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Contribution of Iran in Elucidating the Genetic Causes of Autosomal Recessive Intellectual Disability

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Abstract

Many genes with different inheritance modes contribute to the pathogenicity of intellectual disability (ID) making it the most known genetically heterogeneous disorder. Advanced next-generation sequencing (NGS) technologies have helped researchers identify genes underlying ID at an exponential pace. As a consanguineous country, Iran is a hotspot for discovering novel autosomal recessive intellectual disability (ARID) genes. Here, we aimed to review and compare reported ARID gene discovery both in Iran and globally, and pinpoint the research areas that need to be developed in future. We studied published articles and reviews on all known ID genes. In parallel, the gene-discovery research carried out on the Iranian population were also reviewed to determine the contribution of Iran to identifying novel ID genes. Also we tried to find supporting evidence on the causative role of novel genes identified in Iran including confirmatory functional studies and existence of more affected families. We also briefly reviewed the current therapeutic approaches under development for a subset of eligible ID cases. In total, 8% of all ID and 11.5% of all ARID genes described so far have been identified via studies on Iranian population. Functional studies have been performed on 29% of the genes identified in Iran. More than one affected family has been reported for many of these genes, supporting their causative role in ID pathogenesis. Despite the notable contribution of Iran in gene-discovery research, further functional studies on the identified genes are required.

Keywords: Autosomal recessive, Consanguineous, Intellectual disability, Iran, Next-generation sequencing

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Introduction

Intellectual disability (ID), a common neurodevelopmental impairment, is defined as significant deficits in cognitive and adaptive functioning with onset before 18 years of age and confirmed diagnostically by IQ scores of less than 70.[1] The estimated prevalence of ID varies between 1% and 3% worldwide indicating the overwhelming financial, social and caring burden on both family and society.[2-4] ID can be caused by both exogenous environmental and genetic factors.[1-3] Genetic factors play a pivotal role in the etiology of ID with a proportionally increasing genetic contribution with severity of ID.[5,6]

Similar to clinical heterogeneity, ID also shows extreme levels of genetic heterogeneity, making it difficult to provide a genetic diagnosis in all cases.[7] Cytogenetically visible chromosomal aberrations, as first described in Down and Fragile X syndromes, explain up to 15% of ID cases.[2,8] With the advent of microarray analysis, many submicroscopic copy number variations (CNVs) associated with ID were identified.[9] These submicroscopic changes along with cytogenetically detectable aberrations account for nearly 25% of severe ID cases.[10] The single gene causes fall into different inheritance modes. X-linked single gene causes originate from the genes located on the X chromosome, explaining the disproportionate sex ratio of affected males to females. *FMR1* was the first X-linked gene to be identified and remained the most mutated single gene identified in ID cases.[11] X-linked genetic causes, are believed to account for up to 12% of individuals with ID.[10] In outbred populations such as Western countries, most affected cases occur sporadically with a major contribution from dominant *de novo* mutations.[5,12] *De novo* variants may explain 45%–55% of sporadic severe cases in outbred populations.[4] On the other hand, in countries such as Iran, where consanguineous marriages and large families are common, most cases are thought to be caused by autosomal recessive genes. However, a recent study on Iranian patients and their healthy parents attempting to find *de novo* mutations, indicated that these mutations should not be disregarded, even in consanguineous populations.[13] Autosomal recessive intellectual disability (ARID) remains the most causative inheritance of ID. In outbred societies,

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ARID may cause 10%–20% of cases, but in inbred highly consanguineous populations, it is thought to be at least three times higher.[10] Autosomal recessive genes have begun to be unraveled thanks to the revolutionary NGS technologies and high levels of consanguinity in the study populations. In Iran, for instance, many novel autosomal recessive genes have been identified in recessive cognitive disorders.[5,12]

It is worth noting that, given the high heterogeneity of ID, the genetic diagnosis of cases is very important, as it can provide families with useful information such as disease severity, inheritance mode and prognosis, possible preventive approaches including prenatal diagnosis, preimplantation genetic diagnosis and carrier testing required for family planning decisions.

