

Research Article

Pedigree Analysis of Genetic Mutation in Human Families of District Karak Khyber Pakhtunkhwa Pakistan

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Abstract

Diabetes mellitus and albinism are two distinct genetic conditions that have been observed in human populations, including families in the District of Karak. This study aims to explore the prevalence and genetic mutations associated with these conditions within this specific demographic. Diabetes mellitus, characterized by chronic hyperglycemia and insulin resistance, has a multifactorial etiology with both genetic and environmental components. Albinism, on the other hand, results from mutations in genes responsible for melanin production, leading to hypopigmentation of the skin, hair, and eyes. Diabetes Mellitus is more common in adult as compared to children. During diabetes Mellitus the patient show lot of symptoms such as weight loss, polyuria, polydipsia sometime with blurred vision and polyphagia etc. are reported in patient of diabetes mellitus second disorder which we studied is Albinism which is a heterogeneous group of autosomal recessive disorder which is mainly characterized by abnormalities low amount of melanin in the skin, hair, eyes etc. It means that if the melanin are not produced in sufficient amount it will cause albinism this diseases is very rare but it is mainly caused by different gene mutation. The people with oculocutaneous albinism have pale skin, sandy colour hair, light brown eyes, nystgmus and poor visual activities. Genetic studies of albinism reported that seven non-syndromic OCA genes among which mutation in TYR and OCA genes mutation is mainly reported. This research project was aimed to study pedigree analysis of genetic mutation for autosomal dominant diabetes mellitus and X-linked autosomal recessive albinism in human families of district karak. The two family have been reported one of diabetes mellitus and one of albinism so the detail interviewed were conducted with all the affected individual their parents and normal individual of the family. Pedigree analysis and family tree was drawn to check the linkage for results.

Keywords

Pedigree Analysis Genetic Mutation Karak, Khyber Pakhtunkhwa, Pakistan

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1. Introduction

The term Mutation was coined by Hugo de Veries in 1900, a rediscover of Mendel principles is both the process by which a gene or chromosome changes, structurally as a result of that process [1] mutation is a change in the nucleotide sequence of an organism's genome, virus genome, or extra chromosomal DNA. DNA or RNA can be found in viral genomes. Errors in DNA or viral replication, mitosis, or meiosis, as well as other types of DNA damage (such as pyrimidine dimers caused by ultraviolet radiation), result in mutations, which may undergo error-prone repair especially micro homology-mediated end joining, cause an error during other forms of repair, cause an error during replication or translation synthesis [2].

A list of genes have been reported that are associated with diabetes complications including ACE and AKR1B1 in nephropathy, VEGF and AKRB1 in retinopathy and ADIPOQ and GLUL in cardiovascular diseases [3] Type 1 diabetes is basically described as an autoimmune disease that results in the destruction of pancreatic beta cells, however, single gene mutations and SNPs have been found to be associated with the susceptibility to this type of diabetes. Initially, two gene mutations were linked to the development of type 1 diabetes including the autoimmune regulator (AIRE) gene which affect the immune tolerance to self- antigens leading to autoimmunity [4]. The FOXP3 gene which results in defective regulatory T cells [5]. An addition, a mutation in the histone deacetylase SIRT1 gene predominantly expressed in beta cells involved in the regulation of insulin secretion [6]. It played a role in modulating the sensitivity of peripheral tissues to insulin [7] was detected in type 1 diabetes patients [8].

Recently, additional mutations and SNPs in the CTLA-4 +49A/G and HLA-DQB1 and INS gene VNTR alleles were found to be associated with type 1 diabetes, which have the advantage of differentiating between Latent autoimmune type 1 diabetes and type 2 diabetes [9]. The HLA-DQB1, in combination with HLA-DR alleles and a polymorphism in PTPN22 gene seem to be associated with the age onset of late type 1 diabetes [10]. The first gene implicated in monogenic diabetes was the Glucokinase (GCK) gene which functions as a pancreatic sensor for blood glucose where more than 70 mutations in the gene were identified that affected its activity [11].

A Recent study on GCK gene mutations causing neonatal and childhood diabetes showed that the majority of mutations resulted in the loss of the enzyme function primarily due to protein instability [12].

