The Israeli population carrier screening program

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The Israeli population 2015

8,134,500 inhabitants

Jews (75.1%)

Ashkenazi, non Ashkenazi according to the country of origin

Arabs (21.1%)

Muslim Arabs (80%), including the Bedouins
Christian Arabs (10%)
Druze (10%)

Others

Genetic diseases in Israel

Many diseases are relatively frequent

- isolation
- consanguinity

Among Jews

- Many genetic diseases known among Jewish communities, the genetic basis known later

Among Arabs

- Progressive delineation of genetic diseases in the last decades

National carrier screening program 1978-2008

- 1978 Israeli Tay-Sachs screening program organized and funded by the Ministry of Health
  - Once a week, two centers, hexosaminidase determination, unique central laboratory
  - Done by medical personnel, no genetic counsellors
  - Sequential screening
  - Free of charge

- since the nineties, gradual ability to detect carriers of additional frequent diseases among Jews

Private expansion of carrier screening

The Association of Israeli Medical Geneticists recommends screening

- **SEVERE DISEASE**
- **FREQUENT 1:15,000 (AR = 1:60 CARRIERS)**
- **POSSIBILITY TO DETECT 90% OF CARRIERS**

- Tay-Sachs carrier screening MOH centers
- Other screening tests done in genetic units, privately and mostly partially paid by complementary insurances
- Slow expansion of the national screening program due to financial problems

Since January 2013 the national program is expanded and include all the tests recommended by the Association of Israeli Medical Geneticists free of charge

- **SEVERE DISEASE**
- **FREQUENT 1:15,000 (AR = 1:60 CARRIERS)**
- **POSSIBILITY TO DETECT 90% OF CARRIERS**

National carrier screening program since 2013

ALL THE POPULATION

- **Cystic fibrosis**
- **SMA**
- **Fragile X**

TARGETED

- Other diseases according to origin: Jews according to the community of origin and among Arabs and Druze according to the religion and the locality of origin or according to the tribe among the Bedouins of the Negev

National carrier screening program

- Centers for carrier screening either genetic units or in the community
- The centers are accredited by Ministry of health and are under the responsibility of a medical geneticist
- **Either genetic counsellors or medical personnel** give explanations about all the tests available either funded or private and receive informed consent for the tests
- Sequential screening

All the population first year of expanded program 2013-2014

Disease	examined	Data available	carriers	Carrier rates
Cystic fibrosis	60,810	59,644	1,320	1:45
SMA	64,617	62,444	1,091	1:57
Fragile X	55,498	44,592	299	1:149

Carrier screening in specific Jewish communities

Disease	Data available	No. of carriers	Carrier rates
Tay Sachs (Ashkenazi; North Africa; Balkan)	31,401	697	1:45
Familial Dysautonomia (Ashkenazi; Balkan)	21,379	559	1:38
Canavan (Ashkenazi)	21,348	338	1:63
Pontocerebellar hypoplasia (North Africa; Iraq)	8,746	97	1:90
Costeff disease (Iraq)	1,689	37	1:46
Metachromatic leukodystrophy (Yemen)	891	9	1:99
Infantile cerebral and cerebellar atrophy (Caucase)	520	25	1:21

Carrier screening among Druze

Locality	Disease	Data available	Carriers	Carrier rates
3	Maple syrup urine disease	84	3	1:28
3	Tay Sachs disease	22	4	1:6
5	Mucolipidosis III	95	5	1:19
7	Hyperoxaluria	36	1	1:36
7	Hyperoxaluria III	24	3	1:8
9	Krabbe	103	3	1:34
14	Ataxia telangiectasia	48	2	1:24
19	Wilson disease	10	2	1:5
22	Retinitis pigmentosa	59	2	1:30
22	Hyperoxaluria	70	5	1:14
22	Tyrosinemia	54	0	-
24	Kohlschütter-Tönz	30	4	1:8
24	Hyperoxaluria	37	2	1:19
26	Fanconi A	63	2	1:32
26	Hyperoxaluria	165	7	1:24
26, 27	Cockayne syndrome	94	5	1:19
28	Maple syrup urine disease	37	0	-
29	Cockayne	17	2	1:9
33	Tay Sachs disease	27	0	-
35	Ataxia telangiectasia	4	0	-
35	Mitochondrial depletion	18	0	-
35	Wilson disease	21	1	1:21
44	Argininosuccinic aciduria	118	2	1:59
44	Carbamoyl phosphate synthetase I deficiency	116	0	-
44	Cerebrotendinous xanthomatosis	83	6	1:14
44	Prolidase deficiency	80	2	1:40

Carrier screening among Christian Arabs

Locality	Disease	Data available	No. of carriers	Carrier rates
all	Cockayne	1,062	25	1:42
all	Albinism	931	29	1:32
28	Sandhoff	61	5	1:12
28	Ataxia telangiectasia	55	4	1:14