Materials and Methods

In this study, we aimed to review the genetic causes of ID, by first discussing the single genes known to cause this disorder. Specifically, we have tried to compare the frequency of identified novel ID genes in Iran with the world and highlight the research areas that need further investigation. The known ID genes were extracted by using recently published reviews focusing on identified related genes and considering the genes included in the SysID database (as of October 2018, http://sysid.cmbi.umcn.nl).[14] The gene finding studies on Iranian cohorts and research studies were also reviewed. Then, we investigated the frequency of identified ID genes in Iran compared with the rest of the world in terms of number of genes and inheritance modes, to gain insight into the contribution of Iran in identifying novel ID genes. The functional studies on genes identified in Iran were also investigated. Finally, we reviewed the potential therapies for eligible cases of currently under development.

Prevalence, Causes and Different Types of Intellectual Disability

As previously noted, the prevalence of ID is estimated to vary between 1% and 3% around the world.[2,4] The prevalence tends to be higher in regions with poor socioeconomic status due to environmental factors such as maternal health/education, access to health care, and malnutrition. This discrepancy is prominent in patients with mild ID compared to severe ID which shows a more stable prevalence.[15,16] Additionally, the parental consanguinity is considered as a risk factor for ID, so its prevalence is higher in consanguineous populations and it is also positively correlated with the degree of consanguinity in the respective populations.[6,17] Over one billion of the global population live in countries with a high consanguinity rate.[18,19] The rate of parental consanguinity in Iran is estimated to be about 40%[20,21] which is consistent with the high rate of autosomal recessive mutations reflected in the novel ARID genes identified in this country. Accordingly, the ID incidence in Iran and other countries with more consanguinity rate[22] are expected to be higher than outbred populations. The possibility of ID incidence in children of first-cousin parents are 4.1 to 4.25 times higher compared to non-consanguineous parents.[13] However, in Iran, the prevalence of ID is estimated to be about 2% among children younger than 15 years, with inconsistent estimates in affected adults.[23,24]

Based on the severity and degree of intelligence quotient (IQ) deficit, ID is classified into mild, moderate, severe and profound groups.[25] The contributions of genetic factors including chromosomal abnormalities and single-gene defects are thought to be more prominent in the etiology of more severe forms of ID.[15] ID is also categorized based on the presence or absence of other clinical manifestations along with ID. Syndromic cases present other neurological characteristics such as autism spectrum disorders and epilepsy or even congenital malformations, while non-syndromic cases are defined by solely presenting ID without other prominent clinical features.[1,6]

Environmental and genetic factors are both considered to be potential causative factors of ID.[26] Even though some environmental factors (e.g. infections and perinatal asphyxia events) can cause severe forms of ID, most severe cases are due to genetic factors.[2,26] Maternal exposure to hazardous agents such as chemicals and radiation, and maternal health issues such as alcohol abuse and diabetes can cause variable ID depending on the intensity and dose of exposure. Malnutrition and iodine deficiency, which can exert their deleterious effects much beyond the birth even into adulthood are considered as potential factors to cause common but preventable cases of ID, imposing a heavy health burden on developing countries.[26]

Single-gene causes (which are the focus of this study), can lead to diverse phenotypes in terms of severity of ID (mild to profound) based on the gene involved and the effects of destructive mutations on protein products. It is of note that different mutations in the same gene can cause syndromic or pure non-syndromic forms of ID.[26] It is also hypothesized that some cases of ID may be explained by digenic or oligogenic inheritance with two or more genes involved in disease development.[1,27]

Genetic Techniques used to Novel ID Genes Identification

Association Studies

Studies aiming to search for associated genetic variants in human genome that are significantly more common in patients affected with specific complex diseases compared to healthy controls, have attracted extensive attention. However, genome-wide association studies (GWAS) have often resulted in elusive genetic risk factors, because of recruiting limited sample sizes and lower marker densities.[28,29] To overcome this limitation, high-throughput array-based single nucleotide polymorphism (SNP) genotyping platforms have developed. The analysis

