutic response to serious diseases, to identify molecular genetic markers using molecular characterizations (genetic make-up and genomic profile). As most pathologists deal with infected people only, some people carry genetic factors that confer effectiveness of therapeutic response to a certain disease or disorder to a particular drug.

Conceptual and statistical issues

The various genotypes by drugs interaction on effective therapy response of are illustrated in figures 1-8. Figure 1 shows GE interactin of therapy effectiveness score response (EDS) of 3 different drugs to two different genotypes (G 1 and 2). Both genotypes have no effectiveness response to drug 1. Genotype 2 shows relatively higher response to drug 2 (50 points) than genotype 1 (20 points). Furthermore, genotype 2 has attained best effective response to drug 3 (100 points) compared to genotype 1 (30 points). Therefore, it can conclude that there is a genetic variations of the two genotypes in drugs therapy and response.

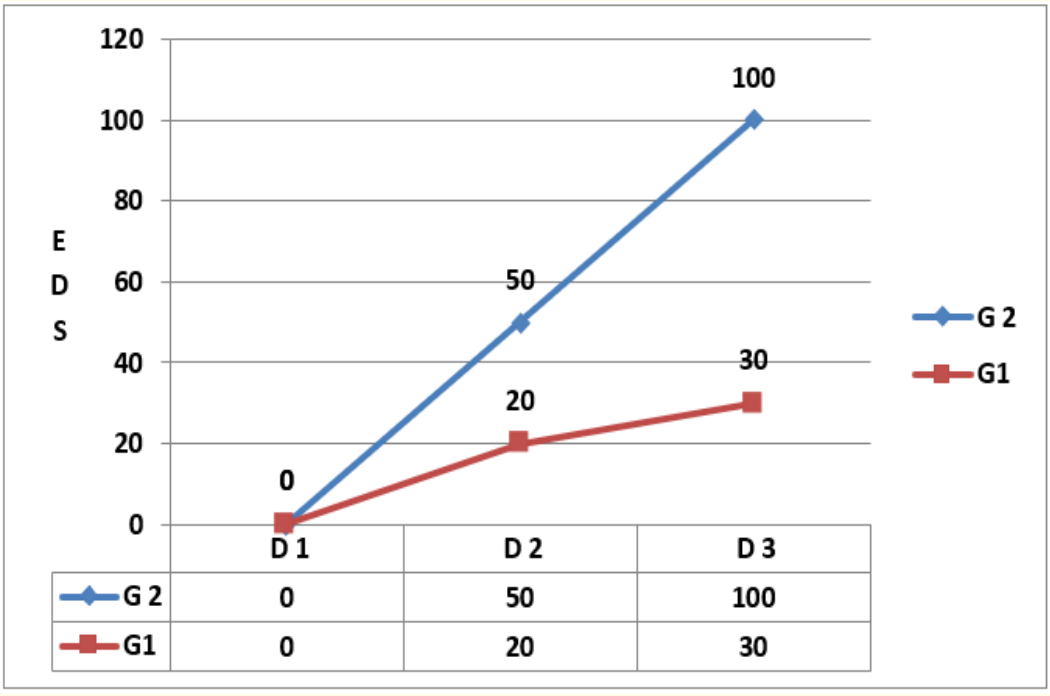


Figure 1: Genotype drugs interaction of two different genotypes (G 1 and 2) on effectiveness of 3 drugs.

Figure 2 shows a high GE interactin of 3 different drugs used in two different genotypes (G 1 and 2). Both genotypes have no effectiveness response to drug 1. However, both genotypes show positive response to drugs 2 and 3. Genotype 2 shows higher response to drug 2 (90 points) than genotype 1 (20 points). Furthermore, genotype 2 show low trend of response to drug 3 (50 points). Whereas, genotype 1 gets best and highest response (90 points) to drug 3. Thus it can conclude that drug 1 has no therapeutic effect, while drug 2 has optimum therapy for genotype 2 and that drug 3 has optimum and suitable therapy for genotype 1. Such GD interaction can direct pathologists to best use of personalized medicine.