Carrier screening in Non-Bedouin Muslim Arabs

Locality	Disease	Data available	Carriers	Carrier rates
Several	Niemann Pick A	4,359	19	1:240
2	Congenital nephrotic syndrome	48	8	1:6
2	Hyperoxaluria	50	4	1:13
6	Molybdenum cofactor deficiency	38	5	1: 8
6	Pycnodysostosis	36	3	1:12
8	CEDNIK	93	2	1:47
10	Epidermolysis bullosa	84	1	1:84
10	Severe combined immune deficiency	167	6	1:28
10	SMARD	163	1	1:163
11	Wolman disease	131	2	1:66
12	Glutaric aciduria type II	86	1	1:86
12	Retinitis pigmentosa	95	14	1:7
13	Cockayne/XP	9	0	-
16	Non ketotic hyperglycinemia	45	3	1:15
16	Pseudo rheumatoid dysplasia	45	2	1:23
16	Retinitis pigmentosa	54	2	1:27
17, 18	Krabbe disease	615	52	1:12
17	Stuve Wiedemann	370	24	1:15
20	Non ketotic hyperglycinemia	167	10	1:17
21	Mental retardation, non syndromic	112	10	1:11
21	SMARD	120	11	1:11
23	Hypophosphatasemia ALPL	99	0	-
25	Smith Lemli Opitz	155	14	1:11
28	Mitochondrial depletion syndrome	19	0	-
30	Factor 7 deficiency	127	3	1:42
31	Biotinidase deficiency	64	0	-
31	Leber amaurosis	69	6	1:12
32	Hereditary Spastic Paraparesis +	139	1	1:139
39	POC1A deficiency	9	0	
40	Rickets, 1,25 dehydroxyvitamin D3 resistant	268	4	1:67
42, 43	Ataxia telangiectasia	70	4	1:18
18	HUPRA	299	22	1:14

Carrier screening in Bedouin Muslim Arabs, not from the Negev

Locality	Disease	Data available	Carriers	Carrier rates
Galilee	Pendred	503	11	1:22
1	Gray platelet syndrome	1	0	-
4	Bartter and Gitelman syndrome	8	0	-
15	Pompe	37	0	-
34	Severe combined immune deficiency, AR	4	0	-
36,37	Mitochondrial Hsp60 chaperonopathy	3	0	
36,37	Hypoparathyroidism, retardation, dysmorphism	35	2	1:18
36,37	Pelizaeus-Merzbacher like disease	35	5	1:7
36,37	Ventricular tachycardia	23	3	1:8
38	Limb girdle muscular dystrophy LGMD2C	14	0	-
41	Congenital insensivity to pain with anhydrosis	27	0	-
41	Limb girdle muscular dystrophy	14	0	-

Carrier screening Bedouin Muslim Arabs from the Negev

Disease	Data available	Carriers	rate
Arthrogryposis			
ERBB	77	6	1:13
PIP	63	9	1:7
MYPBC	36	6	1:6
Ataxia telangiectasia	14	0	-
Bartter syndrome	175	20	1:9
Bardet Biedl syndrome			
BBS2	21	4	1:5
BBS3	21	2	1:10
BBS4	192	11	1:17
Carmi syndrome -Epidermolysis bullosa, pyloric stenosis	43	9	1:5
Cystic fibrosis	40	3	1:13
Complex III deficiency	126	13	1:10
Congenital insensivity to pain with anhydrosis	1920	55	1:35
Cornelia de Lange like (Birk Flusser) syndrome	26	4	1:6
Cystinuria + (2p16 del) syndrome	32	1	1:32
Cardiomyopathy dilated, neonatal isolated	65	4	1:16
Fanconi-C	163	1	1:163
Growth hormone deficiency	123	4	1:31
Glycogen storage disease			
1211del	48	1	1:48
G252A	148	4	1:37
Hemolytic uremic syndrome	21	0	-
Hypoparathyroidism, retardation, dysmorphism	1924	39	1:49
Complement H factor 1 deficiency	21		-
Infantile Bilateral Striatal Necrosis	127	9	1:14
Infantile neuroaxonal dystrophy	101	6	1:17
Infantile sialic acid storage disease	41	1	1:41
Maple syrup urine disease	19	6	1:3
Nephronophthisis	61	2	1:30
Non ketotic hyperglycinemia	23		-
Niemann Pick type C	46	7	1:7
Osteopetrosis	128	11	1:12
Pyruvate dehydrogenase deficiency	27	6	1:5
Persistent hyperinsulinemic hypoglycemia of infancy	79	7	1:11
Pelizaeus-Merzbacher-like syndrome	94	9	1:10

BRIEF REPORT | Genetics inMedicine

The Israeli national population program of genetic carrier screening for reproductive purposes

Joël Zlotogora, MD, PhD[1–4], Itamar Grotto, MD, PhD[2,3,5], Ehud Kaliner, MD, MPH[2,3] and Ronni Gamzu, MD, PhD[3]

COMMENTARY | Genetics inMedicine

State-offered ethnically targeted reproductive genetic testing

Ellen Wright Clayton[1] and Kyle B. Brothers[2]

- **Routinization**
- **Stigmatization**
- **Purpose to reduce frequency of disease**

Routinization?