of large cohort studies have increased the effectiveness of such studies leading to identification of some genetic risk factors for complex disorders.[30,31] Apart from sample sizes and marker densities, genetic heterogeneity is also among the factors complicating the search for genetic risk factors in association studies. The most extreme example of genetic heterogeneity is ID with many genes underlying the disorder.[32] In fact, novel disease-causing gene defects are now thought to be much more common in complex disorders and therefore, systemic resequencing of genes previously implicated in Mendelian disorders has been proposed as an effective strategy for identification of genetic risk factors for complex disorders.[32,33] However, association studies are still used to identify genetic risk factors contributing to ID. Polymorphisms in *SNAP25* gene were associated with cognition impairment in a family-based study in Dutch cohorts.[34] Large genome-wide association studies for brain measures have also been conducted and led to the identification of common variants associated with human hippocampal volumes (12q14, 12q24),[35,36] intracranial volumes (6q22, 17q21)[35,37] and infant head circumference (12q15, 12q24).[38]

Cytogenetic and Microarray-Based Detection of Chromosomal Aberrations and Copy Number Variations

Chromosomal abnormalities, detectable by light microscopy, were first observed in Down syndrome, the most frequent chromosomal abnormality leading to ID.[3,15] This syndrome together with Fragile X syndrome and other far less common microscopically detectable aberrations, such as deletions and unbalanced translocations, account for roughly 15% of ID cases.[2,8] This class of gross abnormalities is characterized as aberrations easily detectable using traditional cytogenetic methods but not all chromosomal abnormalities are seen at this level of resolution. Many cryptic microdeletions/microduplications and CNVs are detectable using array comparative genomic hybridization (CGH) developed by spotting DNA probes as hybridization targets with different levels of resolution.[39] The introduction of array CGH has led to the diagnosis of many pathogenic CNVs in patients with ID[40-43] and the definition of new clinical syndromes.[44,45] CNVs have played an important role in the identification of many single genes underlying ID. Characterizing the breakpoints of either CNVs or larger chromosomal aberrations and further analysis of disrupted genes have made this possible. *MBD5*, for example, was recognized as an ID-causing gene through detecting a 200kb deletion disrupting this gene.[46] As another example, *DOCK8* was identified by mapping the breakpoints of a CNV (deletion) in an affected individual.[47] *SHANK2* was also identified in this way by detecting CNVs deleting coding regions of this gene in two patients with ID.[48] Microarrays offer much higher resolution than conventional karyotyping and are now widely used as a first-tier diagnostic test to detect subtle CNVs in patients with ID or developmental delay.[43]

Linkage Studies

Genetic linkage refers to a situation in which the alleles at loci close enough to each other are less likely to be separated by meiotic crossovers, rather, they will be co-segregated during meiosis.[10] Genotyping DNA markers makes linkage analysis applicable by seeing if any markers are simultaneously inherited with the disease phenotype.[10] Short tandem repeat (STR) markers were first used for this aim in which genome-wide STR markers are genotyped to limit the genomic linkage intervals suspected of harboring causative genes. However, high-density microarrays replaced STR-based genotyping allowing high-throughput SNP genotyping and increasing the identification rate of ID genes.[6]

Two observations -more prevalence of male ID cases by 30% and X-linked segregating ID in some families- made convincing evidence of X chromosome contribution in ID pathogenesis in 1990s. The availability of large families with only male patients made it possible to carry out linkage analysis in these families aiming to identify causative X-linked genes.[25] Linkage study of these families using positional cloning of X chromosome rearrangements and testing the candidate genes within linkage intervals have led to discovery of more than 100 X-linked ID genes.[10]

Contrary to X-linked ID, efforts to find autosomal causes of ID were initially hampered due to lack of large families with segregating autosomal ID and the sizeable autosomal genome. Nevertheless, some well-described disorders associated with ID including neurofibromatosis, tuberous sclerosis and myotonic dystrophy (DM) have been shown to have autosomal dominant defects.[49] However, only a handful of genes were attributed to non-syndromic autosomal dominant ID prior to the advent of NGS technology. This was because of the vast majority of *de novo* mutations in autosomal dominant cases due to lower reproductive fitness of affected individuals which makes the application of family-based linkage analysis and GWAS less effective.[6,50,51] Thus, approaches like sequencing of candidate genes (with previous evidence on their contribution in brain function) in large cohorts were used and mutations of such genes were confirmed in a number of individuals. This approach was used for *SYNGAP1*,[50] *STXBP1*,[52] and *SHANK3*.[53] As previously mentioned, characterization of chromosomal aberrations was another effective approach which was used to identify *MBD5*, *DOCK8*, and *SHANK2* as autosomal dominant genes of ID.

