Genetic Markers and Drug Response in Egyptian Populations: A Pharmacogenomics Perspective

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Contents

1 Abstract

The paper digs into the effects of genetic variability on drugs and medication metabolism and the ability of pharmacogenomics for individualized medicine. Digging into the methodology of genetic differences and their impact on individual drug response required specific examples such as HER-2, Thiopurine S-methyltransferase, and Cytochrome P450 enzyme and also required an explanation of the molecular basis of that process which is the transcription and splicing processes. Despite the benefits of pharmacogenomics and individualized medicine, unfortunately, it's limited in Egypt. Studying the limitations required a survey to prove that the Egyptian medical staff lack knowledge about pharmacogenomics, a journey to a governmental public hospital to show the corruption of the staff and the lack of abilities and machines, a lot of searching about the Egyptian portfolio in genetic variability and how the Egyptian population differs from the whole world but unfortunately, nothing was found which proved that there is a lack of research about that topic in Egypt. Suggesting proper solutions of those problems was a mission of the paper as it suggested raising the salaries of the medical staff, enhancing the health sector, etc… to make the existence of pharmacogenomics stronger in Egypt.

2 Introduction

2.1 The significance of genes in the response to the medications

In the modern era of the medical field, studying the genetic role in drug metabolism has become a significant area of research. The human genome is very complex as it affects every single area of our bodies [1]; so the genetic variations among individuals can affect their ability to metabolize different drugs; some can metabolize faster, some do it slower, and some can't metabolize specific medications at all. To give an example of the complexity and effect of genes, the HER2 gene on the 13th chromosome would be the best one. It's composed of almost 920,000 base pairs including the introns. To view the full sequence of HER2 and the 3D structure of its protein, go to. The HER2 gene codes for the HER2 receptor, which is crucial in treating breast cancer. TDM-1 is an antibody drug that binds to the HER2 receptor to prevent the spreading of the cancerous cells according to the study [4]. Any single mutation in the exons of those 920,000 nucleotides can either lower the number of the receptors in the body or increase it.

2.2 Transcription

Before digging into the realms of personalized medicine some scientific concepts should be understood like the transcription process (**Figure (1)**). According to the reference [5], firstly, a protein called the transcription factor (TF) binds to the promoter region (specific sequences, TATA for example, in the DNA that initiates the process of transcription). The RNA polymerase type 2 binds to the TF and starts the synthesis of the RNA; that process is called the initiation. It uses only one strand of the DNA as a template strand for the RNA. The polymerase moves downstream, unwinding the DNA and elongating the RNA transcript 5' to 3'. After transcription has occurred, the DNA strands re-form a double helix; this process is called elongation. Once RNA polymerase II ends its mission, it runs into a sequence called the terminator which simply unsticks it from the DNA strand; that process is called termination.

However, the RNA made out of this process is hnRNA and what makes protein is mRNA. So, a process called splicing occurs (**Figure (2)**). The difference between the hnRNA and mRNA that the hnRNA has introns which are noncoding sequences between the exons (the coding sequences). Splicing is made through a protein called spliceosome that attaches to the end of to exons to make a bubble of an intron and removes it; then binds the two exons together. After transcription translation of the mRNA to protein occurs.

After understanding the molecular basis of the roles of genes in protein synthesis in the human body, it's easy to understand how individual variations affect every single process in our bodies including metabolism. The variations can be either in the genes themselves as the human DNA includes more than 3 billion base pairs [3], and those pairs vary from one individual to another, or in the process of transcription as a human body can have fewer TFs than the standard so less gene expression and fewer proteins; a spliceosome can splice the hnRNA incorrectly due to mutations and the mRNA will make a whole another protein than the one that is supposed to be synthesized.