- The tests are offered explanation and informed consent
- If an individual is found to be a carrier the significance is explained by a genetic counsellor
- If both partners are carriers they receive full genetic counselling and have all the reproductive possibilities free of charge
    - Prenatal diagnosis
    - Preimplantation genetic diagnosis PGD
    - Giving birth to a child at risk and having early diagnosis and treatment as available

Stigmatization?

- The tests are offered to all the population and not because a disease is known in the family
- The tests are done according to the origin but for all the population
- Up to now there have not been any known event related to stigmatization

Purpose of the screening program

Prevention of the birth of affected children?

GIVE THE POSSIBILITY TO HAVE AN INFORMED CHOICE BEFORE THE BIRTH OF AN AFFECTED CHILD

Differences within the communities

Jews

- Most of the population non religious
- 10% ultra orthodox

Muslim Arabs and Druze

- Most of the population conservative/religious

Dor Yeshorim program

Prevention of marriage at risk

Premarital, ideally performed before meeting of the partners, part of the matching process

Anonymous, both potential partners are tested

Results

- either marriage possible or recommend to avoid marriage
- Individual results are not given

Screening of the Jewish population

- Premarital
  - Dor Yeshorim
  - General centers
- Pre-conceptional
- During pregnancy

Few data are available about the period in which the tests are performed

10% Dor Yeshorim

84% tests done during/ before first pregnancy

Screening of the Arab population

GENERAL SCREENING

- Premarital
- Pre-conceptional
- During pregnancy

SCREENING IN THE COMMUNITY

Screening of the Arab population

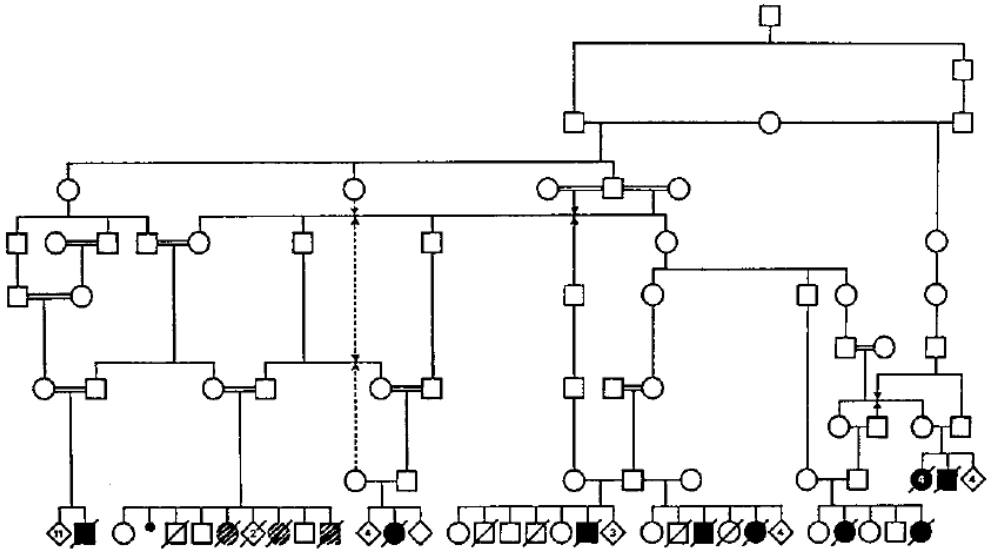
SCREENING IN THE COMMUNITY

Most of the Israeli Arab population is rural

Villages isolated by preference of consanguinity

Many of the genetic diseases are frequent only in one village or one tribe

Krabbe disease in Jerusalem



- Autosomal recessive degenerative disease of brain
- Lethal in infancy (in rule before 2 years of age)
- Deficiency of the lysosomal enzyme galactocerebrosidase
- Village within Jerusalem (1.66 per 1000 livebirths)
- One founder mutation GALC [D528N]

Krabbe disease in Jerusalem Pilot study 1999-2002

- Screening for the mutation in the village
- Including educational program
  - Medical personnel
  - population
- High frequency of the carriers (11%)
- Well accepted
- No stigmatization

A targeted national population carrier screening program for genetic diseases

Implemented in 2002 up to 2013 (part of the general screening)

