European Journal of Medical Genetics 66 (2023) 104887

Contents lists available at ScienceDirect

European Journal of Medical Genetics

journal homepage: www.elsevier.com/locate/ejmg

Early-onset diabetes in Africa: A mini-review of the current genetic profile

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ARTICLE INFO

Handling Editor: A. Verloes

Keywords:
Early-onset diabetes
Neonatal diabetes
MODY
Genes
And Africa

ABSTRACT

Early-onset diabetes is poorly diagnosed partly due to its heterogeneity and variable presentations. Although several genes have been associated with the disease, these genes are not well studied in Africa. We sought to identify the major neonatal, early childhood, juvenile, or early-onset diabetes genes in Africa; and evaluate the available molecular methods used for investigating these gene variants. A literature search was conducted on PubMed, Scopus, Africa-Wide Information, and Web of Science databases. The retrieved records were screened and analyzed to identify genetic variants associated with early-onset diabetes. Although 319 records were retrieved, 32 were considered for the current review. Most of these records (22/32) were from North Africa. The disease condition was genetically heterogenous with most cases possessing unique gene variants. We identified 22 genes associated with early-onset diabetes, 9 of which had variants (n = 19) classified as pathogenic or likely pathogenic (PLP). Among the PLP variants, *IER3IP1*: p.(Leu78Pro) was the variant with the highest number of cases. There was limited data from West Africa, hence the contribution of genetic variability to early-onset diabetes in Africa could not be comprehensively evaluated. It is worth mentioning that most studies were focused on natural products as antidiabetics and only a few studies reported on the genetics of the disease. *ABCC8* and *KCNJ11* were implicated as major contributors to early-onset diabetes gene networks. Gene ontology analysis of the network associated ion channels, impaired glucose tolerance, and decreased insulin secretions to the disease. Our review highlights 9 genes from which PLP variants have been identified and can be considered for the development of an African diagnostic panel. There is a gap in early-onset diabetes genetic research from sub-Saharan Africa which is much needed to develop a comprehensive, efficient, and cost-effective genetic panel that will be useful in clinical practice on the continent and among the African diasporas.

1. Introduction

Early-onset diabetes consists of a spectrum of diseases such as maturity-onset diabetes of the young (MODY), juvenile diabetes, neonatal diabetes mellitus, and rare diabetes-associated syndromic disease. These early-onset diabetic conditions may be associated with single genes and therefore characterized as monogenic diabetes (Vaxillaire et al., 2012). Globally, about 500,000 children are diagnosed of Type 1 Diabetes Mellitus (T1DM) (Patterson et al., 2014) with an estimated 3% annual increase (Group, 2006). Most of the T1DM cases were from Europe and North America (Patterson et al., 2014). A prevalence of 2.5% of monogenic diabetes was reported from United Kingdom pediatric clinics (Sanyoura et al., 2018). MODY has been estimated to account for 1–5% of diabetes cases (Nkonge et al., 2020) and advances in sequencing technologies has made it possible for 14 MODY genes to be identified (Naylor, 2019; Stride and Hattersley, 2002). Over 20 genes which are important for pancreatic beta cell activities have been implicated in neonatal diabetes which mostly occurs

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https://doi.org/10.1016/j.ejmg.2023.104887
Received 28 August 2023; Received in revised form 15 November 2023; Accepted 17 November 2023
Available online 21 November 2023

within the first 12 months of life (Madani et al., 2019). Some of these genes, such as *KCNJ11*, *ABCC8*, *INS*, and *GCK* have also been associated with MODY (Bonnefond et al., 2012; Markou et al., 2019; Piccini et al., 2016). Mutations in the neonatal diabetes genes were implicated in permanent diabetes (Edghill et al., 2010; Ngoc et al., 2022) with *ABCC8* and *KCNJ11* gene variants accounting for over 40% of all neonatal diabetes cases (Edghill et al., 2010). The contribution of these genes and other early-onset diabetes associated genes in Africa diabetes remains unknown. Hence, we hereby, present a literature review on the current genetic profile of early-onset diabetes in Africa.

Early-onset diabetes remains a challenge for affected individuals and their families, and has an impact on the quality of life of these individuals. A diagnosis of diabetes generally influences a change in a patient's life style, psychological and general well-being which is often accompanied by stress (Szopa et al., 2019). About 40% of diabetes patients have psychological problems which reduces their quality of life (Peyrot et al., 2005). Patients with severe cases are faced with a lifelong injection of insulin for patients with insulin-dependent diabetes (T1DM) and daily pills for patients with insulin-independent diabetes (Type 2 Diabetes Mellitus (T2DM)) (Pasquel et al., 2021). Studies on insulin use and quality of life has shown that insulin use in T1DM cases corelates with poor quality of life (Collins et al., 2009; Szopa et al., 2019). This observation may be attributed to the switch from pills to daily injections and the lifelong dependency on insulin injections for T1DM which is not convenient (Szopa et al., 2019). It has also been reported that the affected individuals struggle with not having the freedom to eat or drink what they like and in some cases, they have a negative view of the future (Szopa et al., 2019). It is worth mentioning that there is a direct impact of early-onset diabetes on the education of children living with the condition (Begum et al., 2020). Availability of effective management and treatment options is a crucial factor where the education of children in resource-rich settings is often not affected, and the converse is true in resource-poor settings.

