Genetic polymorphisms influence children's susceptibility to organophosphates

Isabella Karakis, MD[1], Amit Ophir, PhD[2], Aviad Stoler, MsC[3], Yoram Plotsky, PhD[3], , Uri Wormser, PhD[4], Elihu D. Richter, MD MPH[5], Elyakim Doitsch, MA[2], and Yoram Finkelstein, MD PhD[2]

[1]*Dept. Environmental Epidemiology, Ministry of Health, Jerusalem,* [2]*Neurology and Toxicology Service and Unit, Shaare Zedek Medical Center, Israel,* [3]*Galil Genetic Analysis, Katzrin,* [4]*Institute of Drug Research, School of Pharmacy, and* [5]*Occupational and Environmental Medicine, Hebrew University of Jerusalem, Israel*

NEUROTOXIC EFFECTS OF LOW-LEVEL LONG-TERM EXPOSURE TO ORGANOPHOSPHATES

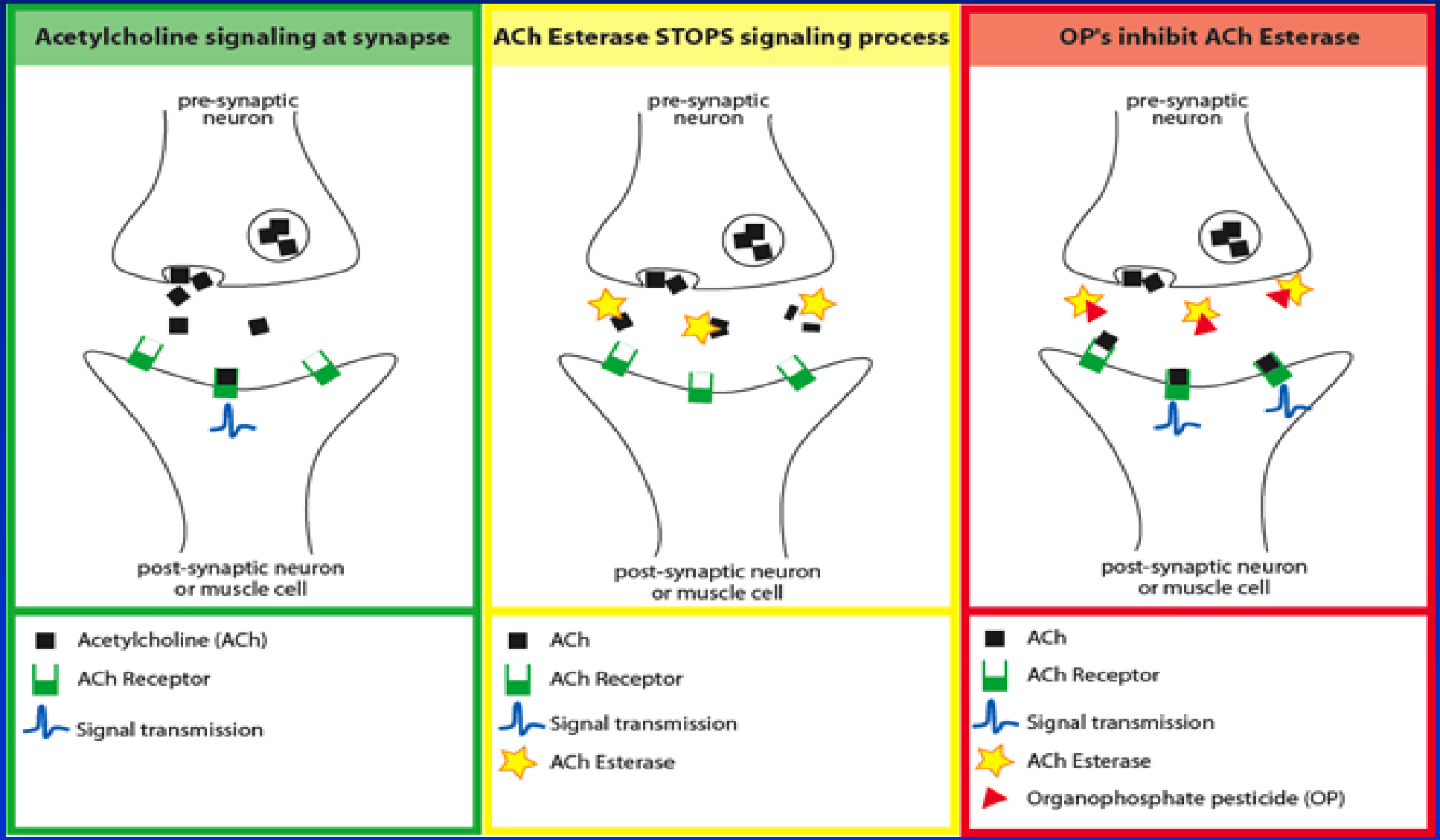
a. Past (1980's): Epidemiologic studies on effects of everyday low-level exposures in workers and residents
b. Re- examination of the same adult cohort with the same and newer methods
c. Examination of the offspring with same and newer methods