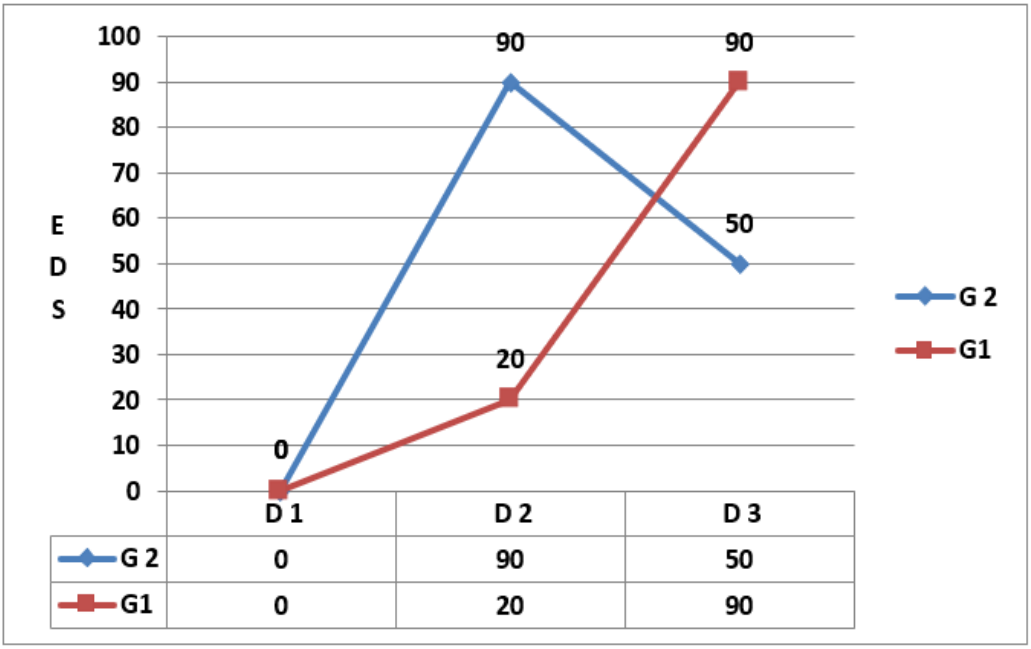
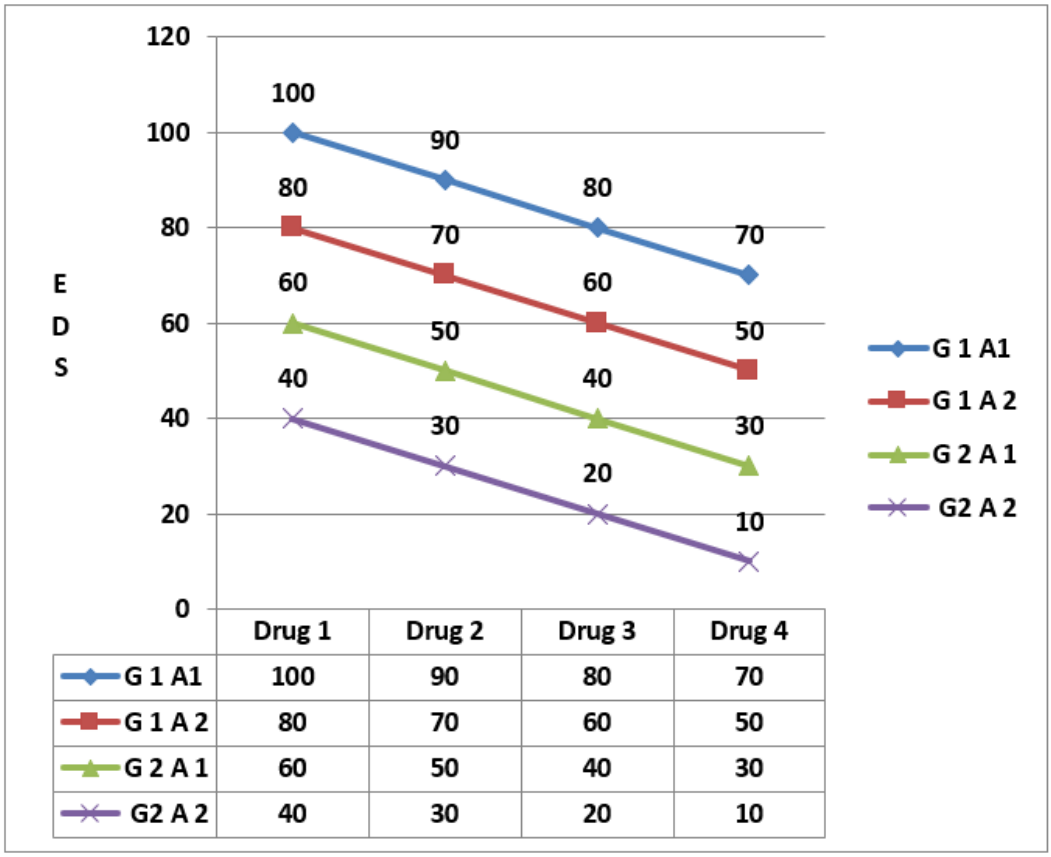


Figure 2: Effectiveness score of 3 drugs in two different genotypes (G 1 and 2). shows GE interactin of the effectiveness of 3 different drugs in the two different genotypes (G 1 and 2).