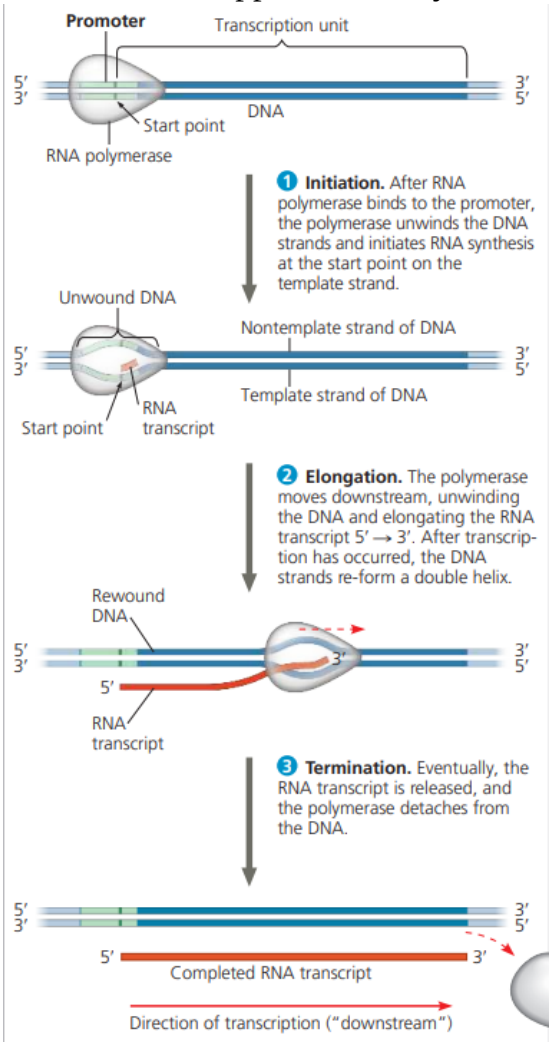


Figure 1 The stages of transcription
Campbell Biology [5], Chapter 17, section 2, figure 17.8

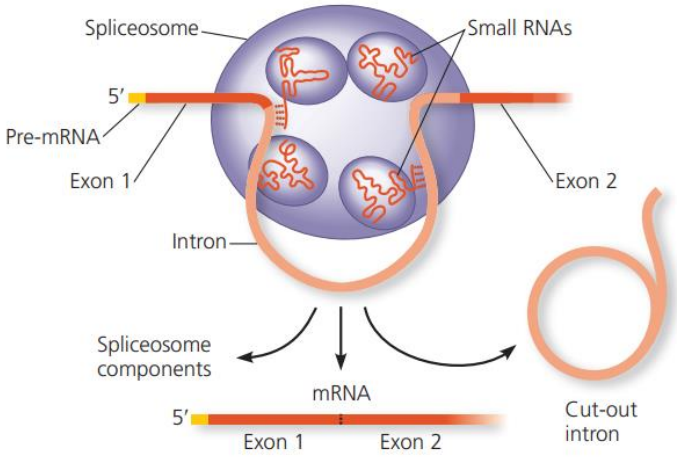


Figure 2 A spliceosome splising an hnRNA
Campbell Biology [5], Chapter 17, section 2, figure 17.13

2.3 Pharmacogenomics perspective

Pharmacogenomics represents a significant advancement in personalized medicine, aiming to tailor drug therapies based on an individual's genetic profile. This field merges pharmacology, the study of drugs and their effects, with genomics, the study of the genome and its functions. By analyzing genetic markers, pharmacogenomics can provide insights into how a patient will respond to specific medications, allowing for more precise and effective treatment plans. One of the primary benefits of pharmacogenomics is its potential to enhance drug efficacy and safety. For instance, by identifying genetic markers associated with drug metabolism, healthcare providers can select medications and dosages more likely to be effective for a given patient while minimizing the risk of adverse effects. This approach improves patient outcomes and reduces the trial-and-error process often associated with finding the right medication and dosage [24].

Pharmacogenomics has already demonstrated its value in several areas of medicine. For example, in cancer therapy, pharmacogenomic testing is used to predict responses to chemotherapy drugs, allowing for more personalized cancer treatment. In cardiology, genetic testing can help identify patients who are at higher risk of adverse reactions to anticoagulants, enabling safer and more effective management of thromboembolic disorders. These successes highlight the transformative potential of pharmacogenomics in creating more individualized and effective treatment strategies [24].