The classical diagnosis of early-onset diabetes may be failing due to issues such as low penetrance observed in some cases, several subclassifications of the disease, and unusual clinical presentations of the disease (Lizarzaburu-Robles et al., 2020; Pinelli et al., 2013; Urbanová et al., 2018). Attempts to address these challenges have led to a global expansion of diagnostics and this was necessitated by an increasing public health concern (Al-Kandari et al., 2020). Improvements in gene sequencing technologies and accessibility of genetic testing to patients has contributed to early diagnosis and improved treatment outcomes in patients (Naylor, 2019; Pinelli et al., 2013). However, only a few of the early-onset diabetes cases are effectively diagnosed especially in developing countries (Patterson et al., 2014). Design and development of population specific genetic diagnostic panels can enhance screening for early-onset diabetes in Africa. We therefore sought to review the genes associated with early-onset diabetes in Africa to identify potential genes that can be considered in the design of a genetic panel.

2. Method

Here, we reviewed the literature to investigate the major early-onset diabetes genes reported from patients of African ancestry. The term "early-onset diabetes" refers to diabetes at early age but the specific age at which the condition is considered as early onset varies among researchers. In alignment with the prevailing consensus (Huang et al., 2019; Pan and Jia, 2018), we have characterized early-onset diabetes as diabetes that manifests before the age of 40. The protocol for this systematic review was registered with PROSPERO (Schiavo, 2019) (ID#: CRD42022324696). The review was conducted using Covidence, a systematic review software which allows multiple reviewers to work through the steps of a systematic review efficiently and effectively (Babineau, 2014).

2.1. Search strategy and screening

The keywords, early-onset, neonatal, juvenile, diabetes, genes, genetics, genomics, and Africa were used to develop the search term below. [(((((Early-onset) OR (Neonatal)) OR (Juvenile)) OR (childhood)) AND (((Genetics) OR (genes)) OR (genomics))) AND (Diabetes)) AND (Africa OR Algeria OR Angola OR Benin OR Botswana OR "Burkina Faso" OR Burundi OR Cameroon OR "Cape Verde" OR "Central African Republic" OR Chad OR Comoros OR Djibouti OR "DR Congo" OR "Democratic Republic of Congo", OR Congo OR Egypt OR "Equatorial Guinea" OR Guinea OR Eritrea OR Eswatini OR Ethiopia OR Gabon OR Gambia OR Ghana OR Guinea OR (Guinea Bissau) OR "Ivory Coast" OR "Côte d'Ivoire" OR Kenya OR Lesotho OR Liberia OR Libya OR Madagascar OR Malawi OR Mali OR Mauritania OR Mauritius OR Morocco OR Mozambique OR Namibia OR Niger OR Nigeria OR Rwanda OR "Sao Tome And Principe" OR Senegal OR Seychelles OR Sierra Leone OR Somalia OR "South Africa" OR "South Sudan" OR Sudan OR Tanzania OR Togo OR Tunisia OR Uganda OR Zambia OR Zimbabwe)].

A literature search was conducted on PubMed, Scopus, Africa-Wide Information, and Web of Science databases from 31st July to 20th December 2022 by two independent reviewers. A total of 319 records were retrieved from the databases. Two reviewers screened the retrieved records using the title and abstract, and 32 publications were retained for data extraction (Fig. 1). The inclusion and exclusion criteria below were used to screen the retrieved records.

Original research studies which met the following inclusion criteria were considered:

1. neonatal, early childhood, juvenile, or early-onset diabetes
2. studies reporting on gene variants associated with diabetics

3. Study participants of African descent

The criteria used to exclude studies were:

1. non-human/animal studies
2. review articles
3. studies reporting on adults or late-onset diabetes

3.1. Data extraction

The data extraction was performed by two independent reviewers. The extracted data were compared and combined. The following data elements were recorded by the reviewers: 1) the last name of the first and last authors, 2) date of publication, 3) location, 4) range, mean, and median age, 5) sample size, 6) diabetic genes investigated, 7) the number of cases and controls, 8) methods used for genetic screening, 9) pathogenic gene variants found, and 10) the number of cases with the pathogenic gene variant. The data were collected and keyed into Microsoft Excel spreadsheet and analyzed using R-studio (version 4.2.1) and GraphPad Prism (version 9.5.0). Quantitative data obtained from the studies were presented using descriptive summary statistics, charts, and plots where appropriate.

3.2. Risk of bias (quality) assessment

To avoid any form of bias, two reviewers independently synthesized the data and assessed the quality of the documents included by using the default quality assessment template in Covidence. The quality assessment was conducted at the outcome level of each study. Disagreement between the reviewers was resolved by discussion and when necessary, an expert was consulted to resolve the disagreement. The genetic tests or screening methods used by the selected studies were assessed for quality using the ACCE Model Process for Evaluating Genetic Tests.

