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ORIGINAL INVESTIGATION

# Autosomal recessive diseases among the Israeli Arabs

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**Abstract**
The Israeli population mainly includes Jews, Muslim and Christian Arabs, and Druze. Data on genetic diseases present in the population have been systematically collected and are available online in the Israeli national genetic database. Among the Israeli Arabs in December 31 2018, the database included molecular data on six diseases relatively frequent in the whole population: thalassemia, familial Mediterranean fever (FMF), cystic fibrosis, deafness, phenylketonuria or congenital adrenal hyperplasia as well as data on 632 autosomal recessive diseases among Muslim Israeli Arabs, 52 among the Christian Arabs and 79 among Druze. A single variant was characterized in 590 out of the 771 genes causing disorders in which the molecular basis was known. Many of the variants reported among Arabs in Israel are novels, most being found in one community only. Some variants are ancient and for instance, consistent with the migration history, several variants are found in the Bedouins from the Negev as well as from the Arab peninsula. In the 181 other disorders more than one variant was characterized either in the same gene or in more than one gene. While it is probable that most of these cases represent random events in some cases the reason may be a selective advantage to the heterozygotes.

## Introduction

The Israeli population includes a Jewish majority, a large Muslim Arab community and two smaller minorities, the Christian Arabs and the Druze. Each community has been relatively isolated for centuries mainly by the preference of consanguineous marriages. As a direct consequence, many genetic diseases in particular with autosomal recessive inheritance are relatively frequent in each of the communities. Data on variants causing monogenic diseases with autosomal recessive inheritance have been systematically collected for more than 20 years in the Israeli national genetic database (INGD, http://INGD.huji.ac.il) (Zlotogora and Patrinos 2017).

In 2010, INGD included 236 monogenic diseases with autosomal recessive inheritance among Muslim Arabs, 11 among Christian Arabs and 31 among the Druze (Zlotogora 2010). Since then extraordinary technological developments led to a significant increase in the number of diagnosed genetic diseases. In 2016, 10 years after launching the database online it included 613 monogenic diseases with autosomal recessive inheritance among Muslim Arabs, 38 among Christian Arabs and 58 among the Druze (Zlotogora and Patrinos 2017). The numbers of diagnosed genetic diseases continue to increase allowing a better characterization of genetic variants, understanding of their distribution in the Israeli Arabs population and the development of public health programs.

## Methods

### The population

In 2017, the Israeli population included 8,628,600 citizens of whom 74.5% were Jews (6,446,100) and 17.8% Muslim Arabs (1,524,000) (Statistical abstracts, 2018). The other communities included mainly Christian Arabs (132,300) and Druze (139,300) each representing less than 2% of the population. Israel is divided in 6 districts (supplementary figure 1) and in one of them, the Northern district, which comprises 16.2% of the Israeli population, are living most of the Druze (112,200), more than half of the Christian Arabs (93,500) and a third of the Muslim Arabs (545,500). The

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Bedouins represent a distinct Muslim community that lived as a nomad population for centuries mostly in the Negev included in the Southern district (approximately 260,000 out of 300,000 Bedouins).

The Arabs are generally living in villages/tribes which were founded by a few individuals more than 10 generations ago. Most of the Muslim Arabs are living in 92 localities of more than 1000 inhabitants. There are three cities with more than 50,000 Muslim Arabs, in one of them Jerusalem is living the largest Muslim Arab population (330,000). Approximately one-third of the Christian Arabs are living in 6 localities where they represent 50% or more of the population while another third live in four cities in which they represent a minority. The remaining half of the Christian Arab population is dispersed in Israel, mostly in localities with a Muslim majority. Almost two-third of the 139,300 Druze live in 11 villages where they represent more than 95% of the population. Another, 20% of the Druze live in three villages in which they represent between 94 and 50% of the population. Almost all the remaining Druze population live in other five localities in which they represent 49–1% of the inhabitants.

## Genetic diseases

Data on genetic diseases diagnosed among Arab patients collected from both the literature and personal communications are included in INGD (http://INGD.huji.ac.il) (Zlotogora and Patrinos 2017). In addition, an inquiry is made to the authors of the reports about details on the origin of the patients. In the database the non-Jewish population is divided in two groups Israeli and Palestinian Arabs, a distinction made according to the nationality reported. The database includes variants that were reported to cause monogenic diseases whether or not the pathogenicity was proven. Variants in a single gene are always related to a single disease while there are few diseases associated to variants in more than one gene.

The data on diseases with autosomal recessive inheritance were analyzed on December 31 2018, excluding diseases that are relatively frequent in the whole Arab population. These diseases are thalassemias, familial Mediterranean fever, cystic fibrosis, adrenal hyperplasia III (21 OH deficiency) and phenylketonuria/hyperphenylalaninemia.