Kiryat Shmona
Sde Nechemia
Map
Satellite
Amir
Kfar Blum
Shamir
Neot Mordechai
The Jordan River
2 mi
2 km
Google
Imagery ©2009 TerraMetrics, Map data ©2009 ORI

BACKGROUND

Our previous studies showed the neurobehavioral effects of repeated annual seasonal exposures to organophosphorous (OP) pesticides in children in kibbutz communities in Hula Valley.

BACKGROUND


Acetylcholine signaling at synapse
pre-synaptic neuron
post-synaptic neuron or muscle cell
Acetylcholine (ACh)
ACh Receptor
Signal transmission
ACh Esterase STOPS signaling process
pre-synaptic neuron
post-synaptic neuron or muscle cell
ACh
ACh Receptor
Signal transmission
ACh Esterase
OP's inhibit ACh Esterase
pre-synaptic neuron
post-synaptic neuron or muscle cell
ACh
ACh Receptor
Signal transmission
ACh Esterase
Organophosphate pesticide (OP)

BACKGROUND:

Mutations in PON1 gene are expressed in Paraoxonase activity variants which may affect several phenotypes as well as the susceptibility to OP neural effects.

Genetic polymorphisms may be observed in SNP`s (Single Nucleotide Polymorphisms) located on the gene encoding PON1 enzyme or its promoter.

RESEARCH OBJECTIVES :

To estimate relationship between PON1 genetic outcomes of and performance of cognitive tasks in a group of 8-12 years-old children in Hula Valley.