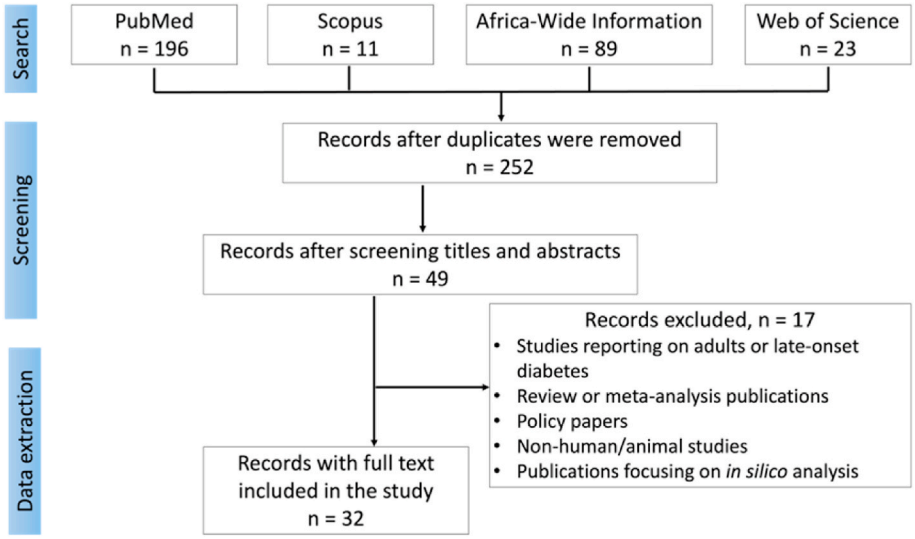

Fig. 1. A flow diagram of the search and screening strategy.

3.3. *Evaluation of clinical significance of identified variants*

The clinical significance of the variants was determined using InterVar, pathogenicity prediction tools and reports from ClinVar. InterVar is a free online bioinformatic tool and variant database which is built for variant interpretation based on the American College of Medical Genetics and Genomics and the Association for Molecular Pathology 2015 guidelines (Li and Wang, 2017). ClinVar is an aggregated database of genomic variants and their relationship with human health (Landrum et al., 2014). The following pathogenicity prediction bioinformatic tools that report meta scores were also used: BayesDel (Tian et al., 2019), MetaLR, MetaRNN, MetaSVM, and REVEL (Tian et al., 2019). The collection of tools below with individual predictions were used to further evaluate the clinical significance of the variants: DANN, DEOGEN2, EIGEN, EIGEN PC, EVE, FATHMM, FATHMM-MKL, FATHMM-XF, LIST-S2, LRT, M-CAP (Jagadeesh et al., 2016), Mutation