2.4 Limitations of pharmacogenomics in Egypt

The spreading of pharmacogenomics is actually very limited in Egypt. Despite its significance in the medical field, it faces some hard challenges to exist in Egypt. The study aims to prove its hypothesis of why the existence of pharmacogenomics is limited in Egypt. The first and the main reason is the lack of awareness about pharmacogenomics, especially among the medical field professionals such as doctors, surgeons, etc..... Secondly, there are no suitable abilities to apply pharmacogenomics. Egypt is a developing country that has a terrible health sector, so most of the hospitals in Egypt don't have the ability to test the patients genetically for a specific gene.

Moreover, the lack of research is a very influencing factor. Most of the papers made about pharmacogenomics discuss the mutations and phenomena among the populations of Western Europe and North America. While searching for papers about the Egyptian population or the whole MENA region, no papers were found. The paper also aims to make some hopeless cases of some patients logical; most of the doctors in Egypt use standardized doses for medications, and some patients don't respond to the treatment. One of the reasons besides the psychological issues is genetic variation. Both of the hypothesis and the study goals will be proved and discussed in the following sections of the paper.

3 TPMT and CYP enzymes

3.1 TPMT Overview

Thiopurine S-methyltransferase (TPMT) is a significant enzyme for metabolizing thiopurine medications. There are mainly three types which are azathioprine, 6-mercaptopurine, and thioguanine. The azathioprine is involved in the therapy of treatment of active rheumatoid arthritis (RA) and the prevention of kidney transplant rejection [7]. Mercaptopurine is mainly used to treat acute lymphocytic leukemia (also called acute lymphoblastic leukemia and acute lymphatic leukemia: a type of cancer that begins in the white blood cells). Those drugs are metabolized by TPMT with the assistance of some other enzymes like hypoxanthine-guanine phosphoribosyl transferase (HPRT) [7].

The TPMT enzyme is transcripted from the TPMT gene (also known as TPMTD) [16] which is located on the 6^{th} chromosome. The gene consists of 26,761 nucleotides including the introns.

3.2 TPMT, A Deeper Dig

TPMT's biochemical role is crucial for the whole process, TPMT methylation is the most significant one. TPMT controls the transfer from the methyl group from S-adenosylmethionine (SAM) to thiopurine drugs as the following chemical equation. [17]

Thiopurine+SAM→Methylated Thiopurine+S-adenosylhomocysteine (SAH)

That reaction mainly eliminates the activity of thiopurines to reduce the effect of their toxicity. The efficiency of TPMT can significantly influence both the effectiveness and safety of thiopurine-based therapies.

The mechanisms of azathioprine, 6-mercaptopurine, and thioguanine are significant in understanding their role. Azathioprine is converted into 6-mercaptopurine (6-MP) in the body. It is then metabolized into various active thiopurine metabolites that prevent DNA synthesis, which is beneficial in suppressing the immune system or killing cancer cells [18]. Moreover, 6-thioguanine (6-TG) is Similar to 6-mercaptopurine, it prevents DNA synthesis and is used primarily in the treatment of acute myeloid leukemia (AML).

Knowing the drugs that the patient is taking or was taking in the past will help to specify the dose of thiopurine drugs. A lot of nonsteroidal anti-inflammatory drugs such as mefenamic acid, tolfenamic acid, naproxen, and ketoprofen are considered as TPMT inhibitors which will increase the risk of toxicity [19].

The activity of TPMT can vary due to genetic variability; individuals with high activity suffer from the rapid metabolism of purines as they are metabolized before they even perform their role. The ones with normal activity perform perfectly with the standard doses and balance between efficacy and safety. In people with low TPMT activity, the mentioned drugs are metabolized slowly which increases the danger of toxicity. That issue can lead to severe side effects such as marrow suppression (also known as myelosuppression: the decrease of production of immune cells), which manifest as anemia, leukopenia (low white blood cell count), and thrombocytopenia (low platelet count). Pharmacogenomics appears in that area as both of the activity of the transcription and the activity of the TPMT to put the most suitable dose to the patients to achieve therapeutic efficacy. Managing the adverse effects is crucial to save the patients from more suffering; routine monitoring of blood cell counts is crucial to

detect early signs of myelosuppression.