- **SEVERE DISEASE**
- **POSSIBILITY TO DETECT 90% OF CARRIERS**
- **FREQUENT 1:1000 (AR = 1:15 CARRIERS)**

Free of charge

In the community, by a genetic counselor

In 2012

- 24 villages and all the Bedouin tribes in the Negev
- 49 different diseases

Bedouins in the Negev

- 230,000 Bedouins in the Negev, 8,500 births/year
- Traditional society
- Very high rates of consanguinity, preference to marry within the tribe
- Many genetic diseases frequent increase infant mortality and morbidity

Screening in the community

Trained nurses, genetic unit Soroka Medical center (Prof Ohad Birk)

Dynamic changes with years

Number of diseases screened: 38 diseases in 2013

Number of individuals screened: 1924 individuals in 2013

- Two diseases all the Bedouins:
  - Hypoparathyroidism, retardation, dysmorphism: 39 carriers (1:49)
  - Congenital insensivity to pain with anhydrosis: 55 carriers (1:35)
- Other 36 diseases according to the tribe

Prenatal diagnosis for monogenic diseases among Bedouins in the Negev in a six year period (2007-2011)

Disease	Number	
	Women	prenatal diagnoses
Congenital insensitivity to pain and anhydrosis	26	47
Hypoparathyroidism, retardation, dysmorphism	19	38
Bartter syndrome	6	11
Infantile bilateral strial necrosis	6	10
Bardet Biedl syndrome	5	8
TOTAL	136	220

47 fetuses affected

36 cases termination of pregnancy

Termination more often after CVS (83%) than amniocentesis (71%)

Screening in one of the Druze villages

- 16,000 Druze only inhabitants, 330 live births/year
- Marriages only within the community
- high consanguinity rates
- Four diseases relatively frequent included in the program since 2002 (Genetic unit Naharia hospital Prof Tzipora Falik-Zakai)

  Argininosuccinic aciduria

  Carbamoyl phosphate synthetase I deficiency

  Cerebrotendinous xanthomatosis

  Prolidase deficiency

Cerebrotendinous xanthomatosis CTX

- Autosomal recessive
- Progressive, rare metabolic disease
- Mutations in sterol 27-hydroxylase, CYP27A1
- Frequent due to a founder mutation: c.355delC
- Effective treatment: oral chenodeoxycholic acid

Am. J. Hum. Genet. 55:907–915, 1994

Cerebrotendinous Xanthomatosis in the Israeli Druze: Molecular Genetics and Phenotypic Characteristics

Eran Leitersdorf,[1] Rifaat Safadi,[1] Vardiella Meiner,[1] Ayeleth Reshef,[1] Ingemar Björkhem,[3] Yechiel Friedlander,[2] Siman Morkos,[4] and Vladimir M. Berginer[5]

Table 1

Clinical Data of 10 CTX Patients Homozygous for the Druze Mutation, Shown According to Age Stratification

	220 IV-7	220 IV-6	220 III-16	222-1	221 V-19	221 V-18	220 III-9	221 V-6	223-1	221 V-5
Background data:										
Gender	F	F	M	M	F	F	M	M	F	F
Age (years)	2	7	16	19	23	27	27	32	39	41
Physical findings:										
Pes cavus	−	−	+	+	+++	+++	+++	+++	+++	+++
Tendon xanthomas	−	−	−	−	+	++	++	+++	−	+++
Cataracts	+	++	++	++	++	++	++	++	++	++
Dementia	−	−	+	+	++	++	+++	+++	+++	+++
Pyramidal signs	−	−	+	+	+	+	++	++	+++	+++
Cerebellar signs	−	−	+	+	++	++	++	++	+++	+++
Convulsions	−	+	++	++	++	++	++	++	++	−
Neurological studies:										
EEG abnormality[a]	ND	+++	++	+++	+++	+++	+++	+++	+++	+++
Brain atrophy[b]	ND	++	++	ND	++	+++	+++	+++	ND	ND

Population screening in a Druze community: the challenge and the reward

Tzipora C. Falik-Zaccai, MD[1,2], Nechama Kfir, MSc[1], Pnina Frenkel, MSc[1], Cindy Cohen, MA[1], Mary Tanus, BSc[3], Hanna Mandel, MD[2,4], Shihab Shihab, MD[3], Siman Morkos, MD[5], Salameh Aaref, MD[5], Marshall L. Summar, MD[6], and Morad Khayat, PhD[1]

Genet Med 2008:10(12):903–909.

Among 1986 individuals screened 188 carriers

carrier rate 1:11

- since 2003, 9 pregnancies
  - 4 PND, 2 affected did not interrupt the pregnancy
  - 5 no PND
  - newborn examined after birth one affected
- 3 Affected children diagnosed after birth receive treatment

Conclusions

- the national program is well accepted and used by all the Israeli communities, adapted to the communities

- educational efforts need to increase the number of tests done pre-conceptional

The future

- Targeted program or universal program?
- Sequential or couple screening?