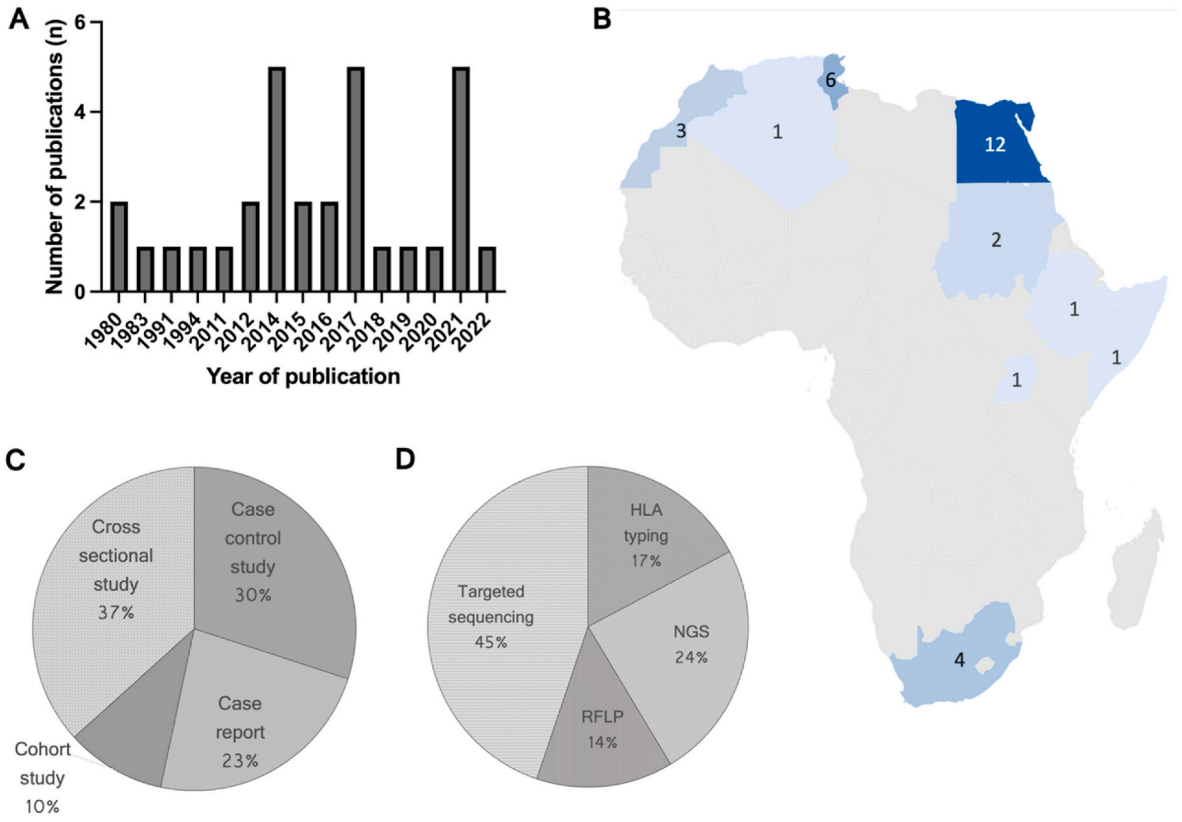

Fig. 2. Characteristics of publications included in this study. (A) The year of publication for the selected records. (B) Geographical representation of publications retrieved. The publications retrieved were from countries in blue shades and the numbers represent the corresponding number of publications. (C) Study design used by the various studies. (D) The molecular methods used to investigate genetics of early-onset diabetes. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

assessor, MutationTaster, MutPred, MVP, PrimateAI, PROVEAN, SIFT, SIFT4G, and PolyPhen (Supplementary data).

4. Results

A total of 32 out of 319 records were retained after screening for data extraction (Fig. 1). The earliest studies among these 32 records were conducted in 1980, while the years 2014, 2017, and 2021 recorded the highest number of studies (Fig. 2A). Most early-onset diabetes genetic studies (22/32) were conducted in North African countries with the highest frequency from Egypt. There was no record from West Africa and few studies were recorded from Central and Southern Africa (Fig. 2B). A review of the study designs used suggested that cross-sectional and case-control studies were the most preferred study designs (Fig. 2C). An array of sequencing and genotyping techniques was used to determine the genetic markers associated with early-onset diabetes. These techniques include targeted and next generation sequencing, restriction fragment length polymorphism (RFLP), and human leukocyte antigens (HLA) typing (Fig. 2D).

4.1. Distribution of early-onset diabetes genes in Africa

Most of the studies reported on participants with less than one year age of onset. Only 5 publications studied people with more than 18 but less than 30 years of age of onset (Fig. 3A). A review of the type of diabetes revealed that most of the participants (about 600 cases) were diagnosed of type 1 diabetes (Fig. 3C).

Analysis of the data retrieved showed that variants in 22 genes were associated with early-onset diabetes cases in Africa (Supplementary data). Six studies conducted HLA typing to determine the distribution of HLA antigens in diabetic patients. Except for HLA, *KCNJ11* was the most studied gene (5 publications) followed by *EIF2AK3* and *SLC19A2* worked on by 4 studies each (Fig. 3B). Most of the associated genes were reported from Egypt and Tunisia (Fig. 3B).

4.2. Pathogenic and likely pathogenic variants identified from early-onset diabetes cases

Among the 22 early-onset diabetes associated genes, pathogenic and likely pathogenic (PLP) variants were found in 9 genes. A total of 64 variants were identified in the 22 early-onset diabetes associated genes of which 19 likely pathogenic variants were found in the 9 genes (Table 1). Seven of the PLP variants were reported on the homozygous state while 8 variants were heterozygous. The most common PLP variants was *IER3IP1*: p.(Leu78Pro) reported in 4 unrelated cases. The majority (16/19 variants) of the PLP variants were non-synonymous with a few (4/19 variants) resulting in premature termination of a protein (Table 1).

4.3. Network analysis

To identify potential drug targets, the nine genes with pathogenic variants were used to construct a protein-protein interaction network on the STRING and gene interaction network on GeneMania databases (Fig. 4). The STRING database consist of known and predicted protein-protein interactions curated from experimental data, computational