## The national Israeli carrier-screening program for reproductive purposes

The national Israeli carrier-screening program for reproductive purposes funded by the ministry of health includes all the severe genetic diseases with a predicted incidence higher than 1 in 15,000 live births (Zlotogora et al. 2016). While some diseases are screened in all the population, the recommendations are different according to the religion and in the case of the Arab population also according to the locality of origin. Details about the diseases, the communities and localities in which the screening program is performed were collected from the ministry of health internet site (supplementary table 2) (https://www.health.gov.il/Subjects/Genetics/prof/Pages/default.aspx).

# Results

## Diseases in the diverse communities

### Muslim Arabs (excluding the Negev Bedouins)

Variants related to 523 diseases were reported in 528 genes among Muslim Arab patients. In 401 genes (75.9%), a single variant was characterized, in 58 genes two variants and in 36 genes three variants (Table 1). Four variants or more were reported in 33 genes among which 10 different variants we reported in 3 genes (CNGA3, LAMA3, GJB2) and 21 different variants in ABCA4. Among the 842 different variants reported in 528 genes, 133 were founder variants.

The national carrier-screening program for reproductive purposes specific to the Muslim Arabs included at the end of 2018, variants causing Niemann-Pick type A for all non-Bedouins Muslim Arabs in the center and the North of Israel and Pendred syndrome for Bedouins in the North of Israel. Additional recommendations for carrier screening specific to Muslim Arabs excluding the Negev Bedouins included specific variants in 56 different genes in 40 localities.

### Muslim Arabs, Negev Bedouins

Variants related to 109 diseases were reported in 110 genes among Negev Bedouin patients. In 78 genes (70.9%) a single variant was characterized, in 24 genes two variants, in 7 genes three variants and one gene 4 variants (Table 1). Among the 151 different variants reported in 110 genes, 75 were founder variants.

The national carrier screening program for reproductive purposes specific to the Negev Bedouins included at the end of 2018, variants causing hypoparathyroidism, retardation, dysmorphism syndrome and congenital insensitivity to pain in all the tribes and variants in 54 different genes in specific tribes.

### Christian Arabs

Variants related to 52 diseases were reported in 52 genes among the Christian Arab patients. In 45 genes (86.5%) a single variant was characterized, in 5 genes 2 variants and in one gene 4 variants (Table 1). Seven variants were reported

**Table 1** Genes in which variants were reported among Israeli Arabs affected with autosomal recessive disorders

| According to the number of variants reported in each gene | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Number of variants | Number of genes | | | | | | | | |
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | >7 | Total |
| Muslims | | | | | | | | | |
| Non-Negev Bedouins | 401 | 58 | 36 | 9 | 8 | 3 | 2 | 11 | 528 |
| Negev Bedouins | 78 | 24 | 7 | 1 | 0 | 0 | 0 | 0 | 110 |
| Christians | 45 | 4 | 2 | | | | 2 | | 52 |
| Druze | 66 | 9 | 5 | 1 | | | | | 81 |
| All | 590 | 96 | 48 | 12 | 8 | 3 | 3 | 12 | 771 |

| According to the total number of variant and their type | | |
|---|---|---|
| Number of variants | Total | Founder |
| Muslims | | |
| Non-Negev Bedouins | 842 | 133 |
| Negev Bedouins | 151 | 75 |
| Christians | 73 | 20 |
| Druze | 103 | 32 |
| All | 1169 | 260 |

in ABCA4 and 9 variants in TYR. Among the 73 reported different variants in 52 genes, 20 were founder variants.

The national carrier-screening program for reproductive purposes specific to the Christian Arabs included at the end of 2018, variants causing albinism, hyperammonemia and Cockayne syndrome in all the community, and four other diseases in one of the localities.

### Druze

Variants related to 79 diseases were reported in 81 genes among Druze patients. In 66 genes (81.5%) a single variant was characterized in 9 genes 2 variants, in 5 genes 3 variants and one gene 4 variants (Table 1). Among the 103 different variants reported in 81 genes, 32 were founder variants.

The national carrier screening program for reproductive purposes specific to the Druze included at the end of 2018, variants in 29 different genes in 15 villages. In several instances screening for a same variant was performed in several villages; however, none of the variants was screened in all the Israeli Druze population.

## Presence of a same variant in more than one community

Eight variants in six genes were found in both Christian and Muslim Arabs. In one gene ABCA4, the gene in which the largest number of variants were reported in INGD, there were three variants that were found in these two communities.