3.3 CYP Overview

Cytochrome P450 enzymes (CYP) are a wide diverse group of heme-containing enzymes found in almost all of living organisms; the enzymes play an essential role in metabolizing various substances such as drugs, steroids, and fatty acids. To give an overview of their biochemical role, their role in oxidative biotransformation must be mentioned. Their classification is simple to understand, firstly they are classified into main families such as (CYP1, CYP2, etc…); the families are then classified into subfamilies such as (CYP1A, and CYP1B). And lastly, every enzyme from the CYP group has its own unique name such as (CYP3A4) [20].

3.4 CYP, A Deeper Dig

Firstly, the structure of CYP enzymes is characterized by the presence of a heme group. That group is responsible for the oxidation of substrates. The structure includes a huge protein with a hydrophobic region that binds to the substrates and then the heme group binds to the matter and makes a coordination bond that enables the substrate to make oxidative reactions. While deepening down into the mechanism of that essential role, the six general steps of the catalytic cycle will be found. Firstly, the substrate binds to the active hydrophobic region of the enzyme. Then, the heme iron is reduced from the ferric Fe^3 to the ferrous Fe^2 by an electron donor. Then an oxygen molecule binds to the ferrous iron. Furthermore, the molecule is activated, and the reactive intermediate oxidizes the substrate. Lastly, the oxidized product is released from the enzyme [21].

The function of CYP enzymes is crucial for the existence of the human race as they are mainly involved in the first phase of drug metabolism; they make the drugs more hydrophilic which makes them easier to be excreted, CYP3A4 is one of the most significant and it's involved in the metabolism process of approximately 50% of the known drugs [22].

CYP are also involved in the detoxification of xenobiotics (foreign compounds) by converting them into more water-soluble compounds; this process is significant in protecting the body from the harm of xenobiotics [23].

CYP are affected by genetic variability, polymorphisms can be widely various among individuals with different phenotypes including poor, intermediate, extensive, and ultrarapid metabolizers. As mentioned in the section on TPMT, the poor will metabolize the drugs slowly, and so on and so on. Genes aren't the only factors affecting CYP, environmental factors, inhibitors, inductors, etc… are also important factors.

Modern biotechnology aims to use those differences to enhance the total experience of getting treated. Making genetic tests and biological systems will help give the patients the most accurate dosage and predict the drug response more accurately; that is exactly what pharmacogenomics aims to do [24].

4 Pharmacogenomics, Egyptian Limitations and Challenges

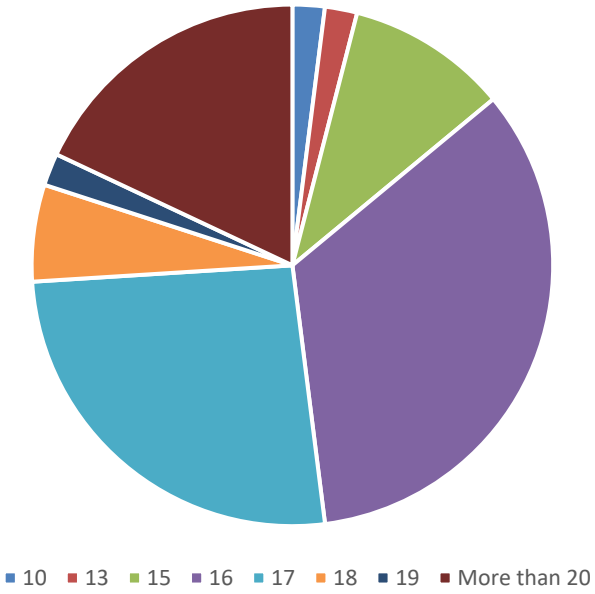
After knowing the benefits and significance of pharmacogenomics, searching for the reasons of its inexistence of in the MENA region and Egypt specifically will be the topic discussed on the next sections.