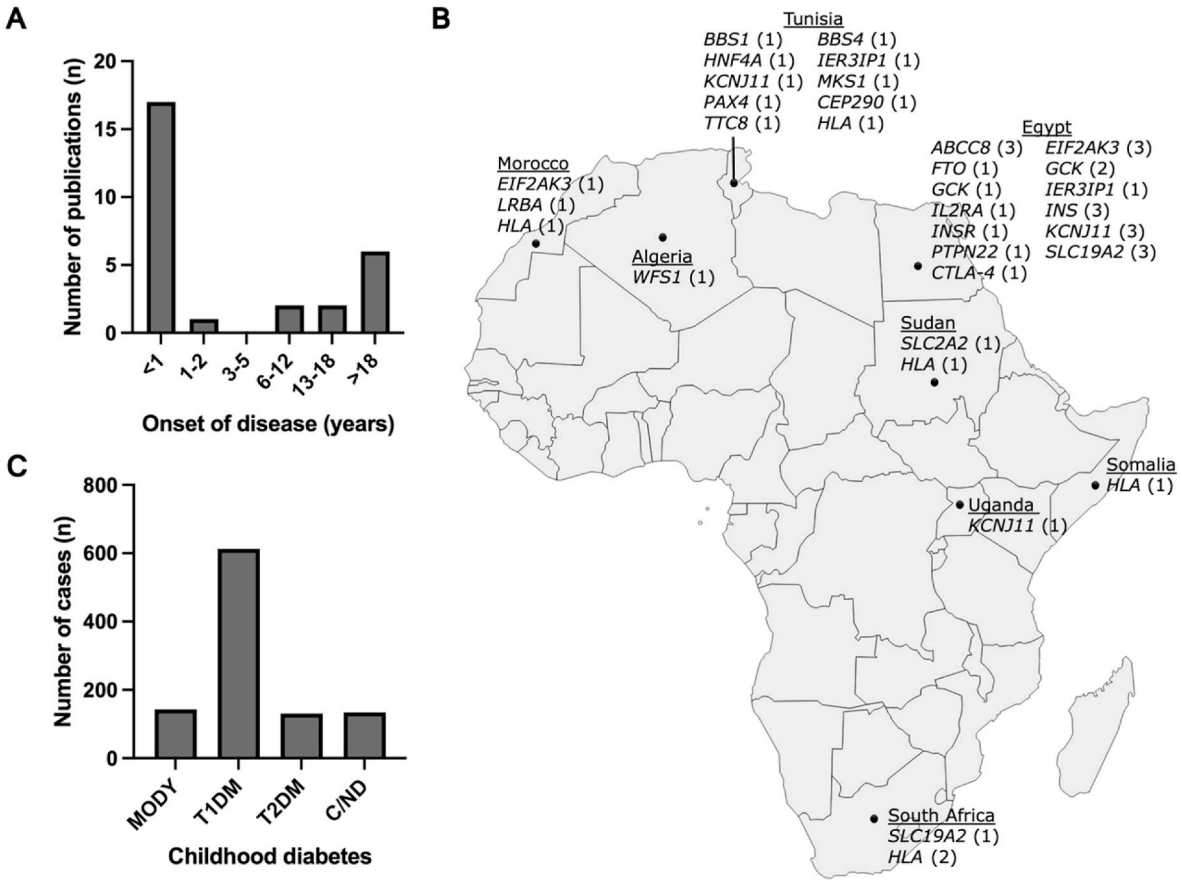

Fig. 3. Characteristics of study participants and distribution of identified genes. (A) Age of onset of diabetes. (B) Geographical distributions of genes associated with early-onset diabetes in Africa. The number of studies reporting on the associated genes were written in parenthesis. (C) Distribution of early-onset diabetes types diagnosed in Africa. Maturity onset diabetes of the young (MODY), type 1 diabetes (T1DM), type 2 diabetes (T2DM), unidentified childhood/neonatal diabetes (C/ND).

Table 1
A list of pathogenic and likely pathogenic variants.

Gene	Nucleotide change	Protein change	Unrelated cases	Age of onset	Country	Reference
ABCC8	(NM_000352.6):c.1792C>T	p.(Arg598Ter)	2(het)	<1 year	Egypt	Madani et al. (2019)
ABCC8	(NM_000352.6):c.970G>A	p.(Val324Met)	1 (het)	<1 year	Egypt	Abdelmeguid et al. (2022)
ABCC8	(NM_001287174.2):c.4220G>T	p.(Gly1407Val)	1 (het)	<1 year	Egypt	Abdelmeguid et al. (2022)
ABCC8	(NM_000352.6):c.3766G>A	p.(Ala1256Thr)	1(hom)	<1 year	Egypt	Abdelmeguid et al. (2022)
ABCC8	(NM_001287174.2):c.4138C>T	p.(Arg1380Cys)	2	1–10 years	Egypt	Laimon et al. (2021)
ABCC8	(NM_000352.6):c.1069G>T	p.(Val357Phe)	1	1–10 years	Egypt	Laimon et al. (2021)
EIF2AK3	(NM_004836.7):c.1958G>C	p.(Arg653Thr)	2(hom)	<1 year	Egypt	Madani et al. (2019)
EIF2AK3	(NM_004836.7):c.1147G>T	p.(Glu383Ter)	1(hom)	<1 year	Egypt	Abdelmeguid et al. (2022)
GCK	(NM_000162.5):c.562G>A	p.(Ala188Thr)	2(hom)	<1 year	Egypt	Madani et al. (2019)
IER3IP1	(NM_016097.5):c.233T>C	p.(Leu78Pro)	4	<2.5 years	Egypt	Abdel-Salam et al. (2012)
IER3IP1	(NM_016097.5):c.62T>G	p.(Val21Gly)	1(hom)	2 months	Tunisia	Rjiba et al. (2021)
INS	(NM_001185097.2):c.265C>T	p.(Arg89Cys)	1(hom)	<1 year	Egypt	Abdelmeguid et al. (2022)
KCNJ11	(NM_000525.4):c.521C>G	p.(Ala174Gly)	2(het)	<1 year	Egypt	Madani et al. (2019)
KCNJ11	(NM_000525.4):c.601C>T	p.(Arg201Cys)	1(het)	<1 year	Egypt	Madani et al. (2016)
KCNJ11	(NM_000525.4):c.602G>T	p.(Arg201Leu)	1(het)	<2 years	Egypt	Ahmed et al. (2017)
KCNJ11	(NM_000525.4):c.679G>A	p.(Glu227Lys)	1 (het)	2 months	Tunisia	Kamoun et al. (2017)
LRBA	(NM_006726.4):c.7042C>T	p.(Arg2348Ter)	1	<1 year	Morocco	Johnson et al. (2017)
[a]*MKS1*	(NM_017777.4):c.1423C>T	p.(Arg475Cys)	1(het)	21 years	Tunisia	Dallali et al. (2021)
SLC19A2	(NM_006996.3):c.1160G>A	p.(Trp387Ter)	1(hom)	<1 year	Egypt	Madani et al. (2019)