The phenotypic heterogeneity of this condition is due to different gene mutations affecting various steps in the melanin biosynthetic pathway, resulting in varying degrees of decreased melanin pigmentation. At present at least 16 different genes have been identified which, when mutated, result in different types of albinism [13]. OCA1 results from mutations in the Tyrosinase gene (TYR, MIM 606933) and is the second most common subtypes occurring in approximately 1 per 40,000 individuals in most populations. Tyrosinase is a cop-

per-containing enzyme expressed in the melanocytes, and catalyzes the oxidation of tyrosine to L-dihydroxy-phenylalanine (DOPA) and the subsequent dehydrogenation of DOPA to dopaquinone, the first two rate-limiting steps in the melanin biosynthetic pathway the Partial or complete lack of functional Tyrosinase results in reduction or absence of melanin pigment in the skin, hair, and eyes throughout life from birth. Despite impressive advancement in the genetics of albinism, and a large number of reported TYR mutations very little information is available on Indian patients [14]. Worldwide, OCA affects 1 in 17,000 individuals, which means that ~1 in 70 people are carriers of the defective OCA allele [15]. Molecular genetic studies have so far reported seven genes (TYR, OCA2, TYRP1, SLC45A2, SLC24A5, C10ORF11, and MC1R) and an uncharacterized locus (OCA5) responsible for causing on-syndromic OCA subtypes. The product of these OCA genes are involved in the melanin bio-synthesis pathway [16]. Among the known OCA genes, TYR and OCA2 are the most commonly reported defective genes globally, and in Pakistani families as well. Genetic studies have shown that the splice mutation 1045–15 T>G in OCA2 is the most frequent pathogenic allele (11.3% prevalence) among OCA patients [17].

2. Materials and Methodology

2.1. Study Area

This research study was conducted in District karak. District Karak is a district in Kohat division in Khyber Pakhtunkhwa province of Pakistan. It is situated to the south of Kohat district and on the north side of Bannu and Laki Marwat district on the main indus highway between Peshawar and Karachi. It gained a district status in 1982. Data collection was initiated in the month of September 2021 and completed in July 2022. The Data were collected in the two sites of district karak which including Urban area of Tehsil Karak and Rural area of Tehsil Takht-e-Nasrati.

2.2. Study Subject

All the participating family belong from district karak. These family were educated and know the purpose and benefits of the study. We have currently study the genetic mutation in different family of human in district karak. Generally we study two families inheriting different genetic disorder from generation to generation were included in the current study. These families were sampled from different parts of District karak, KP. We have visited to various parts of district karak using different resources or tools to identify the affected families. We visited homes of all the affected families and here we recorded the clinical information. Participants were interviewed the elder or relative of the family to give information about the family structure and History of the disease. After obtaining these information we have to make or construct the family pedigree.

Firstly for obtaining information a lot of difficulty were faced due to lack of knowledge but finally managed to get information using local source which help to identify these family from remote parts of district karak KP. A detailed pedigree of the diseases were constructed by interviewing the many members of the family specially the elders and finally a detailed relevant clinical examination was done using a standard Performa to conform the diagnosis of diabetes mellitus and Albinism.

2.3. Pedigree Analysis

Extensive pedigrees were created for each family using the standardized pedigree nomenclature to understand the pattern of inheritance of the ailment and the segregation of the disease gene in the family [18]. The elders of the family were thoroughly interviewed in order to elicit as much information as possible about the prior generations. Because the families who are part of the study are At times, the clan has been consanguineous for generations, and practically everyone in the clan is a relative. As a result it was easy to confirm the exact genealogical links between them in the ancestors and descendants so for each family, extensive pedigrees were drawn using a conventional approach for the purpose of genetic inference, following the segregation pattern within the each family. Extensive personal interviews with family elders yielded the exact genealogical links for all the afflicted individuals in different loops. Males were represented by squares, while females were represented by circles. Phenotypically Normal people were depicted with simple symbols, whereas those who were afflicted were depicted with more complex symbols. Symbols that are filled Individuals were assigned a Roman numeral for each generation Arabic numerals were used to identify generations within a generation. Individuals who had died were A line is drawn over the symbol to indicate this. Individuals that were found to be carriers were identified by placing a single dot in the middle of the symbol.

2.4. Purposes of Pedigree Analysis

The goal of pedigree data analysis is to determine whether a genetic mechanism exists for the manifestation of a certain characteristic or group of traits to explicate that mechanism if one exists, and to classify individuals based on their genotypes. By Data collected on one or more groups of related individuals is referred to as pedigree data having a larger group than just parents and children (families). Therefore, more than There will be two generations participating. While it is feasible to investigate genetics, without such information, processes based on families, pairings of relatives, or even unrelated individuals can be used Pedigree data provides the most genetic information for individuals. A normal pedigree may consist of a hundred or more individuals spanning three or more generations, and such a group of individuals is capable of producing significantly more genetically information that may be gained from the same number of people divided into smaller groups Several unrelated little groups.