Homozygosity Mapping for Autosomal Recessive Genes

The genome-wide genotyping (using different DNA markers), serving as a prescreening technique followed

by sequencing linkage intervals, has led to the discovery of several novel ID genes, especially for X-linked ID with large affected families available.[25] Before the NGS era, a limited number of genes responsible for ARID, had been defined using genome-wide genotyping coupled with homozygosity mapping in large affected consanguineous families.[10,18] In this technique, homozygous genomic regions shared by the affected family members (obtained by genome-wide STR or SNP genotyping), are then screened usually by sanger sequencing to discover the mutations in genes located at homozygous intervals.[6] The first large study in this area, which was based on homozygosity mapping of 76 Iranian consanguineous families using genome-wide SNP-array genotyping, revealed 8 families with single linkage intervals (logarithm of odds [LOD] scores above 3) representing novel loci (MRT4-11), and 4 families with single linkage intervals for non-syndromic ARID (LOD scores between 2 and 3).[54] Similar studies on Iranian[55] and Syrian[56] consanguineous families with ID, revealed more gene loci for ARID. The prominent finding in these studies was that ARID is highly heterogeneous with many underlying genes since none of the identified intervals overlapped with each other. Identified genes for ARID using this approach included *PRSS12,*[57] *TRAPPC9,*[58] *CRBN,*[59] *GRIK2*,[60] *CC2D1A,*[61] *TUSC3,*[62] *MED23*[63] and *ZC3H14.*[64]

Next-Generation Sequencing Technologies

Next-generation sequencing (NGS) has revolutionized the genetic diagnosis of ID, and characterized it as an extremely genetically heterogeneous disease. Whole exome sequencing (WES), the most commonly used platform for NGS technologies, sequences the entire protein-coding regions (exome) of the genome, and was first applied in the gene finding era in 2009.[65]

WES was initially used to identify the genetic cause of specific syndromes showing ID assuming that all affected individuals harbor mutations in the same gene.[2] This led to the identification of *MLL2*[66] and *SETBP1*[67] (causative genes for Kabuki and Schinzel-Giedion syndromes) mutations. For sporadic non-syndromic cases, identification of underlying genes is more laborious, possibly due to the lack of a group of patients with similar clinical manifestations expected to carry causative defects in the same gene. However, sporadic cases are the most common form of ID in outbred populations.[5,12]

The first study to address the potential role of *de novo* mutations in sporadic cases of ID using Trio-based exome sequencing (comparing the sequences of sporadic case with both healthy parents), identified mutations in 9 genes indicating the importance of *de novo* dominant mutations in outbred populations.[68] Another study on patients with severe ID revealed 10 *de novo* dominant mutations.[4] Using the trio-based exome sequencing on 100 Iranian patients and their consanguineous parents indicated that *de novo* mutations should not be overlooked, even in inbred societies.[13] This study identified 44 and 17 trio families with homozygous (inherited) and *de novo* mutations, respectively, indicating that almost 72% of mutations in the Iranian cohort are inherited whereas 28% are *de novo*. The most prevalent range of mutations in consanguineous populations, however, is thought to be autosomal recessive.[5,13] As expected, employing the trio exome sequencing of sporadic cases in outbred population has the liability to spare recessive mutations and since the aim of current review is mostly to focus on these mutations, we will consider the frequency of identified novel ARID genes later.

WES has drastically accelerated the discovery of genes associated with ID, especially autosomal recessive ID for which high numbers of consanguineous families with affected offspring are available in inbred populations.[5,27,69-71] *TECR,*[72] *MAN1B1*,[73] and *ST3GAL3*[74] were the first ARID genes to be identified by WES.