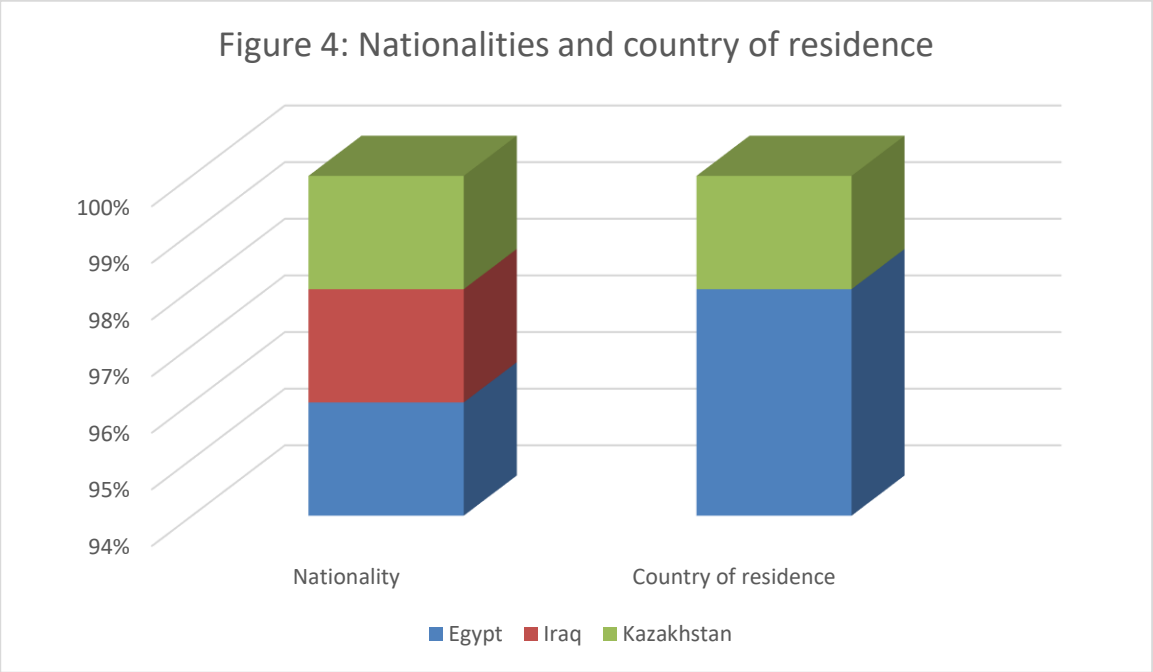
4.1 Lack of Awareness

The paper showed a hypothesis in the above to try to put logical reasons of that issue; one of them was the lack of consciousness. In order to prove the hypothesis, a Google form was created to collect thoughts and opinions. Access the questions from **here.** The first questions were about general information to determine the general background of the responses. The age of the responders was one of the most significant factors to determine the knowledge background. The average of the ages was 19; as shown in **Figure 3.**

Most of the responders were Egyptians (96%), and 98% of them were living in Egypt as shown in **Figure 4.**

Figure 3: ages of the responders





32% of the responders were involved in the medical field. Access the responses from **here.** A doctor responded that an IBS (a disorder that affects the stomach and intestines, also called the gastrointestinal tract) patient wasn't responding to some medications for an unknown reason.

Moreover, 26 responders out of 34 non-involved in the medical field and put less than 5 on a scale from 1 to 10 if they heard about pharmacogenomics which means that most of the people don't know anything about pharmacogenomics; 9 responders out of 16 involved in the medical field didn't know about pharmacogenomics which demonstrated that the medical staff in Egypt doesn't have enough consciousness about pharmacogenomics. The paper's mission will be to raise awareness of the medical field so the paper will be sent once finished to the people involved in the medical field.