[a] Oligogenic inheritance of variants in *MKS1*, *BBS1*, *BBS4*, *BBS8*, and *CEP290* genes were reported as the possible cause of the condition in the affected individual. None of the variants in these genes alone could explain the observed phenotype but the cumulative synergetic effect of the genes was implicated.

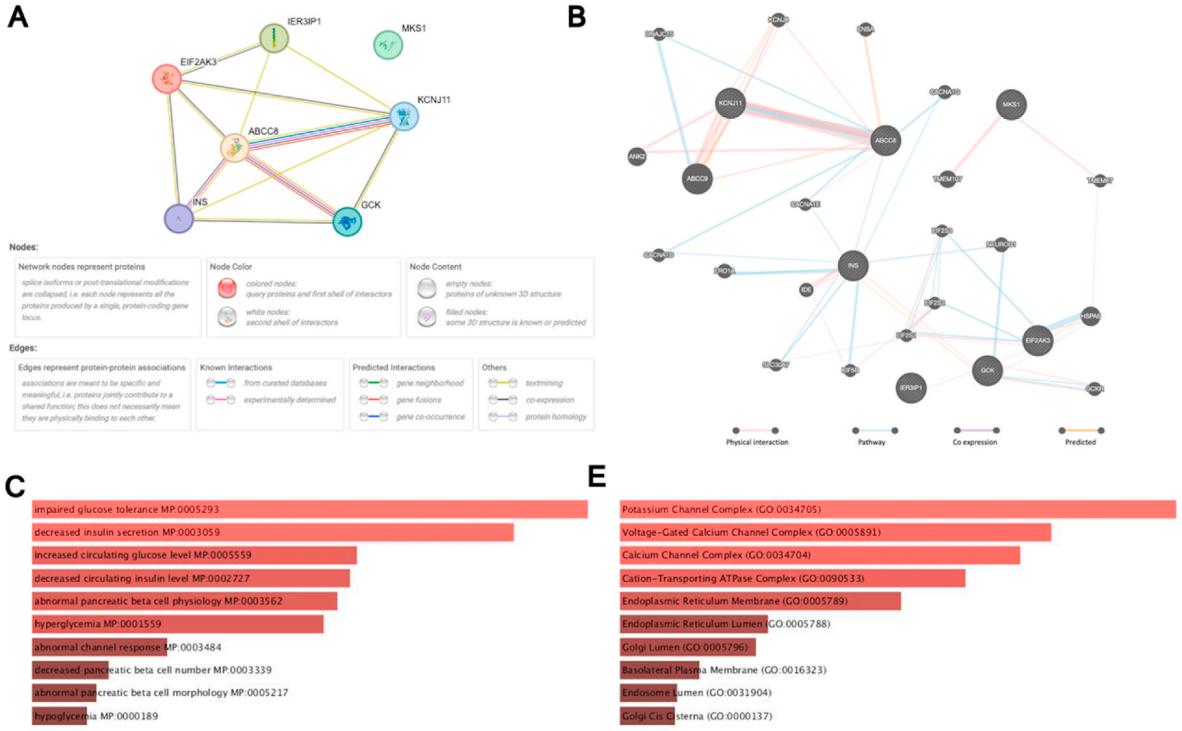

Fig. 4. Earl-onset diabetes related interaction networks: (A) protein-protein interaction network from the STRING database. (B) Gene interaction network from GeneMania database. The size of the nodes corresponds to the number of connections. Gene ontology analysis of early onset diabetes genes showing the top hits from (C) MGI Mammalian Phenotype Level4 2021 ontology and (D) GO Cellular Component 2023. The ontologies were obtained obtained from Enrichr database (Xie et al., 2021).

predictions and publications (Szklarczyk et al., 2010). Genemania is a database for predicting gene interactions and consist of over 660 million network interactions (Montojo et al., 2014). Two proteins, ABCC8 and KCNJ11, were found to have the highest number of connections in both STRING and GeneMania interaction networks (Fig. 4A and B) suggesting their role in the network. Although our network analysis did not identify novel drug targets, the key contribution of some of the known genes in the network could be exploited for drug repurposing. Gene ontology (GO) analysis was conducted with the all the genes retrieved from the networks. Impaired glucose tolerance and decreased insulin secretion were found to be the top two GO hits obtained from the MGI Mammalian Phenotype Level4 2021 onthology (Fig. 4C). Similarly, ion channels were found to be the cell components associated with the disease, hence may serve as targets for new drugs (Fig. 4D).