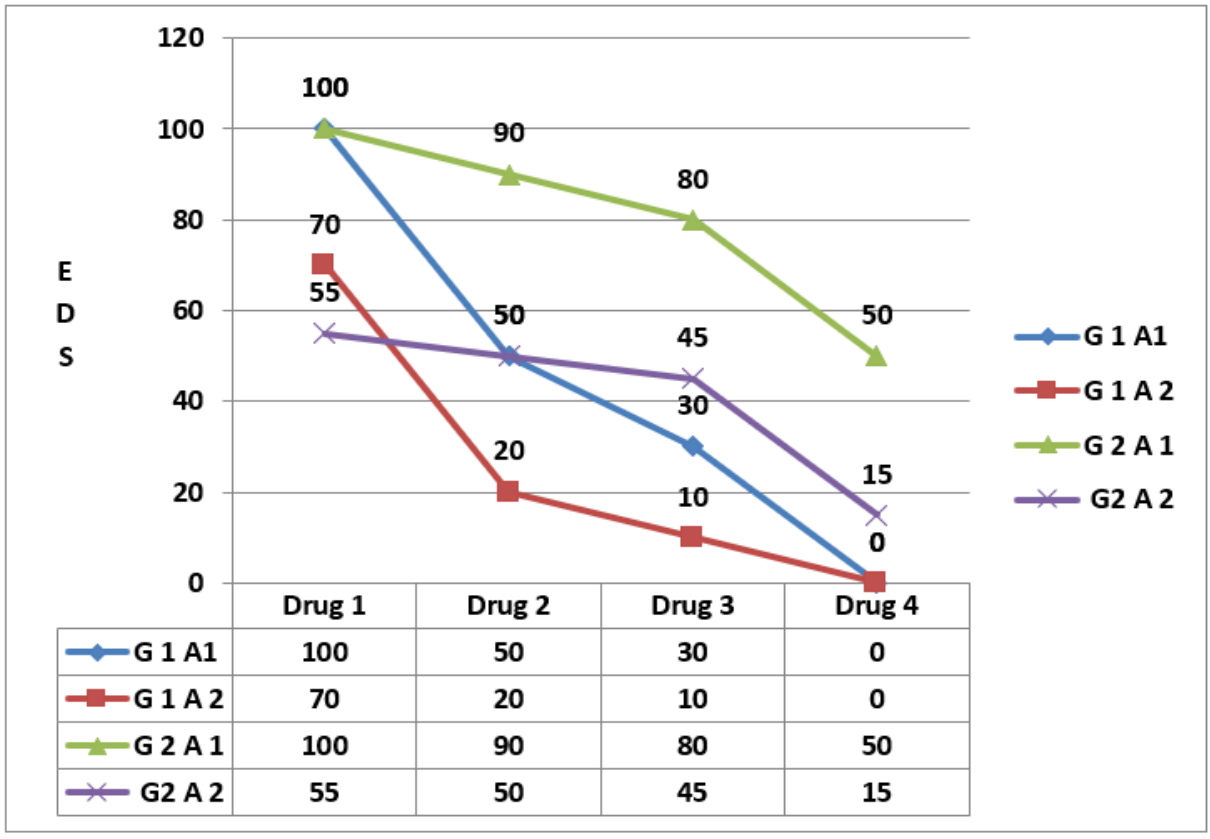
Moreover, although genotype 1 has little bit better therapy response to the four drugs compared to genotype 2 (Figure 3), the genotypes-age groups (G 1 A 1, G 1 A 2, G 2 A 1 and G 2 A 2) show similar trend in the therapy response score treated with four drugs. This indicate no interaction between drugs, age of people and various genotypes interaction. Young people of genotype 1 (G 1 A 1) shows therapy effective response score of 100 points for drug 1 decreased to 90, 80 and 70 points for drugs 2, 3 and 4, respectively. However, advanced age people of genotype 1 (G 1 A 2) shows therapy effective response score of 80 points for drug 1 decreased to 70, 60 and 50 points for drugs 2, 3 and 4, respectively. On the other hand, young people of genotype 2 (G 2 A 1) shows therapy effective response score of 60 points for drug 1 decreased to 50, 40 and 30 points for drugs 2, 3 and 4, respectively. Nevertheless, advanced age people of genotype 2 (G 2 A 2) shows therapy effective response score of 40 points for drug 1 decreased to 30, 20 and 10 points for drugs 2, 3 and 4, respectively.



	Drug 1	Drug 2	Drug 3	Drug 4
G 1 A1	100	90	80	70
G 1 A 2	80	70	60	50
G 2 A 1	60	50	40	30
G2 A 2	40	30	20	10

Figure 3: Similar therapy response score of two genotypes (G 1 and G 2) by two age groups (A 1 = young and A 2 advanced age) treated with four drugs, (no genotype drugs interaction).

