The Future of Genetics: Where are We Going in the Next Forty Years?

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This issue of IMAJ includes two articles offering some interesting and relevant perspectives on the future of genetics in the world generally and in Israel in particular. Following completion of the Human Genome Project, many more autosomal recessive diseases will be preventable by screening couples for carrier status. The spectrum of mutations that are characteristic for each ethnic group in the Israeli population will be determined, and questions will be raised as to which genes should be tested and which should not.

Zlotogora and Leventhal [1] propose their suggestions for the criteria according to which the Tay-Sachs disease screening program should be extended to other genetic disorders common in the Jewish community. Their recommendation to limit such a screening program to mutations for which there is a consensus that the disease they may cause is severe enough to envisage the possibility of therapeutic abortion makes sense, both ethically and economically. They also discuss the weighty aspect of the "melting pot," i.e., the phenomenon that whereas at present most of the subpopulations within the Jewish community are still relatively distinct, as more and more marriages take place between members of the different ethnic groups these distinctions are going to become increasingly blurred. Whereas, for example, it is still accurate today to talk about a carrier rate for Tay-Sachs disease of 1 in 30 in the Ashkenazi population, with such a high rate of inter-group marriages, the carrier frequency will change considerably over even the next 10 years and necessitate a revision of carrier rates across the whole population. Clearly, the same is true for all the other genetic diseases, since although many of these can currently be regarded as being common within a specific ethnic group or groups, they will be less and less so with time.

Another point of particular salience in Israel is that among the ultra-orthodox community (*Haredi* in Hebrew), and also to some extent within the modern orthodox community (*Dati*), termination of pregnancy for genetic disorders is not permitted (nor is contraception, except in certain specific situations – a point not mentioned by the authors). Consequently, primary prevention (screening for premarital counseling), which is perfectly acceptable according to Jewish religious law (*Halacha*), is especially relevant for these communities. Additionally, as the authors inform us, the fact that most of the marriages are arranged, at least within the ultra-orthodox community, ensures that the carrier status of the potential marriage partners is taken into account when arranging the marriages, thus precluding a marriage between two carriers of the same recessive disease. Similarly, and even more effectively, such a screening program should also be offered to the Arab community, where consanguineous marriages are very frequent (about 40% of all the marriages in the Israeli Arab community). In such marriages, the rate of autosomal recessive diseases exceeds 14% [2,3]. Therefore, the criteria proposed by Zlotogora and Leventhal as to which genes should be tested for the purpose of prenatal diagnosis constitute a very feasible basis for the future.

In another article in this issue of *IMAJ*, Ben-Asher et al. [4] discuss the Human Genome Project and its significance with regard to genetics in Israel. They delineate the role of the Weizmann Institute Genome Center in the Project, and its specific contribution, in conjunction with those of other centers at Tel Aviv University and the Hebrew University of Jerusalem. They describe in detail the research being undertaken at the Weizmann Institute in genomic DNA sequencing, bioinformatics, and DNA arrays. The search for disease-causing genes is especially relevant for the Israeli population, given that the ethnic groups are today still sufficiently distinct to allow linkage analysis of a particular disease among members of affected families originating from a single ethnic group, which narrows the genomic interval containing the disease-causing mutation. However, this is something of a "race against time," for the reasons discussed by Zlotogora and Leventhal [1] – namely, that the "melting pot" phenomenon of inter-group marriages will result in

substantial mixing of these ethnic groups. Thus, the DNA banks of the various ethnic groups, as established by the Human Genome branch of Tel Aviv University, are invaluable for the future understanding of the complexity of the human genome and its relevance to those diseases common among Jews. Interestingly, one would expect the "melting pot" phenomenon of inter-group marriages to occur far less within the Arab community, since not only do the members of this community rarely marry outside of it, but the very high incidence of consanguineous marriages in this community ensures the perpetuation of a specific disease-causing gene within an extended family (*Hamula*).

Referring to the genetic basis of common diseases such as hypertension, heart failure, asthma, various mental diseases such as schizophrenia, and others, the authors describe the methods used in the Weizmann Institute to correlate specific single nucleotide polymorphisms with diseases. They explain how computational genomics can help researchers find information and web-available tools relevant to their field of research, and stress the unequalled opportunity that exists in Israel of combining the two fields of mathematics and computing on one hand, and of life sciences and biomedicine on the other, under the umbrella of computational genomics and bioinformatics. This is exemplified by the development at the Weizmann Institute Genome Center of GeneCards, a database of human genes, their products, and their involvement in diseases, all based on information retrieved from public web-accessible databases. Another genomic tool, also developed locally, is Unified Database. This also automatically extracts relevant information from public web-accessible resources that contain human genome mapping information. Yet another product is the genome-wide analyzer GESTALT, which integrates several existing sequence analysis algorithms to create a single graphical display for visualizing a given genomic sequence. The center's DNA array unit implements the relevant technologies for the benefit of the entire Israeli academic and medical community. These technologies are the photolithography-based oligonucleotide array, "spotted arrays," and inkjet chips. In addition to a detailed description of these technologies, the authors discuss their applications, significance and prospects.

The future of genetics will be shaped more and more by the development of such techniques and methodologies. To be sure, the time is not far off until the genes causing most if not all of the common (and some of the less common) genetic diseases will be identified. We can expect in the not too distant future that genetic testing will be available for about 25 common conditions such as colon cancer, that gene therapy will prove successful for several conditions, that most doctors will begin practicing genetic medicine, and that pre-implantation diagnosis will be widely available. It is envisaged that eventually gene-based designer drugs will be available for common conditions such as diabetes and hypertension, that cancer therapy will be targeted to the molecular fingerprint of the tumor, that the genes involved in aging will be fully identified, and that gene therapy and gene-based drug therapy will be available for most diseases. It is predicted that within the next 30 to 40 years, the use of a full computer model of human cells will replace laboratory experiments, and that the complete genomic sequencing of an individual will be a routine procedure costing less than $1,000 [5].

References

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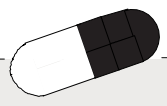
Capsule



Direct prion propagation in yeast

The prion hypothesis suggests that infectious protein conformations can be transmitted from cell to cell and that this mode of transmission underlies certain fatal neurodegenerative disorders like Creutzfeld-Jacob disease. In yeast, the [*PSI*+] phenotype is thought to model prion diseases, but direct demonstration that a protein, rather than the gene encoding a particular protein, can cause the prion phenotype in vivo has been lacking. Sparrer et al. introduced the "pathological" form of the yeast prion protein, Sup35p, through liposomes into normal yeast cells and induced the [*PSI*+] phenotype, thus demonstrating directly that a protein alone can propagate a phenotype.

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