However, except for the extremely specific goal of research. In the case of genetic linkage, an informative statistical analysis of such data appears to have been performed entirely disregarded When geneticists want to find out more about anything, they use this method create a genetic hypothesis based on pedigree data in order to split the pedigree divide the data into families (i.e. groups of parents and children) and analyses it as if it were a family. Families were chosen at random. Even though this approach 'wastes' information, it isn't always statistically insignificant. Such investigations have most likely done little harm in the past previously, they were mostly used to investigate dichotomous features with the goal of generating a 'dominant' or 'recessive' inheritance mode of course, the families are not independent, but under a simple null hypothesis they are in each family, there is segregation. However, if we're looking at quantitative characteristics, or a set of features whose expression is heavily affected by the environment, More powerful analysis is required. The goal of this study is to demonstrate approach to this topic in broad form and with a decent bit of generality. A confirmed pedigree can aid in determining a person's most likely inheritance pattern. A family with a single-gene disease. Pedigree analysis is also relevant in this case determining testing approaches, assessing recurrence risks, and in some cases in some cases, the prognosis.

3. Results and Discussion

All the members which are affected they are interviewed more precisely and then data were collected from the elders members of the affected family. The results of Diabetes mellitus are shown in below pedigree.

The vertical line which are seen in the pedigree shows parents to their children. The square and circle under the horizontal line denotes offspring of the above family members as shown in Generation-II. Here Generation is denoted by Roman number while the members of family as denoted by numbers.

In Generation-I there are two members one is deceased male member and other is deceased female member. The age of male member are 75 year while the age of female member are 73 in Generation-I Both the members belong from a one family. These two members are cousin and are married with each other. Both the deceased Male and deceased Female member are not affected from Albinism and it produced Six offspring which include Two male and Four female member.

In Generation-II there are total six members each member will be explain separately. The first male members of this generation are affected from Albinism. The affected male member is married with her cousin which are normal. The age of male member are 58 year while the age of normal female member are 57 year. After cousingeniuses marriage it produce six offspring which include three normal male and three normal female member. The second male members of this generation are not affected from Albinism.

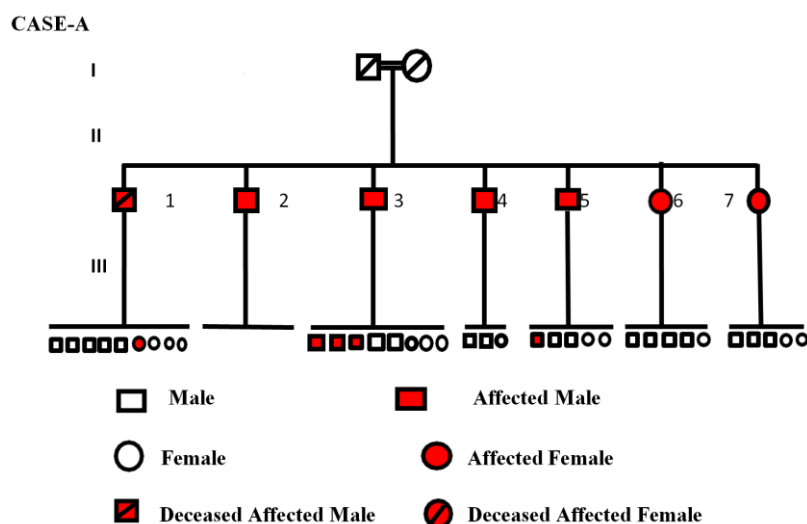


Figure 1. Pedigree of Family-A Description.