A pioneering large-scale study trying to detect ARID genes in 136 consanguineous Iranian families using homozygosity mapping followed by exome sequencing of homozygous intervals resulted in the identification of 50 novel genes for recessive cases of ID.[5] Further studies on consanguineous families revealed more ARID genes, again indicating a high level of ID heterogeneity.[5,12,27,69-71,75] Using WES and GWAS, a recent cohort study on 404 Iranian consanguineous families revealed probable pathogenic variants in 219 families, broadening the functional spectrum of ARID genes compared with previously implicated genes.[12] Since there is a low level of gene overlap in the different consanguineous populations, it is expected that many ARID genes still remain to be identified. In a recent study, for example, out of 228 (known and novel) genes identified in Iranian families affected with ID, only 28, 25 and 11 of those have also been reported in Arab, Pakistani and Turkish consanguineous families, respectively.[12]

Whole genome sequencing (WGS) can detect intronic and non-coding regulatory mutations, which are not detectable by WES.[10] Despite this advantage, the huge dataset of results render the analysis too challenging. In addition, the unknown diagnostic implications of results and its relatively high cost are the reasons of its limited application.[76] In a WGS study on 50 cases of severe ID (IQ <50), in whom no genetic diagnosis had been reached by microarray, targeted gene analysis or WES, many *de novo* single nucleotide variants (SNVs) and CNVs were detected, providing a genetic diagnosis for 21(42%) patients.[76] WGS confers a higher yield of identified gene mutations which can provide diagnostic implications for some affected individuals.[77] However, performing parallel WES and WGS on Iranian consanguineous families showed only a limited additional diagnostic yield of WGS, casting doubt on its practical superiority over WES.[12]

Finally, it is worth noting that the above mentioned techniques are not separately applicable platforms and can be combined to give a higher degree of accuracy and diagnostic yield in the gene finding process. Combining homozygosity mapping and WES, for instance, has been successful and has been proposed as the strategy of choice for elucidating causative genes in inbred populations.[5,12] A large-scale cohort was performed[5] and single-gene discoveries such as *GTPBP2*[78] and *NSUN2*[79] were achieved on Iranian consanguineous populations using this combined approach.

A Glance at the Identified ID Genes to Date

The number of genes underlying ID is growing rapidly. Considering recent reviews on ID genes, a comprehensive review containing a database of all identified ID genes with regular updates is available online (http://sysid.cmbi.umcn.nl).[14] This database contains the known validated as well as candidate ID genes. In this database, a curated set of ID-associated genes known as "primary ID genes" has been compiled through literature and OMIM search. These known ID genes (more than 1100 so far), have been confirmed by sufficient number of patients and/or by clinical information. The criteria of putting genes in this group were as follow; sufficient affected individuals and families with mutations in the same gene, indicating ID and cognitive impairment as a core phenotype (not secondary due to neurodegenerative diseases), non-treatability (excluding treatable metabolic syndromes in which cognitive ability can be resumed by providing certain factors) and confirmed clinical phenotypes. The published ID genes without fulfilling this criteria are compiled into "candidate ID genes". However, many candidate ID genes are increasingly validate as confirmed ID genes. We, therefore, focused mainly on this database (updated in October 2018) to obtain a list of all known genes underlying ID. In this database, about 2149 genes (including primary ID genes and candidate ID genes) have been attributed to ID[14,80] (supplementary table). This number is expected to increase in the coming years due to the vast heterogeneity of ID and future progress in next-generation technologies. Of all the genes described, autosomal recessive genes rank first in frequency followed by autosomal dominant and then X-linked genes.

Through a literature review of large cohorts and other studies on gene discovery in Iran, we have compiled a separate list of genes identified in Iran through studies on the Iranian population (supplementary table). The aim was to provide a comparative tool to focus on the contribution of Iran in the identification of novel ID genes.