In 16 cases, the same variant was found among Druze and Muslim, one variant in 15 genes and two variants in one gene (GAA) two variants were common to both communities.

No variant was found to be common to the three communities.

## Geographic distribution of the variants

Data concerning the locality of origin of the patients were available in 77.5% of the cases.

In the Northern district, there were 14 diseases in which more than three variants were reported in a single gene (supplementary table 1). In most of the cases, in at least one of the localities in which the disease was diagnosed, two different variants were reported and in 4 instances three variants were reported in a single locality. In one locality, four different variants were reported in GJB2. In the Jerusalem district, similar observations were made for six diseases (supplementary table 1). It should be noted that in four out of the six diseases these observations were made in the city of Jerusalem in which a large part of the population has ancestors originating from different part of the region.

In a Muslim town in the center of Israel, including approximatively 55,000 inhabitants and the surrounding villages, Meckel syndrome was diagnosed in several patients, each homozygous for 1 of 5 variants in three different genes associated with the syndrome (TMEM67, TMEM216 and TMEM231). Among the Bedouins from the Negev eight different variants have been characterized in five of the genes

included in the Bardet-Biedl syndrome associated gene family (BBS10; BBS2; BBS4; BBS9; CEP290).

## Discussion

Between 2010 and 2018, a significant increase in the number of genes with variants causing autosomal recessive diseases among Israeli Arabs was documented in INGD. In this period, the number of genes raised from 236 to 638 among Muslim Arabs, from 11 to 52 among Christian Arabs and from 31 to 81 among the Druze. A similar trend was observed among Jews from 159 genes with variants causing autosomal recessive diseases reported in INGD in 2010 to 382 in 2018 (unpublished observations). The significant increase in the number of genes with variants causing autosomal recessive diseases among Israeli Arabs was mostly the result of the availability of better possibilities to make a molecular diagnosis in genes already well known. However, in 25.9% of the cases, the new variants were in genes in which the causal relation with a disease was reported after 2010 (26.8% of the cases among Muslim Arabs, 24% in the Christian Arabs and 18% among Druze). In more than half of these cases (52.2%), the first report was either made in the Israeli Arab population or included one or more family from this population.

Consanguinity is traditional in the Middle East and marriages between relatives are frequent among Israeli Arabs. The preference for consanguineous marriages, in particular between first cousins that are the children of brothers, has been a long tradition among Arabs and Druze of the region. In a survey made in 1990–1992, marriages between second cousins or closer were reported in 60.1% of the Negev Bedouins, 47% of the Druze, 36.7% of Muslim Arabs not including the Negev Bedouins and 22.4% of the Christian Arabs (Vardi-Saliternik et al. 2002). Since then a decrease in consanguinity rates, mainly of first-cousin and closer marriages was reported among the Israeli Arabs (Na'amnih et al. 2014; Sharkia et al. 2016). In 2008, among Negev Bedouin, marriages between second cousins or closer decreased to 44.8% of the couples (Na'amnih et al. 2014). In addition, among couples that married in 2005–2009s cousins or closer marriages decreased to 24.3% among Muslim Arabs excluding Negev Bedouins, 28.4% among Druze and 18.2% among Christian Arabs (Na'amnih et al. 2015). In endogamous populations such as the Arabs in Israel where there is a long tradition of marriages between close relatives, the coefficient of relationship between individuals having remote common ancestors is often higher than the one corresponding to second cousins and, therefore, their marriage must be considered as consanguineous. Nowadays, the Druze and most of the Muslim Arabs in particular the Negev Bedouins are still living in relatively isolated communities and remote links between the spouses are frequent. Therefore, even though the proportion of marriages between second cousins or closer is decreasing, the rate of consanguineous marriages remains very high due to distant relations between the spouses. Conversely, the Christian Arabs are mostly dispersed in Israel and marriages are mostly either consanguineous between second cousins or closer, or between non-related individuals. Since the number of recessive variants related to diseases is found at similar levels in all individuals, the appearance of affected individuals with autosomal recessive disorders in a specific community is related to its inbreeding coefficient. Therefore, a larger number of different diseases is expected to be diagnosed in the communities with higher inbreeding coefficients and indeed, the number of diseases in INGD is higher among the Druze (79) than among Christian Arabs (52) even though the communities are almost of the same size.