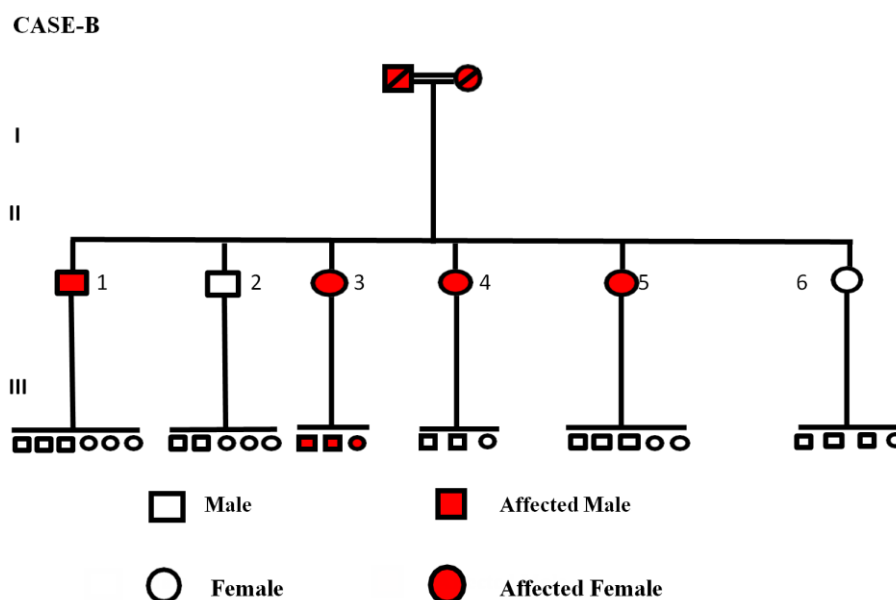


Figure 2. Pedigree of Family-B Description.

The unaffected male member is with married female which are out of family and she is normal. The age of male member are 56 while the age of normal female member are 54. After the marriage it produce five offspring which include two normal male and three normal female member. The third Female members of this generation are affected from Albinism. The affected Female member is married with their cousin and he is normal. The age of male member are 52 while the age of normal female member are 50. After marriage it produce three offspring which include two affected male and one affected female member. The four Female members of this generation are affected from Albinism. The affected Female member is married with male which is out of family and he is normal. The age of male member are 50 while the age of normal female member are 48. After marriage it produce three

offspring which include two normal male and one normal female member. The five Female members of this generation are affected from Albinism. The affected Female member is married with male which is out of family and he is normal. The age of male member are 49 while the age of normal female member are 54. After marriage it produce five offspring which include three normal male and two normal female member. The six Female members of this generation are affected from Albinism. The affected Female member is married with male which is out of family and he is normal. The age of male member are 45 while the age of normal female member are 42. After marriage it produce four offspring which include three normal male and one normal female members. The result of Albinisms in the above pedigree shows that it is an autosomal recessive disorder in which the

mutant genes are transfer from one generation to the next Generation like from Generation-I to Generation-II to Generation-III (Figure 1). In Generation-I both the members are normal from albinism due to responsible gene for albinism are hidden in this generation while in Generation-II the four members are affected with Albinism it means that the autosomal recessive mutant genes are transfer to the generation-II so the result shows that mutant gene are expressed in these four members of this generation but in Generation-III few members are affected because some members are married with out of family

4. Conclusion

The conclusion was obtained from the above results and discussion of diabetes mellitus and Albinism affected Families of district karak. The two families cases have been reported one for diabetes mellitus and other for albinism. We have detailed interviewed were conducted with all the affected members, their parents and normal individual. Pedigree analysis and tree was drawn to access the results and check the linkage. This study was done to study the biological changes which are affecting body weight loss, polyuria in diabetes and skin colour, hair colour, and eyes vision problem in albinism and also has negative impact on society both socially and biologically. We concluded that from the above pedigree analysis that the diabetes mellitus is an autosomal dominant diseases it means that gene will flow from one generation to next generation which will cause mutation. There are several genes which will cause mutation in the patient of diabetes mellitus these genes are reported majorly as ACE, AKR1B1, VEGF, AKRB1, ADIPOQ, GLUL (Alkayyali S, Lysenko 2014). Albinism is autosomal recessive disease which is caused by different genes and these genes such as TYR, OCA2, TYRP1, SLC45A5, C100, RF11 and MC1R (Khan et, al 2015.) are responsible for albinism. These mutant genes are transfer from one generation to the next Generation. So gene therapy is only solution to reduce the chances of mutation in these genes.

Conflicts of Interest

The authors declare no conflicts of interest.