5. Discussion

In the past decade, there has been a rise in the global prevalence of early-onset diabetes and in countries like China the condition is considered an epidemic (Pan and Jia, 2018). The increase in the global

prevalence of early-onset diabetes may be explained by an increase in sedentary lifestyle with low physical activity and diet. Diabetes is a complex trait with several gene variants (Vaxillaire et al., 2012) interacting with behavioral and environmental factors to result in the condition. Furthermore, genetic variants have been associated with poor glycemic control (Alfaqih et al., 2022). It is important to study the gene variants associated with early-onset diabetes to improve its diagnosis and treatment. Here, we sought to discuss the gene variants associated with early-onset diabetes in Africa and the need to increase research capacity on the continent to contribute effectively to the clinical management of the condition.

In clinical practice, especially in the developed countries, molecular genetic testing for some early-onset diabetes such as neonatal diabetes and MODY are available (Naylor et al., 2014; Shields et al., 2010; Stride and Hattersley, 2002; Thurber et al., 2015). This advancement was preceded by several years of research efforts to identify gene variants associated with the disease. There are several studies across the globe reporting on the genetics of early-onset diabetes (Kanakatti Shankar et al., 2013; Shields et al., 2010; Thurber et al., 2015); however, only few of these are from Africa. Within the continent, most of the retrieved records were from North Africa, with only few studies from East Africa and South Africa. There was no genetic study retrieved from West Africa. Considering the multigenic nature of diabetes, NGS emerges as the promising diagnostic tool (Firdous et al., 2018), however, the majority of studies from Africa used single gene sequencing (Sanger sequencing) approaches. Although Sanger sequencing is cheaper and requires less computational power to analyze the sequence data, it may be time-consuming and expensive, considering the number of genes involved in the pathogenesis of diabetes. Hence, there is a need to develop cost effective and population specific targeted gene panels for an effective diagnosis of the condition. It is worth noting that the targeted NGS has become a common technique for investigating known genetic cause of some diseases and should be considered for routine clinical practice.

MODY is a heterogenous early-onset diabetes with 14 associated genes mainly inherited in an autosomal dominant fashion (Stride and Hattersley, 2002). Each gene is linked to at least a sub-type of MODY: MODY1 (HNF4A), MODY2 (GCK), MODY3 (HNF1A), MODY4 (IPF1), MODY5-(HNF1B), MODY6 (NEUROD1), MODY7 (KLF11), MODY8 (CEL), MODY9 (PAX4), MODY10 (INS), MODY11 (BLK), MODY12 (ABCC8), and MODY13 (KCNJ11) (Amara et al., 2014; Bonnefond et al., 2012). Although these genes have been associated with MODY, the majority of them are common to neonatal diabetes especially in the case of *INS*, *GCK*, *ABCC8* and *KCNJ11* which were reported in several neonatal diabetes cases (Edghill et al., 2010; Ngoc et al., 2022). These genes should not be exclusively characterized as MODY genes but should be clinically tested in suspected neonatal diabetes cases. In addition, some of the previously associated MODY genes may not be the responsible cause of diabetes (Bonnefond et al., 2013; Laver et al., 2022). A recent study of a large cohort has provided gene-level evidence that variants in *BLK*, *KLF11*, and *PAX4* may not be associated with diabetes in children and should not be included in clinical panels (Laver et al., 2022).

Variants in known diabetes genes may cause pancreatic beta cells dysfunction and lead to the development of early-onset non-insulin dependent diabetes (Firdous et al., 2018). Among the common diabetes genes, 6 of them (*ABCC8, INS*, *GCK*, *HNF4A*, *KCNJ11*, and *PAX4*) were reported in African patients. *ABCC8, INS*, and *GCK* were reported from Egypt (Abdelmeguid et al., 2022; Laimon et al., 2021; Madani et al., 2019); *HNF4A*, and *PAX4* from Tunisia (Amara et al., 2012, 2014); and *KCNJ11* from Egypt (Gohar et al., 2017; Madani et al., 2016), Tunisia (Kamoun et al., 2017), and Uganda (Nyangabyaki-Twesigye et al., 2015). As stated previously, *PAX4* variants may not contribute to the development of diabetes. Pathogenic variants were found in 4 out of the 6 genes and these are *ABCC8*, *GCK*, *INS*, and *KCNJ11*. Sulfonylurea receptor 1 (SUR1) protein is encoded by *ABCC8* (OMIM #600509) which is located on chromosome 11p15.1 and required for normal insulin secretion. A SUR proteins are a complex of potassium channels associated with familial hyperinsulinemic hypoglycemia (Glaser et al., 1994). *GCK* (OMIM #138079) located on chromosome 7p13 codes for glucokinase, an enzyme which catalyzes the phosphorylation of glucose. The insulin gene, *INS* (OMIM#) is located on chromosome 11p15.5 and responsible for insulin production which is required for glucose control in the blood. Potassium channel, inwardly rectifying, subfamily J, member 11 (*KCNJ11*, OMIM #600937) encodes ATP-sensitive potassium channels in the pancreas, neurons, and muscle cells. *KCNJ11* is located on chromosome 11p15.1 and has similarities with the SUR proteins. The identification of these genes, mostly from North Africa, has provided some information for the delineation of the molecular mechanism of the disease which may give guidance on its clinical management.