Many of the variants reported among Arabs in Israel are novels, almost all being found in one community only. Some variants are ancient and for instance, consistent with the migration history, several variants are found in the Bedouins from the Negev as well as from the Arab peninsula (Zlotogora 2010). Because of centuries of inbreeding, each village represents an isolated community in which a variant either existed in the founders, occurred de novo or was introduced by marriage with a carrier from another locality, may expand and become very frequent within the locality (Zlotogora et al. 2007). As a result, many severe diseases were diagnosed in which the very high frequency was limited to one locality or one tribe. This was the basis for the initiation of a national targeted program for the detection of carriers for reproductive purposes among Arabs in 2002 (Zlotogora et al. 2009). This program is nowadays part of the national program aimed to detect couples at risk for severe diseases that are relatively frequent (carrier frequency of 1:60 or higher) in the Israeli population (Zlotogora et al. 2016). At the end of 2018, specific targeted carrier screening was performed in different Bedouin tribes of the Negev and in individuals originating from 54 different localities. Among these localities, in 40 the program aimed to detect carriers among Muslim Arabs, in 15 among Druze and in one among Christian Arabs. As discussed above, the Christian Arab community is relatively dispersed as opposed to the Negev Bedouins or the Druze that remain very isolated. These differences are reflected in the national screening program in the number of diseases screened and the number of localities in which the screening is performed. The number of genes in which pathogenic variants are screened represent 52.7% of those characterized among the Negev Bedouins (58 out of 110), 35.8% of the genes characterized among the Druze (29 out of 82) and only 13.6% of the genes characterized among the Christian Arabs (7 out of 52). Frequent local founder pathogenic variants are screened in 15 out of the 19

major localities in which Druze are living as opposed to only one of the localities in which Christian Arabs are living. On the other hand, among the Christian Arabs specific pathogenic variants in three genes are screened for in the whole community and none in all the Druze population.

The observation that several variants either in a same gene or in related genes are responsible for the relatively high frequency of genetic diseases in a small geographic region was made several years ago and is confirmed in the present study. For instance, in the case of metachromatic leukodystrophy, in the original report five variants were found in seven villages of the Nazareth region within the Northern district (Heinisch et al. 1995). Nowadays seven variants were reported among patients living in nine different localities in the Northern district. In one of the original localities near Nazareth, two different variants, each found in homozygosity in the affected children, were reported. Another example is Bardet-Biedl syndrome among the Bedouins from the Negev for which eight different variants were characterized in five of the genes included in the Bardet-Biedl syndrome associated gene family. In addition, after the completion of the present summary, homozygosity for a variant in *SCAPER* was reported in several individuals affected with Bardet Biedl from a Negev Bedouin kindred (Wormser et al. 2019). The observation of multiple variants in a same gene responsible for the high frequency of a disease was made in other isolated communities and several explanations were proposed to try to understand this phenomenon. For instance, the existence nine different mutations in the *CPN3* gene 3, linked to the high frequency of limb-girdle muscular dystrophy type 2A in the genetic isolate from La Reunion Island was explained by a digenic model (Richard et al. 1995). This model was never proven even though nowadays its molecular resolution may be relatively easy. The possibility that the existence of multiple variants is secondary to random events was often raised. For instance since in general the number of variants reported in a gene increases in parallel to the time that passed since the gene was first reported, this relation was suggested to explain the phenomenon. Indeed, among the Israeli Arabs from the Northern district, in almost all the cases, multiple variants were found in genes that were reported in the nineties (supplementary table 1). However, in this population as well as in several other isolated communities multiple mutations were already reported in the first molecular analysis of the patients (Heinisch et al. 1995; Richard et al. 1995). Random events followed by genetic drift is the currently accepted explanation of the relatively high prevalence of 4 lysosomal storage disorders, namely, Tay Sachs, Gaucher, Niemann-Pick and Mucolipidosis type IV among Ashkenazim (Risch et al. 2003). Nevertheless, it is difficult to relate only to random events the existence of multiple variants in several genes encoding for enzymes from a common biochemical pathway. Another proposed explanation for the observations of multiple allelic variants and variants in different genes reported in isolated populations, is the existence of a selective advantage. In the case of Bardet Biedl syndrome the high prevalence observed in the Negev Bedouins was also found in Newfoundland due to at least nine different variants (Davidson et al. 2003). Both populations are living in extreme climatic conditions and it may be envisaged that a heterozygous advantage given by variants the Bardet-Biedl syndrome associated gene family allows survival in such environments (Davidson et al. 2003). While the existence of selection is not proven, in populations in which a selective advantage was demonstrated, the epidemiological data on the disorders involved are parallel to those for genetic disorders found in high frequency in isolated populations.

The large numbers of diagnosed autosomal recessive diseases in the Israeli Arabs population and the characterization of the causing variants allow a better understanding of the occurrence and distribution of genetic variants in consanguineous populations. This knowledge was the basis for the development of a unique targeted population carrier screening program.

## Compliance with ethical standards

**Conflict of interest** The author states that there is no conflict of interest.

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