The pre-hypothesis suggests that autosomal recessive genes are the most prevalent ID causing genes in consanguineous populations, which was consistent with our findings from analyzing genes described in Iran. Most recessive variants in Iranian population were homozygous and compound heterozygosity was rare. For 26 genes, the mutations were observed in two or more consanguineous families.[12] Based on the two large cohorts on Iranian population,[5,12] affected families were distributed in different ethnicities and geographical locations of Iran. Identical likely disease-causing variants for 6 genes (*AP4S1, GAMT, PRRT2, RNFT2, TMEM67*, and *VPS13B*) were identified in two different families. For seventh gene (*AP4M1*), the same variant was observed in three families. Haplotype analyses confirmed identity-by-descent for these variants. To our knowledge, none of these recurrent variants has been observed outside of Iran reflecting the consanguineous architecture of Iranian population. In total, 8% of all ID genes and 11.5% of all ARID genes, have been identified in Iran (Figures 1A and 1B). Despite recent advances in AR gene discovery, it is estimated that most AR genes are still unknown and remain to be identified.[1,10]

As the repertoire of candidate ID genes is ever-expanding, there is a real need for validating functional studies to provide confirmatory data on the effects of ID genes[1] and this is an area which must be greatly improved, especially in Iran. Out of 173 novel genes identified in Iran, about 29% have been studied functionally (Figure 2).

The observation of additional (particularly unrelated) phenotypically similar families harboring mutations in the same gene provides stronger evidence for the gene's role in causing ID. This finding together with the absence of mutations in the gene of interest in control individuals is a preliminary step to validating the gene as having a causative role in the disease process.[1] Of the total novel ID genes first identified in Iran, 61 have also been reported in more than one ID-affected family (some of which are in populations other than Iran) which can provide more convincing evidence for the causative role of genes (supplementary

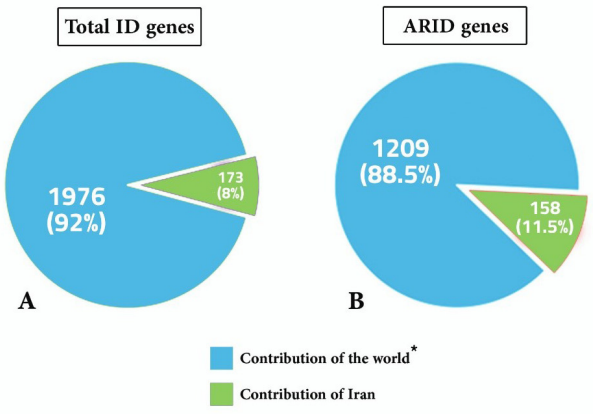

Figure 1. (A) Pie chart showing the contribution of Iran in the identification of novel ID genes regardless of inheritance mode of identified genes. **(B)** Pie chart showing the contribution of Iran in the identification of novel ARID genes. Out of a total of 1367 ARID genes, 158 genes (11.5%) were identified in Iran through studies on the Iranian population. *Excluding Iran.

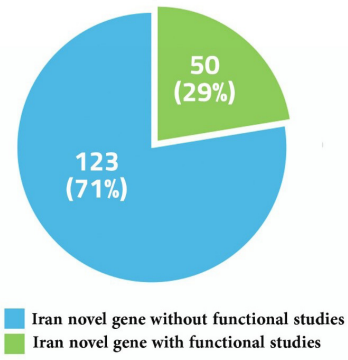

Figure 2. Pie Chart Showing the Percentage of Functional Studies Carried out on Novel ID Genes Identified in Iran. In total, 50 out of 173 (29%) identified genes have been studied functionally, indicating that more efforts are required in this arena.

table). Mutations in *SRD5A3*, for example, have been reported in about 20 cases from several families showing 2 distinct allelic phenotypes including *SRD5A3*-CDG and Kahrizi syndrome.[81] Out of the 61 genes in more than one affected family, 10 genes have been reported in more than five families (in Iranian and other populations) indicating that these genes are probably common causative ID genes. The genes reported in more than one affected family are listed in Table 1.

Therapeutic Approaches in ID

ID, for which limited therapeutic modalities are available, has long been considered to be a disorder with no efficient treatments. This is probably because of the complexity of biological processes related to the neural network and irreversible neuronal damage leaving most treatment approaches focused on ameliorating behavioral comorbidities. Cognitive therapy, for example, is widely used to reduce the behavioral problems of ID patients such as anger, depression and anxiety, aiming to change the problematic behaviors of patients.[82]