4.2 Lack of Abilities

The Egyptian health sector is known as a miserable terrible sector, especially the governmental sector. To grip the truth without getting affected by the bias of some journalists; a journey to El-Warraq Central Hospital was made. The first that was observed is the depressing entrance and lobby of the hospital. There was a ticket seller that was to get to the doctor you want, it was for only 5 EGP which is 10 US cents; we got a ticket for the internist. Then, the clinic entrance was crowded with people. There were two long lines, one for men and one for women. After waiting for 45 minutes while standing on the feet which are really bad conditions for some cases. After getting into the clinic, I was surprised that the office boy was just making 4 patients get in at every turn. There was no privacy for any patient; The doctor didn't make any effort, he was sitting on a chair asking every one of the four patients what they feel to write a medical recipe for them without medical examination and diagnosis. Lastly, I wanted a report that I'm sick and I want some days of rest, the staff really made it complicated and said that I have to go there for at least 3 days to get that report. One of the security men asked for 200 EGP (4 USD) to get me that report in 5 minutes; he was honest but he got me an empty report that was signed by a doctor and stamped by the hospital which means that I could write anything in it and it will be an official document.

That short story showed the corruption of the health sector and how miserable it is. So, in the case of El-Warraq Central Hospital, which is the case of most public hospitals, it's really hard and complicated to apply pharmacogenomics because of the corruption of the staff and the lack of suitable machines as the lab just had the smell of the public bathrooms. The managers are corrupt as well, as there are reports that pharma companies changed the concentrations and regulations of some medicines to make a profit [14].

Another reason why it's hard to apply pharmacogenomics is the lack of research. While searching to discover the common cases in Egypt and how active are the enzymes in the Egyptian populations, nothing was found. All was found was about the populations of North America, Western Europe, and East Asia. Without knowing the common cases in a specific population, the doctors won't be able to decide a specific dose, for example, when the patient has poor activity.

4.3 Results Conclusion & Recommended Solutions

The reasons of the inexistence of pharmacogenomics in the Egyptian medical field were discovered through 3 steps, creating a survey, going to a hospital, and researching. The first reason was the lack of consciousness as more than 50% of the responders didn't know anything about it. The second reason was the lack of abilities as a corruption of the staff of the specimen hospital was discovered and a lack of suitable machines was observed. The third and last one was the lack of research as while searching, there were no papers about the Egyptian populations. So, the paper's hypothesis in putting predicted reasons is proved as all of the predicted reasons are real major challenges that require a lot of efforts to be solved.

The paper should give suitable suggestions on how to solve those issues to be beneficial. Firstly, giving sessions about pharmacogenomics in medicine, pharmacy, dentistry, etc… faculties to raise the consciousness of the medical staff of the future about personalized medicine. The second issue which is complicated can be solved by improving the quality of hospitals, hiring new doctors, increasing the number of hospitals so there will be no more crowded hospitals, and increasing the salaries of the medical staff to decrease the corruption levels; making periodic inspections to make sure that every patient gets his privacy and his diagnosis. Lastly, making money prizes for every researcher will spend some months discovering the mysteries of the genes of the Egyptian populations.

5 Conclusion

In conclusion, pharmacogenomics shows the mechanisms and methodologies of personalized medicine which increases both the safety and therapeutic efficacy. The study highlighted the significance of pharmacogenomics using multiple important examples; however, the main mission is to address the reasons of the inexistence of pharmacogenomics in Egypt. The major reason which was the lack of consciousness among the citizens and the medical field staff was addressed by a survey that took the opinions of 50 people of different ages, nationalities, and cultures. The second one was addressed by a journey to El-Warraq Central Hospital and corruption among the staff and a lack of abilities were observed there. The paper put some suggested solutions to solve those problems such as enhancing the health sector, making great money prizes for every researcher researching Egyptian genetic differences, and putting pharmacogenomics as a subject in the medical curriculum to raise the awareness of the medical field about that topic.

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