Conference Report

Eur J Hum Genet 1995;3:378–381

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Israel-France Binational Symposium on 'Hereditary Diseases, Molecular Diagnosis and Gene Therapy'

Held in Jerusalem, November 7–9, 1994

This was the second gathering of the French and Israeli human genetics communities following the initiative of the Association Franco-Israélienne pour la Recherche Scientifique et Technologique. The Jerusalem symposium assembled around 100–120 people originating from both countries. The major aim of this meeting was to encourage exchanges and interactions between French and Israeli genetic groups and to discuss recent progress and achievements in the following topics: genome organization, population genetics, gene mapping, molecular genetics of hereditary diseases, cancer genetics and gene therapy.

The first section of the conference presented the strategies to generate a high-quality physical map of the human genome using integrated physical and genetic maps (D. Cohen, Fondation Jean Dausset, CEPH, Paris, France) [1]. The integrated map currently covers close to 90% of the human genome including 2,000 anchoring points. New strategies for filling the gaps were presented (I. Chumakov, Fondation Jean Dausset, CEPH, Paris, France). Regarding the yeast genome, to date 7/16 chromosomes have already been sequenced, illustrating the success of the International Yeast Collaboration. It is striking that close to 40% of the open reading frames identified by sequencing do not show any homology to known genes (P. Slonimski, Groupement de Recherches et d'Études sur les Génômes, Gif-sur-Yvette, France) [2]. Study of the putative functions for these genes can take advantage of the functional assays which can be performed in yeast. Methodological advances for detecting nucleotide variations in DNA or genome sequencing were discussed (T. Meo, Institut Pasteur, Paris, France) [3]. Modular sequencing is expected to increase the sequencing power by a factor of 50 (L. Ulanovsky, Weizmann Institute of Science, Rehovot, Israel). Combination of chemical cleavage technique and the use of automated sequencers allow mutation detection in large fragments of human DNA. Finally, the various mechanisms of genetic stability were reviewed and discussed with respect to both speciation genetics and mutations resulting in hereditary disorders.

A whole session was devoted to the genetic resources in the Israeli and French populations. The occurrence and frequencies of genetic disorders in populations are determined by migration patterns, selection forces and genetic drift (J. Feingold, Université Paris VII, Paris, France). Surprisingly, in an isolate like the island of la Réunion, different haplotype backgrounds were found among patients with autosomal recessive limb-girdle muscular dystrophy type 2A implying that different mutations are responsible for the disorder even though the genealogical data pointed to a common founder [4]. A similar observation was reported among Arabs from the Galilee region of Israel for various recessive disorders like Hurler syndrome

Organizers

- Israel: Ariella Oppenheim, Zelina Ben-Gershon, Yair Degani, Max Herzberg, Eran Leitersdorf, Yosef Shiloh, David Yaffe and Beki Shimoni.
- France: Jacques Beckmann, Philippe Benesh, Marc Fellous and Arnold Munnich.

Received:
August 22, 1995
Accepted:
August 22, 1995

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1018–4813/95/
0036–0378$8.00/0

and metachromatic leukodystrophy [5, 6]. In the Israeli-Arab community, the inbreeding coefficient reaches 0.02 in rural areas; this provides the opportunity for linkage disequilibrium studies by means of homozygozity mapping (L. Jaber, Bridge-to-Peace Pediatric Center, Taibe, Israel) [7]. For instance, a unique haplotype is found among Usher syndrome type I carriers among the Samaritans (B.S. Bonné-Tamir, Tel Aviv University, Tel Aviv, Israel) [8]. A similar situation is found in some of the Jewish communities and a unique mutation causing Creutzfeld-Jakob disease is found among the Libyan Jews (R. Gabizon, Hadassah Hebrew University Hospital, Jerusalem, Israel).

Gene mapping and positional-cloning strategies in human hereditary disorders were illustrated by three examples: spinal muscular atrophy (A. Munnich, Hôpital des Enfants Malades, Paris, France), limb-girdle muscular dystrophy (J. Beckmann, CEPH and Généthon, Paris, France) and ataxia telangiectasia (Y. Shiloh, Tel Aviv University, Tel Aviv, Israel). It should be noted that a few months after the symposium each of these genes has been first cloned by the group of the presenting scientist [9–11]. The genome-wide approach to multifactorial diseases was illustrated by the search for susceptibility genes to type I diabetes (C. Julier, Wellcome Trust Center for Human Genetics, Oxford, UK) [12] and multiple sclerosis (E. Seboun, Généthon, Evry, France), suggesting the usefulness of this technique to explore other 'multifactorial' disorders.