Through better understanding of neuronal biology, specific therapeutic approaches are being developed to improve ID at the biological level, particularly for metabolic disorders. Phenylketonuria, for example, was the first metabolic disease found to be a treatable disorder in which a phenylalanine-restricted diet can prevent clinical features by reducing the blood phenylalanine level.[83,84] The efficacy of Phenylketonuria treatment is a paradigm for neonatal screening of diseases in which early diagnosis can drastically improve the clinical outcome. Enzyme replacement therapy (ERT) is now available for several metabolic disorders such as Hurler syndrome, Pompe and Fabry diseases. ERT has shown improved prognosis and intellectual function, however, the effectiveness of treatment is improving, especially in the dose optimization.[85,86] ERT treatment may have partial beneficial therapeutic effects on some organic acidemias, though it is less efficient in urea cycle defects or tyrosinemia.[86] ID-presenting inborn errors of metabolism with potential therapies have been listed in a systematic review considering the clinical effectiveness of therapeutic modalities.[84] Apparently, therapeutic approaches targeting dysfunctional pathways and networks, rather than genes, are more promising. Consistent with this concept, the GABAergic system, which is affected in Fragile X and Rett syndromes, can be targeted as an eligible pathway.[1] Additionally, re-introducing the functional *MECP2* gene in mouse model of Rett syndrome has shown some improvements in certain neurological and behavioral functions.[87]

Some ID disorders are linked to decreased levels of histone acetylation. Histone modifications favoring chromatin accessibility are thought to be important in memory formation and learning.[88] In therapeutic approaches which directly target deficient pathways, histone deacetylases (HDAC) can offer promising targets. It has been demonstrated that HDAC inhibitors can be protective due to their role in boosting neurogenesis and neuronal migration.[89] Rubinstein-Taybi and Kabuki syndromes, disorders with disturbed histone modification, have shown improvements by prescribed HDAC inhibitor agents in mouse model.[90]

Exon skipping using antisense oligonucleotides makes it possible for the truncating mutation-containing exon to be skipped leaving the rest of the gene from the point of the mutation intact. Major complications of this approach concern immunogenicity to the delivered vector and finding the vectors capable of passing through the blood–brain barrier where they should exert their effect.[91] Other novel therapies for ID including stem cell replacement therapy and gene therapy are emerging although their efficacy has not yet been determined and needs further studies.[86]

Table 1. ID Genes Identified in Iran in More Than One Affected Family

Number of Affected Families	ID Genes
2	*ADRA2B; ASCL1; CACNA1G; CASP2; FASN; FRY; INPP4A; ABCA2; AIMP1; AK1; ALS2; BOD1; CAPN9; CEP104; CTNNA2; DIAPH2; DLX6; FBXO7; GCN1; GLS; IPP; ITGAV; MADD; NAA10; PARP1; PIDD1; RNFT2; SCAPER; TAF1; TAF2; TRMT1; TTC5; TTI2*
3–4	*CAPN10; ELP2; LINS1; NDST1; ZNF526; LARP7*
≥5	*ADK; C12orf57; ERLIN2; KIF7; LAMA1; MAN1B1; POLR3B; PRRT2; SRD5A3; TUSC3*

Discussion

ID is one of the most important disorders with extreme genetic heterogeneity, imposing a massive social and economic burden on health care systems. Today, NGS has found its way into the genetic diagnostic of diseases, especially for diseases in which genetic heterogeneity is a key feature.[2] This is particularly the case for ID which has been well studied and its genetic causes have started to be unraveled at an exponential pace. As previously noted, more than 2000 genes with a wide range of cellular functions are thought to be involved in the pathogenesis of diseases presenting ID as a key clinical feature.[26] The contribution of research community of Iran in finding the novel ID genes has been outstanding and well-acknowledged. The vast majority of ID (mostly ARID) genes identified in the Iranian population were discovered using high-throughput exome sequencing.[5,12] This was partly due to the availability of large consanguineous families with multiple affected members allowing the possibility to search for ARID genes. In addition, access to a well-established health care system with integrated genetic services has significantly contributed to this achievement. Utilizing the health care system in Iran from health houses to public/private clinics and hospitals, in parallel with counseling centers in all provinces,[92] provided a widespread network for genetic counseling services. Such collaborations between health systems and welfare organizations have had a synergistic effect in accessing remote areas across the country and bringing knowledge, expertise, human resources and advanced techniques together to improve diagnostic and preventive interventions in Iran. Factors such as high rate of consanguineous marriages, large family sizes and the admixture of various ethnicities in Iran, have enabled counseling networks to recruit the large consanguineous families with multiple affected members that are appropriate for mapping and identifying the involved autosomal recessive ID genes.