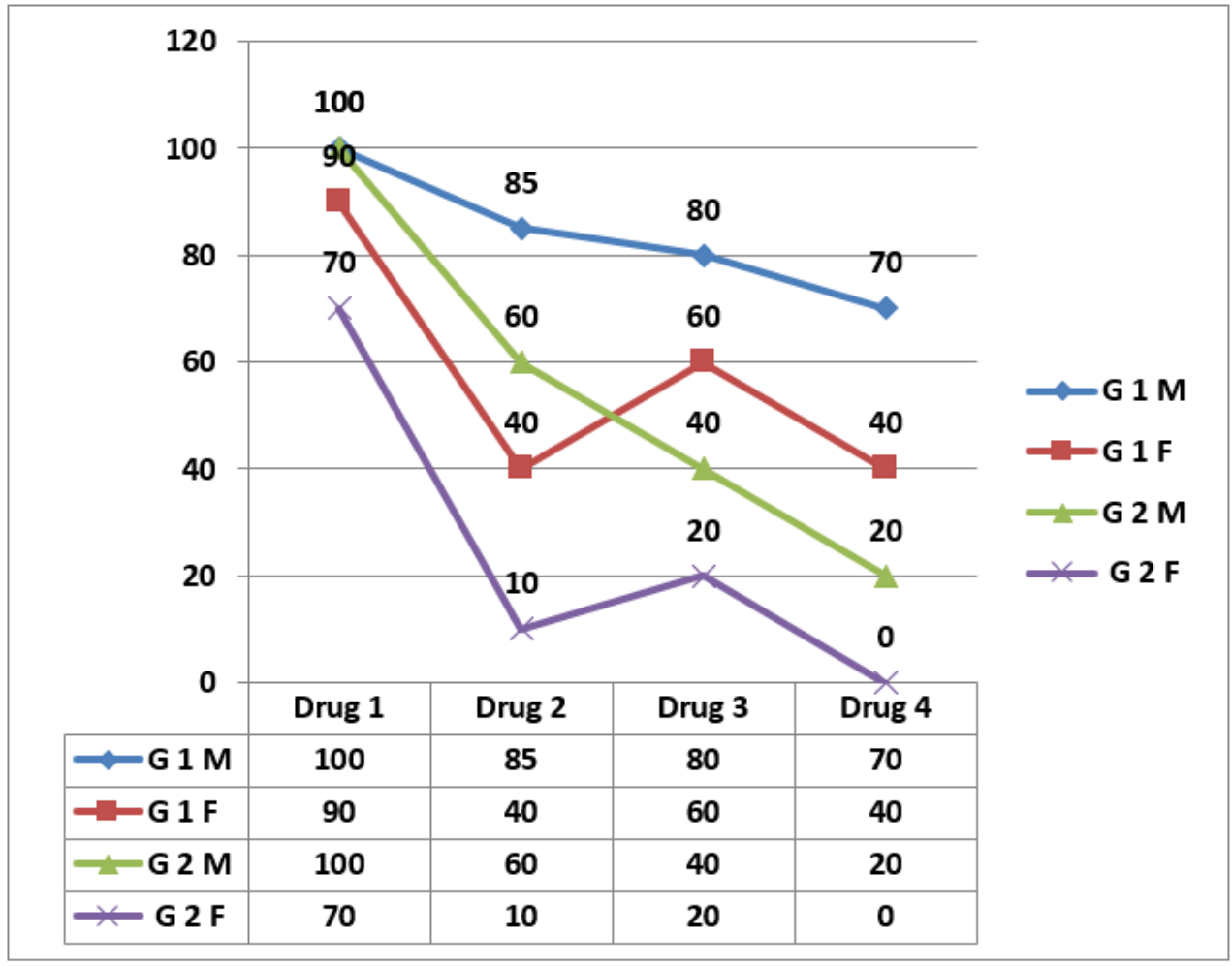
On the other hand, figure 4 indicates GD interaction among two genotypes (G 1 and G 2) by two age groups (A 1 = young and A 2 = old) treated with four different drugs. The interaction among these three variables (represent three-way ANOVA, as genotype, age and drugs are the three categorical independent variables). Genotype 1 and 2 of the young people (G 1 A 1 and G 2 A 1) respond efficiently to therapy of drug 1 (100 points). Response of young people of genotype 2(G 2 A 1) to drug 2 dropped from 100 to 90 points), whereas, response of young people of genotype 1 (G 2 A 1) unmarkedly decrease in therapy response to drug 2 (dropped from 100 to 90 points). This indicate a non-similar response in trend of the two groups (exist of GE interaction). Similarly, response of advanced age of genotype 1 (G 1 A 2) and genotype 2 (G 2 A 2) to drug 2 drop from 70 to 20 and 55 to 20 points, respectively. Such interaction showed that genotype 1 and 2 of either young or advanced age is not responding efficiently to drugs 2. Furthermore, interaction among genotypes - age respond differently to drugs 3 and 4. Advanced age of genotype 1 (G 1 A 2) and young age of genotype 1 (G 1 A 1) show no response to drugs 4. This kind of interaction is in three-way ANOVA where genotypes, age of people and drugs are the independent categorical variables recommend focusing on these important variables in personalized medicine.