References

- [1] Snustad, D. P., & Simmons, M. J. (2015). Principles of genetics (6th ed.). John Wiley & Sons.
- [2] Sharma, S., Javadekar, S., Pandey, M., Srivastava, M., Kumari, R., & Raghavan, S. (2015). Homology and enzymatic requirements of microhomology-dependent alternative end joining. *Cell death & disease*, 6(3), e1697-e1697.
- [3] Alkayyali, S., & Lyssenko, V. (2014). Genetics of diabetes complications. *Mammalian genome*, 25(9), 384-400.
- [4] Nagamine, K., Peterson, P., Scott, H. S., Kudoh, J., Minoshima, S., Heino, M.,... Antonarakis, S. E. (1997). Positional cloning of the APECED gene. *Nature genetics*, 17(4), 393-398.
- [5] S. E. (1997). Positional cloning of the APECED gene. *Nature genetics*, 17(4), 393-398.
- [6] Bennett, C. L., Christie, J., Ramsdell, F., Brunkow, M. E., Ferguson, P. J., Whitesell, L.,... Ochs, H. D. (2001). The immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) is caused by mutations of FOXP3. *Nature genetics*, 27(1), 20-21.
- [7] Sun, C. (2007). Zhang F, Ge X, Yan T, Chen X, Shi X, Zhai Q. SIRT1 improves insulin sensitivity under insulin-resistant conditions by repressing PTP1B. *Cell Metab*, 6, 307- 319.
- [8] Bignon-Laubert, A., Böni-Schnetzler, M., Hubbard, B. P., Bouzakri, K., Brunner, A., Cavelti-Weder, C.,... Brorsson, C. (2013). Identification of a SIRT1 mutation in a family with type 1 diabetes. *Cell metabolism*, 17(3), 448-455.
- [9] Haller, K., Kisand, K., Pisarev, H., Salur, L., Laisk, T., Nemvalts, V., & Uibo, R. (2007). Insulin gene VNTR, CTLA - 4+ 49A/G and HLA - DQB1 alleles distinguish latent autoimmune diabetes in adults from type 1 diabetes and from type 2 diabetes group. *Tissue antigens*, 69(2), 121-127.
- [10] Okruszko, A., Szepietowska, B., Wawrusiewicz-Kurylonek, N., Górka, M., Krętownski, A., & Szelachowska, M. (2012). HLA-DR, HLA-DQB1 and PTPN22 gene polymorphism: association with age at onset for autoimmune diabetes. *Archives of Medical Science: AMS*, 8(5), 874.
- [11] Osbak, K. K., Colclough, K., Saint - Martin, C., Beer, N. L., Bellanné - Chantelot, C., Ellard, S., & Gloyn, A. L. (2009). Update on mutations in glucokinase (GCK), which cause maturity - onset diabetes of the young, permanent neonatal diabetes, and hyperinsulinemic hypoglycemia. *Human mutation*, 30(11), 1512-1526.
- [12] Nair, P., Wenzel, S., Rabe, K. F., Bourdin, A., Lugogo, N. L., Kuna, P.,... Goldman, M. (2017). Oral glucocorticoid-sparing effect of benralizumab in severe asthma. *New England Journal of Medicine*, 376(25), 2448-2458.
- [13] Tomita, Y., & Suzuki, T. (2004). Genetics of pigmentary disorders. Paper presented at the American Journal of Medical Genetics Part C: Seminars in Medical Genetics.
- [14] Sundaresan, P., Sil, A. K., Philp, A. R., Randolph, M. A., Natchiar, G., & Namperumalsamy, P. (2004). Genetic analysis of oculocutaneous albinism type 1 (OCA1) in Indian families: two novel frameshift mutations in the TYR Gene. *Mol Vis*, 10, 1005-1010.
- [15] Gul, H., Shah, A. H., Harripaul, R., Mikhailov, A., Prajapati, K., Khan, E.,... Shah, A. H. (2019). Genetic studies of multiple consanguineous Pakistani families segregating oculocutaneous albinism identified novel and reported mutations. *Annals of Human Genetics*, 83(4), 278-284.
- [16] Khan, M. A., Khan, M. A., Akhlaq, M., & Zubair, M. (2015). Medico-genetics of oculocutaneous albinism; an updated study with Pakistani perspective. *PJMR*, 54, 33-37.

- [17] Gul, H., Shah, A. H., Harripaul, R., Mikhailov, A., Khan, E. U., Shah, W.,... Khan, M. A. (2021). Mutation Analysis of a Pakistani Oculocutaneous Albinism Family Identifies a Novel Splice Site Defect in OCA2 Gene.
- [18] Bennett, R. L., Steinhaus, K. A., Uhrich, S. B., O'Sullivan, C. K., Resta, R. G., Lochner-Doyle, D.,... Hamanishi, J. (1995). Recommendations for standardized human pedigree nomenclature. Pedigree Standardization Task Force of the National Society of Genetic Counselors. [Guideline Research Support, Non-U S Gov't Research Support, U S Gov't, P H S]. Am J Hum Genet, 56(3), 745-752.