A number of specific diseases and their molecular basis were discussed in detail including lissencephaly (O. Reiner, Weizmann Institute of Science, Rehovot, Israel) [13], Gaucher disease (M. Horowitz, Tel Aviv University, Tel Aviv, Israel) [14], factor XI deficiency (U. Seligsohn, Chaim Sheba Medical Center, Tel Hashomer, Israel) [15] and human sex determination pathology (M. Fellous, Institut Pasteur, Paris, France). The interesting and challenging topic of genotype-phenotype correlations in hereditary disorders was evoked regarding the RET gene mutations in Hirschprung's disease (S. Lyonnet) [16], the Duchenne muscular dystrophy gene (U. Nudel, Weizmann Institute of Science, Rehovot, Israel) and CFTR mutations (B. Kerem, Hebrew University, Jerusalem, Israel) [17]. Mechanisms of gene disorders were discussed such as unstable expanded trinucleotide repeats in neurodegenerative diseases (A. Brice) and approaches to dosage effects in Down syndrome (Y. Groner, Weizmann Institute of Science, Rehovot, Israel) [18] using transgenic models. An insight into understanding disease mechanisms was also provided by expression techniques, either in situ hybridization on tissues, in vitro studies of enzyme efficiencies or in vivo experiments with transgenic mice (e.g. the DP71 protein at the dystrophin locus). Gene superfamilies were discussed, including the olfactory receptor genes: an estimated 130 olfactory genes are dispersed across the human chromosomes (D. Lancet, Weizmann Institute of Science, Rehovot, Israel) [19].

Another specific topic covered the progress in cancer genetics: chromosome 22 alterations associated with human tumors of neuroectodermal origin, the molecular cytogenetics of leukemia (fusion of two genes by a translocation process or individuals with Down syndrome and overexpression of the ALM1 gene) (G. Thomas, Institut Curie, Paris, France [20]; D. Levanon, Weizmann Institute of Science, Rehovot, Israel; R. Berger, INSERM, Paris, France [21]; D. Ben-Yehuda, Hadassah Hebrew University Hospital, Jerusalem, Israel).

In a final session, gene therapy, that is to say the therapeutic use of genes as drugs, was discussed, and indicated that gene therapy of some human disorders remains a formidable challenge in the future with considerable improvements necessary to transform this project into reality (A. Kahn, Institut Cochin de Génétique Moléculaire, Paris, France). In particular, vectors should be improved to decrease cytopathic and immunologic reactions and to maximize the duration of transgene expression; in addition delivery systems must target the most affected cells. In particular, adenoviral vectors seem to be efficient for gene delivery in various cell types. Models for gene therapy, e.g. for Niemann-Pick disease (S. Gatt, Hadassah Hebrew University Medical School, Jerusalem, Israel) or β thalassemia (A. Oppenheim, Hadassah Hebrew University Hospital, Jerusalem, Israel) were discussed as were approaches developed for activity in the brain taking advantage of a rat brain microvessel epithelial cell line (RBE4) (A.D. Strosberg, Institut Cochin de Génétique Moléculaire, Paris, France) [22].

While in the mammalian genome, most sequences are expressed from both the maternal and paternal alleles, several categories of monoallelic expression are known including genes of the X chromosome in females, imprinting and allelic exclusion (Y. Wahrman, Hebrew University, Jerusalem, Israel [23]; H. Cedar, Hadassah Hebrew University Medical School, Jerusalem, Israel [24]). For instance, the olfactory receptor genes in the mouse are organized within asynchronously replicating domains and randomly transcribed from only a single allele in each cell. Allelic exclusion may be an important mechanism for ensuring that each olfactory neuron expresses a single receptor gene allele [24].

Biotechnological industries were represented at the meeting and a session was devoted to recent achievements in molecular tools and applications in medical biology.

The next meeting is planned for the Mediterranean area and will provide an opportunity to invite geneticists from the region to improve Franco-Mediter ranean-Israeli collaboration.

Acknowledgments

The Israeli Ministry of Sciences and Art and Ministry of Health. The French Ministry of Foreign Affairs Institut National de la Santé et de la Recherche Médicale. Association Franco-Israélienne pour la Recherche Scientifique et Technologique.

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