	Drug 1	Drug 2	Drug 3	Drug 4
G 1 A1	100	50	30	0
G 1 A 2	70	20	10	0
G 2 A 1	100	90	80	50
G2 A 2	55	50	45	15

Figure 4: Significant genotype drugs interaction of therapy response score of two genotypes (G 1 and G 2) by two age groups (A 1 = young and A 2 advanced age) treated with four drugs.

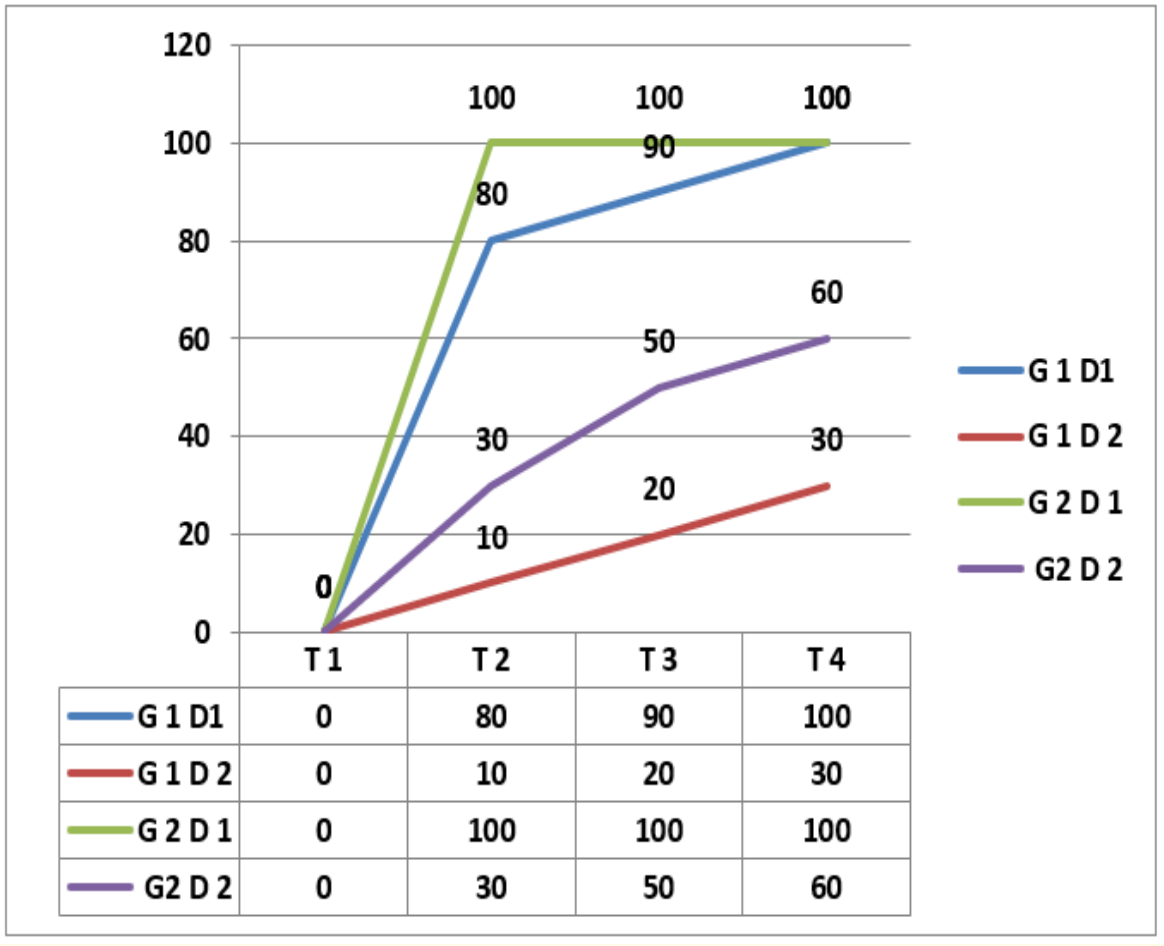
Figure 5 indicates the interaction among two genotypes (G 1 and G 2) by sex (M = male, F = female) treated with four different drugs. Male of genotype 1 respond efficiently to all drugs compared to other groups (ranged from 70 to 100 points, of therapy response score). However, male of genotype 2 shows a drop in response score from 100 for drug 1 to 20 points for drug 4. Whereas, trend response of female of genotype 1 drop from 70 for drug 1 to 60 points for drug 3, but show little bit less efficiency for drug 2 and 4 (40 pints). On the other hand, markedly decrease in therapy response of drug 1 (100 points) to 60, 40 and 20 points for drugs 2, 3, and 4, respectively. Nevertheless, female of genotype 2 show the lowest therapy efficiency score compared to other groups, where the response drop from 70 points for drug 1 to 20 points for drug 3 and to 10 point for drug 2 to no response for drug 4. Such interaction showed that genotype - sex is not responding at a similar efficiency score to drugs. This kind of interaction is of a three-way ANOVA where genotypes, sex and drugs are the independent categorical variables.