Nevertheless, by identifying more ID genes, the need for supportive data has increased to verify the causative role of these identified genes by performing the functional assays. It is now believed that the genes contributing to ID are involved in a variety of molecular functions from development and metabolic processes to regulatory and synaptic functions.[93] Functional studies can provide confirmatory evidence of the role of genes in ID pathogenesis, which finally can validate them as having the capability of causing ID when mutated. There are many platforms for performing functional experiments from *in vitro* approaches using patient-derived cells to *in vivo* studies of gene mutations in model organisms.[1] Performing such validating studies has largely been neglected in Iran but it has drawn more attention lately. We have recently begun to functionally validate some genes identified in our previous studies including *ZBTB11*,[94] *CNKSR1*,[95] *CLIP1*,[96] and *TRMT1*. However, there is still great scope for elucidating the functional implications of the novel ID genes currently identified. Using therapeutic approaches for eligible cases of ID is another exciting but underdeveloped area of research. However, for some single-gene ID cases with potentially applicable treatments, numerous gene therapy approaches are currently being studied in animal models and even humans and have shown some promising results.[6] In addition, recently introduced stem cell replacement therapy is under investigation to examine its usefulness in the treatment of neurodegenerative diseases with ID phenotype.[97] Rationally, it has been hypothesized that therapeutic approaches are more promising when targeting the same disrupted pathways or networks caused by mutations in different sets of genes instead of focusing on the single-gene level.[1] This concept has been demonstrated for therapies using HDAC inhibitors[98] and GABAergic system antagonists.[99] Performing functional studies can also help in this regard by providing information on commonly disrupted pathways in ID so that they can be used as promising therapeutic targets.

In conclusion, finding novel ID genes is of great importance as it can provide insight into the genetic causes of this disorder. However, as more ID genes are continuing to be discovered, it is important to perform functional studies on the candidate ID genes identified so as to reveal whether they are truly causative genes. Studies on the functional aspects of novel identified ID genes and studies focusing on using therapeutic interventions in potentially treatable ID cases are not well developed in Iran, so it is important to perform this research to fill the gaps in our knowledge. This will consequently provide affected families with accurate genetic diagnoses and proper therapeutic modalities. Taking advantages of high-throughput sequencing technologies and validating functional studies, the known ID genes can also be used for developing the diagnostic tests for identifying mutations in ID patients. These diagnostic gene panels are particularly useful in NS-ID cases that are clinically indistinguishable. Since the spectrum of mutations is highly diverse and non-overlapping in different populations, particularly for autosomal recessive mutations in consanguineous populations[5,12,27,69-71,75] such as Iran, identification of genetic causes in different consanguineous families can significantly expand the number of genes in diagnostic multi-gene panels which in turn can increase the diagnostic yield of disease. However, as more genes are increasingly linked to ID, it is likely that the genome-wide sequencing approaches will be soon the first-tier diagnostic test for ID. These sequencing technologies have significantly improved the diagnostic yield for ID. Identification of novel ID genes can also be important in improving diagnostic yield so that more patients can be provided with a conclusive molecular diagnosis. Identification of causing mutations in solved cases can be used in carrier testing to prevent transmission of disease-causing mutations to the offspring,

prenatal diagnosis and prenatal genetic diagnosis to ensure that fetus is not affected.

Authors' Contribution

RA searched the literature, collected and analyzed data; SK searched the literature and wrote the manuscript; MB helped and edited the analysis process and edited the manuscript; SSA collected data and searched the literature; HB, SED, FG, SM, FB, MA, FK all collaborated in data collection and literature review; KK and HN critically reviewed and edited the manuscript and analysis process; HN also conceived and designed the study.

Conflict of Interest Disclosures

The authors have no conflicts of interest.

Ethical Statement

This study is a review study with no inclusion of any personal information. However, this was part of a research project on ID which has been ethically approved by the Ethics Committee of University of Social Welfare and Rehabilitation Sciences.

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