GROUP STUDIED

8-12 years-old schoolchildren in kibbutzim

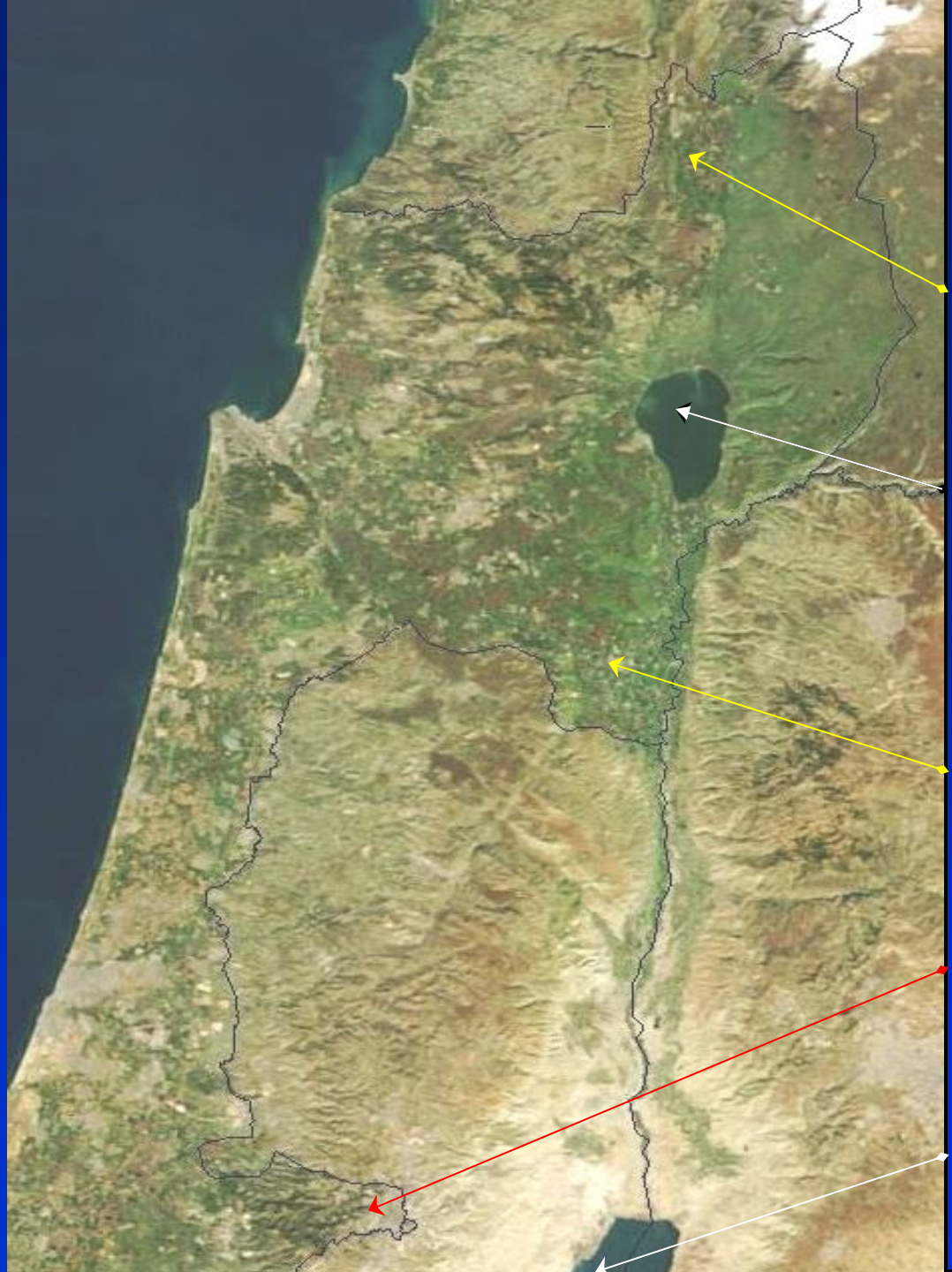
“second generation” in families with 30-50 y

in exposed settings.

Schoolchildren (N=96) studied: two sub-groups:

- Children (N=51) who reside and attend school in Hula valley.
- Children (N=45) residing in hills around Hula valley and attend school in valley.

Comparison group (N=40) included age- and gender-matched children residing in a different kibbutz in Jordan Rift Valley in which use of pesticides has been minimal ("organic agriculture") for decades.