	Drug 1	Drug 2	Drug 3	Drug 4
G 1 M	100	85	80	70
G 1 F	90	40	60	40
G 2 M	100	60	40	20
G 2 F	70	10	20	0

Figure 5: Significant genotype drugs interaction of two genotypes (G 1 and G 2) by sex (M = male and F = female) of therapy response score of four drugs.

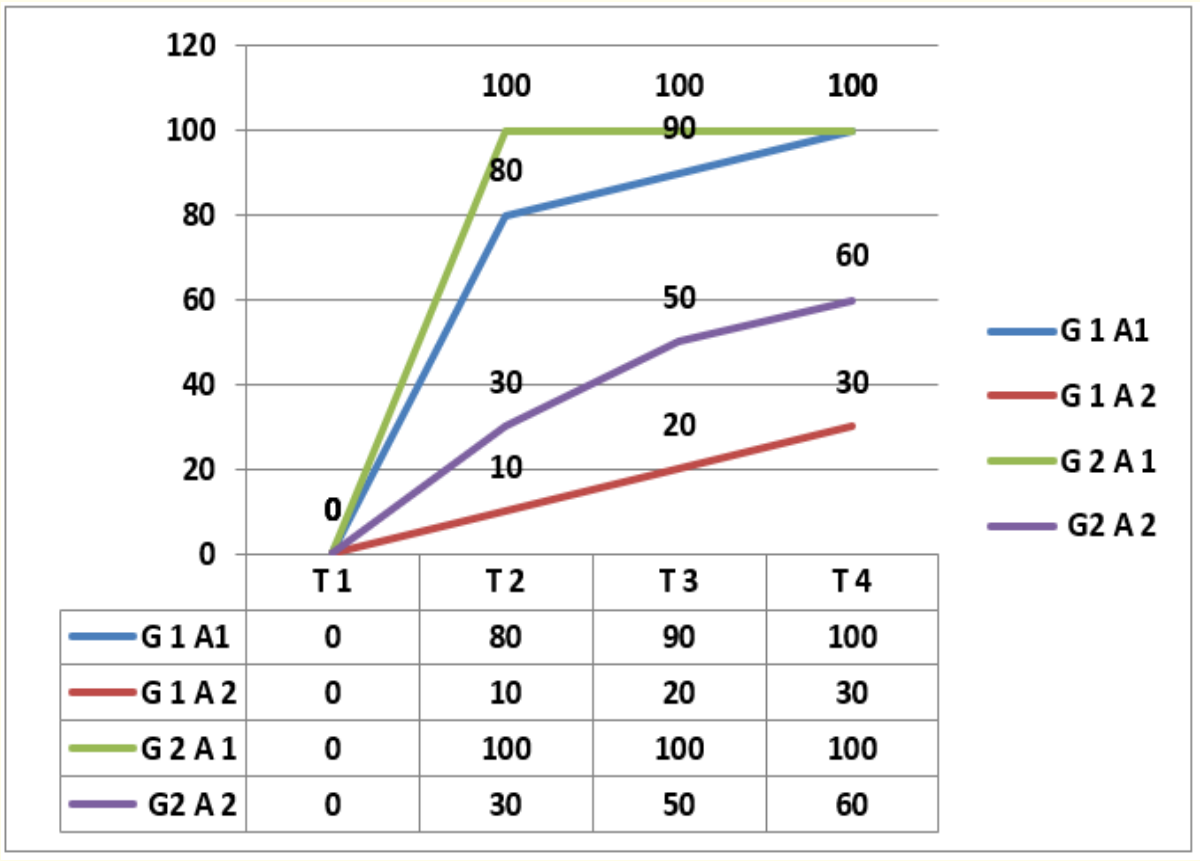
Figure 6 indicates effectiveness of therapeutic response between two genotypes (G 1 and G 2) by two drugs (D 1 = drug 1 and D 2 = drug 2) treated for 4 periods (duration of each period depends on the type of disease and drug used). The interaction among these three variables (represent three-way ANOVA, as genotype, drugs and periods are three categorical independent variables) to influence effectiveness of therapeutic response scores. Genotype 2 used drug 1 (G 2 D 1) showed fast response to therapy of drug during the 3 periods of therapy (100 points). While G1D1 showed little bit less response compared to G2D1 being 80, 90 and 100 for period 2, 3 and 4, respectively. On the other hand, G1D2 and G2D2 showed low response (10 and 30 points) on period 2 increased to 20 and 50 points on period 3 and to 30 and 60 points on periods 4. This indicate a non-similar response in trend of the two genotypes to the two drugs used (exist of GE interaction). Such interaction showed that genotype 1 and 2 used drug 1 are responding efficiently to the drugs compared to genotypes 1 and 2 used drug 2. Furthermore, interaction among genotypes respond differently to drugs during the 3 periods. This kind of interaction recommends focusing on genotypes as well as to type of drugs in personalized medicine.