Similar to other forms of diabetes, T2DM is heterogenous, and it has some genes (*HNF4A, HNF1A, HNF1B,* and *KCNJ11*) in common with neonatal diabetes and MODY. We have identified only two genes (*KCNJ11* and *HNF4A*) which could be classified as T2DM genes from the African population. However, these genes were not associated with early-onset T2DM. For example, mutations in *KCNJ11* gene which was previously reported as a T2DM susceptibility gene (Hani et al., 1998), were associated with infant monogenic diabetes in an Egyptian cohort (Gohar et al., 2017; Madani et al., 2016). *HNF4A* was also associated with early-onset diabetes in Tunisian patients. T1DM on the other hand did not have several associated genes, the records retrieved rather investigated the association of HLA alleles to disease susceptibility (Briggs et al., 1980; Hammond and Asmal, 1980; Shires et al., 1983).

Our network analysis shows that *KCNJ11* and *ABCC8* are the two genes with highest interactions. These two genes are well studied diabetes genes with confirmed causal association with the disease. The STRING network analysis has shown that these two genes should be considered as targets for the development of antidiabetic drugs. We postulate that regulating the activity of these genes may be beneficial in the management of diabetes for a significant population of individuals with early-onset diabetes. Similar results of antidiabetic drugs were obtained when the two genes were queried separately on PHAROS, a druggable genome database (Nguyen et al., 2017). Most of the PHAROS predicted drugs are known antidiabetic medications used in the clinics (Bajaj and Kalra, 2021; Kecskemeti et al., 2002; Seltzer, 1989), which can be considered for treating African patients with early onset diabetes particularly in patients who are not responding to first line drugs such as insulin and metformin. Children with genetic etiologies for early-onset diabetes when diagnosed early can be transitioned to sulphonylurea therapy which has several benefits (Li et al., 2018). Clinical studies have shown that patients with neonatal diabetes who were transitioned to sulphonylurea had improved glycemic control, reduced long-term complication, and enhanced quality of life among other benefits (Philla et al., 2013; Shepherd, 2006; Thurber et al., 2015). Also, there is a reduced cost associated with sulphonylurea therapy with a higher potential of glycemic stability.

5.1. Limitations and perspectives

Few articles were retrieved from West African populations which shows the limited research efforts in the sub-region. Most the West African studies were focused on late-onset diabetes or the use of natural products as antidiabetics. With the limited data from West Africa, the study could not adequately report on the genetic landscape of early-onset diabetes in Africa. In addition, diabetes is highly heterogenous with several associated genes and clinical presentations. There are several classifications and sub-classifications of the disease that share similar characteristics and phenotypes. MODY which is a form of monogenic diabetes has more than 13 different sub classifications and MODY shares some of its associated genes with neonatal diabetes and T2DM (Amara et al., 2014). Secondly, most African studies used Sanger

sequencing and other single gene approaches to screen for early-onset associated genetic variants (Amara et al., 2014). These techniques are not able to solve most cases hence the genetic causes of the disease in the African population remains largely unknown. It is therefore difficult to diagnose and manage the disease in African clinics.

We have retrieved 22 genes associated with early-onset diabetes of which 9 were found to have PLP variants. These genes can be prioritized in screening African patients in resource limited settings or used to develop a targeted NGS panel which may be relatively cheaper and more effective compared to widely used single gene approach. It is worth mentioning that a diagnostic panel of the current genes may not be useful in screening sub-Saharan Africans. Africa is genetically diverse (Campbell and Tishkoff, 2008), and our review highlights the need for an extensive study of the sub-Saharan African populations to enrich the collection of early-onset diabetes associated genes. With this enrichment of genes, we will be able to understand the molecular mechanisms of the disease pathogenesis as well as develop population specific molecular diagnostic tools.

6. Conclusion

Investigating the molecular genetics of early-onset diabetes is crucial for understating the mechanism of the disease pathogenesis, diagnosis, and the search of effective treatment options. There are however only few studies on the genetics of early-onset diabetes from Africa with majority of them from North African countries. To identify possible genetic markers, these studies mostly used single gene approaches which are cheaper but not effective in identifying new genes. In this review, we have identified some early-onset diabetic genes which can be used to develop a diagnostic panel for screening African patients. There is a need to study other African populations, especially the sub-Sharan African populations to identify early-onset diabetes genes which can be used to improve the diagnostic efficiency of an African gene panel.

Author contributions

Conceptualization, S.M.A.; literature search, S.M.A., J.A.M., K.S.A., J.A., and R.O.Y.; data extraction and original draft preparation, S.M.A., J.A.M., and R.O.Y.; writing-review and editing, S.M.A., J.A.M., K.S.A., J. A., and R.O.Y. All authors contributed important intellectual content presented in this manuscript. All authors have read and agreed to the final version of the manuscript.

Funding

No funding was obtained for this study.

Ethical Approval

Not applicable.

Availability of data and materials

Not applicable.

Declaration of competing interest

The authors declare no conflict of interest.

Data availability

No data was used for the research described in the article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejmg.2023.104887.

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