The Jordan Rift Valley

Hula Valley

Sea of Galilee

Beit Shean Valley

Jerusalem

Dead Sea

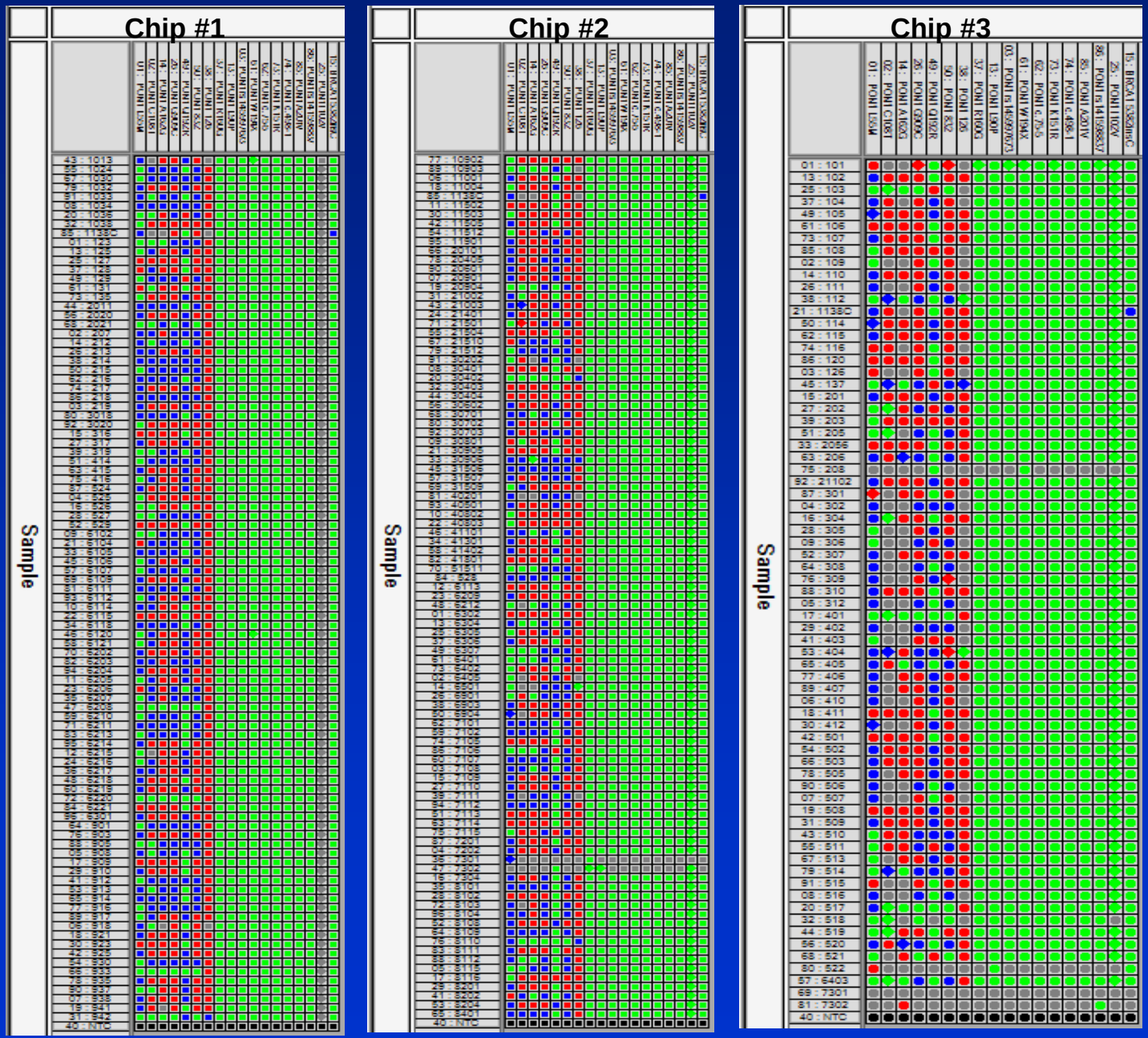
Cognitive Tests for Executive Skills

- **Trail Making Tests A and B** for screening, attention and graphomotor ability
- **Digit Span Test (forward and backward)** for auditory memory involving attention (WISC-III)
- **Digit Symbol Test** for eye-hand coordination in new learning processes (WISC-III)
- **Arithmetic Test** (WISC-III)
- **Bender–Gestalt Test** for visual-motor Gestalt
- **Digit Cancellation Test** as a measure of short-term memory and reaction time
- **Diamond Test** for screening and attention ability
- **Rapid Automatized Naming** for reading competence
- **Purdue Pegboard** for manual dexterity