	T 1	T 2	T 3	T 4
G 1 D1	0	80	90	100
G 1 D 2	0	10	20	30
G 2 D 1	0	100	100	100
G2 D 2	0	30	50	60

Figure 6: Significant genotype drugs interaction of therapy response score of two genotypes (G 1 and G 2) for 4 periods of treatment treated with two drugs.

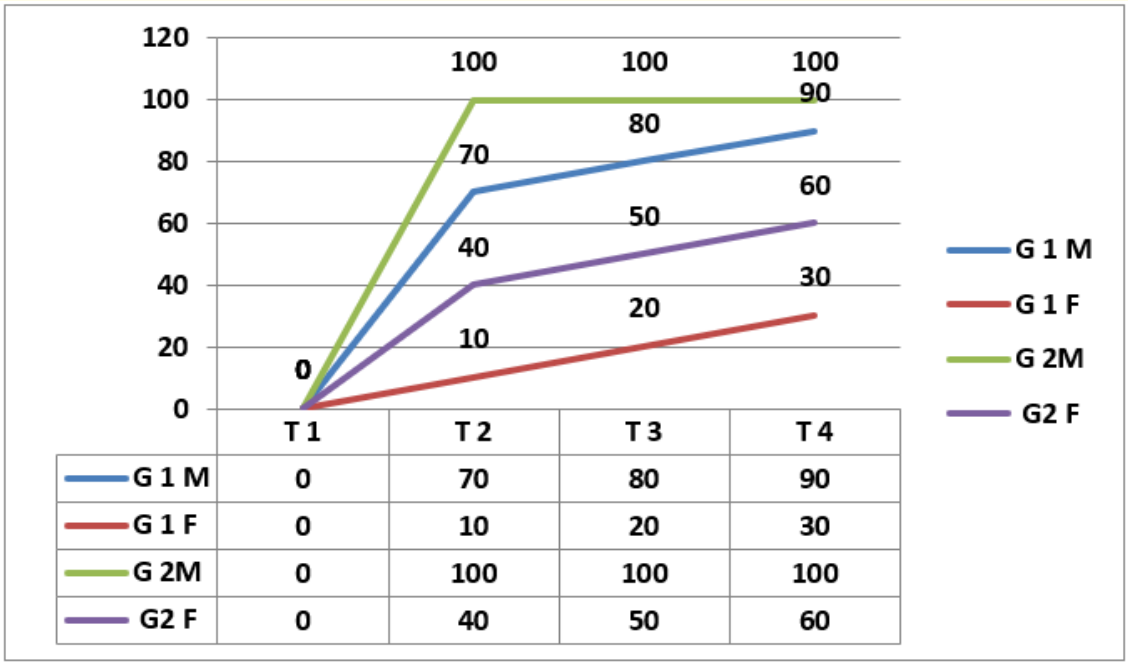
Figure 7 indicates effectiveness of therapeutic response between two genotypes (G 1 and G 2) by two age groups (A 1 = young and A 2 = old) treated with drug for 4 periods. The interaction among these three variables (represent three-way ANOVA, as genotype, age and periods are three categorical independent variables) to influence effectiveness of therapeutic response scores. Genotype 2 of the young people (G 2 A 1) showed fast response to therapy of drug the 3 periods of therapy (100 points). While G1A1 showed little bit less response compared to G2A1 being 80, 90 and 100 for period 2, 3 and 4, respectively. On the other hand, G1A2 and G2A2 showed low response (10 and 30 points) on period 2 increased to 20 and 50 points on period 3 and to 30 and 60 points on periods 4. This indicate a non-similar response in trend of the two genotypes (exist of GE interaction). Such interaction showed that genotype 1 and 2 of young age are responding efficiently to drugs. Furthermore, interaction among genotypes - age respond differently to drugs. This kind of interaction recommends focusing on genotypes as well as to age in personalized medicine.



	T 1	T 2	T 3	T 4
G 1 A1	0	80	90	100
G 1 A 2	0	10	20	30
G 2 A 1	0	100	100	100
G2 A 2	0	30	50	60

Figure 7: Significant genotype drugs interaction of therapy response score of two genotypes (G 1 and G 2) by two age groups (A 1 = young and A 2 advanced age) treated for four periods.

Similarly figure 8 indicates effectiveness of therapeutic response between two genotypes (G 1 and G 2) by gender groups (M = male and F = female) treated with drug for 4 periods. The interaction among these three variables (represent three-way ANOVA, as genotype, gender and periods are three categorical independent variables) to influence effectiveness of therapeutic response scores. Genotype 2 of the male people (G 2 M) showed fast response to therapy of drug for the 3 periods of therapy (100 points). While G1M showed little bit less response compared to G2M being 70, 80 and 90 points for period 2, 3 and 4, respectively. On the other hand, G1F and G2F showed low response (10 and 40 points) on period 2 increased to 20 and 50 points on period 3 and to 30 and 60 points on periods 4. This indicate a non-similar response in trend of the two genotypes by gender (exist of GE interaction). Such interaction showed that genotype 1 and 2 of male are responding efficiently to drugs compared to female. Furthermore, interaction among genotypes - gender respond differently to drugs during the 3 periods. This kind of interaction recommends focusing on genotypes as well as to gender in personalized medicine.



	T 1	T 2	T 3	T 4
G 1 M	0	70	80	90
G 1 F	0	10	20	30
G 2M	0	100	100	100
G2 F	0	40	50	60

Figure 8: Significant genotype drugs interaction of therapy response score of two genotypes (G 1 and G 2) by gender groups (M = male, F = female) treated for four periods.

Suggestions to tackle the future challenge on effectiveness of therapeutic response

A well-defined experimental design should be contain many experimental groups representing GD interaction (combination of categorized variables classified by age, gender and different drugs) to identify GD combination groups for stratified effectiveness of therapeutic response via screening people who will show fast effective of therapeutic response versus people, who did not show any effectiveness of therapeutic response across various GD combination groups. Such experimental design allows investigating and identifying best gene in these GD combination groups, which may suggest the possibility of that gene to be responsible for better effectiveness of therapeutic response. Nevertheless, It is not enough to consider the average treatment response (the symptom levels following treatment) for each genotype (patient), but it is important to consider the time required to cure the disorder or disease. Genetic variations can contribute to individual variability in drug response and safety, including drug-drug interactions. Pharmacists are using best approach for optimizing treatment strategies aimed at decreasing disease incidence and improve therapy. Some alleles that vary in frequency between specific populations have been shown to be associated with differential responses to specific drugs [4].

Elucidation the assessment of using statistical GD interaction is a vital issue for pathologist, pharmacists, molecular biologist, geneticists, toxicologists and statisticians. Most pathologists deal with infected people.

The suggested project experimental design will be based on randomized complete block design with several categorical GD combination groups, where blood and/or tissue samples for genomic profile will be collected from at least 1000 persons of each different categorical GD combination groups as follow:

- Healthy persons as negative control group, who do not treated with any drug treatment (this group can be breakdown according to age and gender).
- Healthy persons as positive control group, who do treated with drug treatment (this group can be breakdown according to age and gender).
- Infected persons of any type of cancers, CHD or any disorder case, who effectively will show fast response to drug (this group can be breakdown according to age and gender
- Infected persons of any type of cancers, CHD or any disorder case, who respond moderately to the drug (this group can be break down according to age and gender).
- Infected persons of any type of cancers, CHD or any disorder case, who did not respond to drug (this group can be breakdown ac cording to age and gender).

Genomic profile should be investigated through DNA extraction from each person of the above GD combination group. The quality and quantity of DNA will be checked and quantification will be done by for spectrophotometer. Furthermore, biopsy specimens will be collected for pharmaceutical, histopathological and immunohistochemistry characteristics. Diversity of molecular markers at the DNA level within and among individuals within groups can be used to detect genetic markers and consequently early diagnose effectiveness of therapeutic response at early stage of life. Persons with high effectiveness of therapeutic response rank score to drug treatment would be better than people who did not show response to drug. Such evaluation can resulted in Genetic Marker Assisted in Identification Genotypes Response to drugs.

Moreover, genotypes by drugs interaction (GE), can be define as different effective responsiveness of various genotypes (low vs. high effective therapeutic and between them) to different drugs. Figures 1 to 8 show illustration of what is all about GE interactions.

It is important to remind the readers of some statistical background, mainly analysis of variance (ANOVA). The two-way ANOVA with 2 independent categorical variables (genotypes (G) and drugs (D), and dependent continuous variable (effectiveness of therapeutic response score (DRS). In common applications of ANOVA, one can compare means of the independent categorical variables through calculation of the variability between the groups to the variability within the groups. Furthermore, it is important to check differences in means of different levels of the different combinations of the 2 independent categorical variables (GD interaction) for the dependent continuous variable (score). For the purpose of illustration of the represented different levels of the GD interaction, score was coded and ranged from 0 to 100.

Conclusion

It may concluded that there are genetic variations among individuals, families and population in effective therapeutic response. Both of genetics and drugs as well as their interaction contributed to effective therapeutic response. Person's age, sex, genotypes, drugs and duration of treatment are important issues and should be considered by clinical profession, pathologists, pharmacists and molecular geneticists in investigating, diagnosing, preventing, and treating diseases.

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