Genetic analysis

- Saliva samples were collected and extracted using Oragene DNA according to the manufacturer's protocol.
- SNP genotype (TaqMan) was tested for 17 known genomic alterations in the PON-1 gene and screened using Nano-Fluidic Chip 96.96CS Genotyping Dynamic Array IFC and BioMark™ HD System (Fluidigm).
- SNP genotyping was performed according to the manufacturer's protocol and analyzed by Fluidigm Analysis Software V.3

Fluidigm Arrays - raw results



RESULTS

Association was found between the codon region L55M and the performance of Trail Making B and Digit Cancellation B Tests:

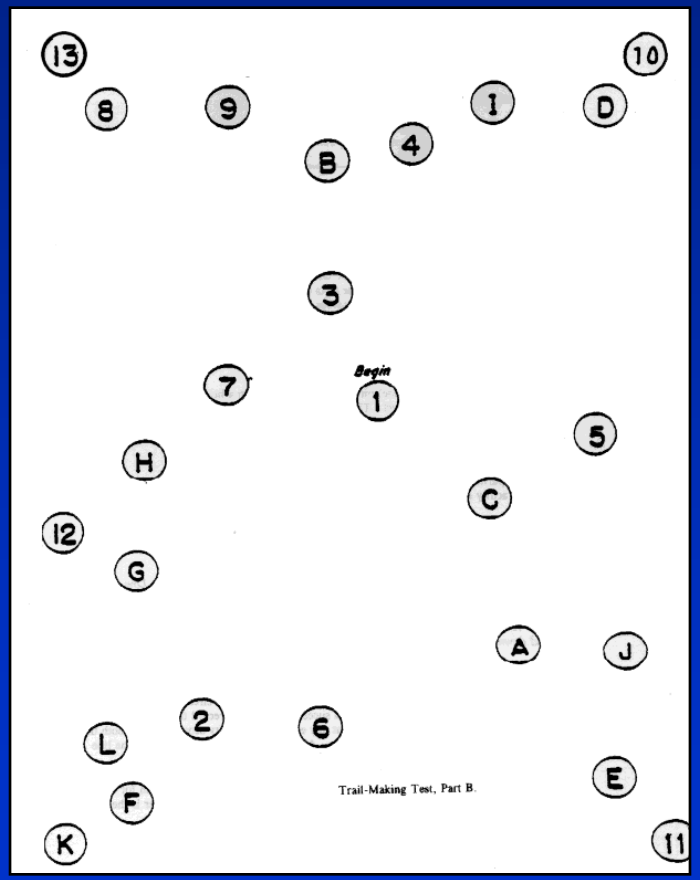
The individuals with the heterozygote variant A:T scored the least in both tests.

The individuals with the homozygote variant A:A obtained the highest scores in Digit Cancellation B Test.

Both homozygote variants A:A and T:T obtained similar scores in Trail Making B Test.

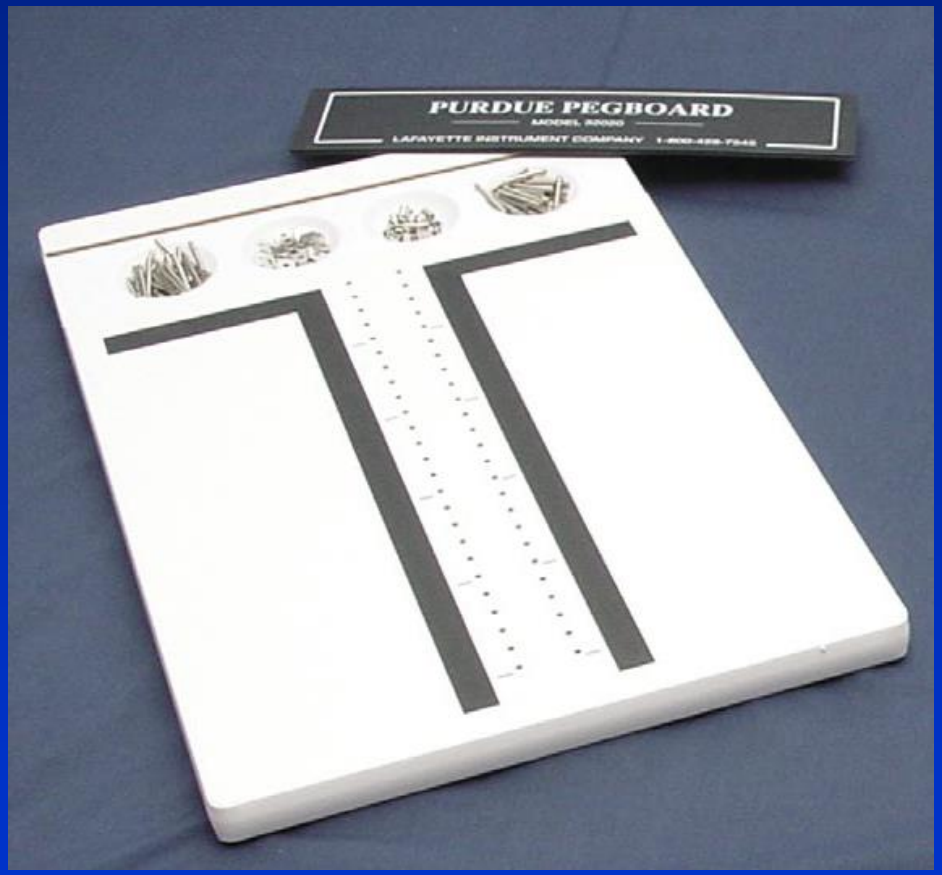
Trail Making B Test

for screening, attention and graphomotor ability



Purdue Pegboard Test

for manual dexterity



RESULTS

The performance of Purdue Pegboard Test for manual dexterity was associated with SNP located at G909C:

The individuals with the heterozygote variant C:G scored the least in Purdue Pegboard Test of manual dexterity comprising all its sub-tests –Rt. hand, Lt. hand and both hands.

All these associations were standardized to different levels of exposure to OP drift.

CONCLUSIONS

Several PON1 polymorphisms are associated with the cognitive abilities of manual dexterity and executive skills: first and foremost in the multi-channel attention span, visual scanning, task switching and execution speed.

There may be environmental-susceptibility interactions and epigenetic effects in children with low-level endemic exposure to OP drift.

Current Paradigm:

A genetic factor may influence children's susceptibility to organophosphates.

PON-1 gene polymorphisms might reflect genetic susceptibility of children to effects of long-term low-level exposure to organophosphates.

This study was supported by:

Environment and Health Fund - *RGA0903*

The Chief Scientist, Israel Ministry of Environmental Protection - *No. 7-2-1*

The Chief Scientist, Israel Ministry of Industry, Trade and Labor - *No. 08-1-1028*

Genetic polymorphisms influence children's susceptibility to organophosphates

Isabella Karakis, MD[1], Amit Ophir, PhD[2], Aviad Stoler, MsC[3], Yoram Plotzky, PhD[3], , Uri Wormser, PhD[4], Elihu D. Richter, MD MPH[5], Elyakim Doitsch, MA[2], and Yoram Finkelstein, MD PhD[2]

[1]*Dept. Environmental Epidemiology, Ministry of Health, Jerusalem,* [2]*Neurology and Toxicology Service and Unit, Shaare Zedek Medical Center, Israel,* [3]*Galil Genetic Analysis, Katzrin,* [4]*Institute of Drug Research, School of Pharmacy, and* [5]*Occupational and Environmental Medicine, Hebrew University of Jerusalem, Israel*