PREFACE

"Advances in Genetics Research" presents original research results on the leading edge of genetics discovery. Each article has been carefully selected in an attempt to present substantial research results across a broad spectrum. In this continuing series compilation, the authors present and discuss varied topical data such as the assessment and testing by genoproteomics and therapeutic planning of hereditary ovarian cancer; the examination of gene flow in five major taxa at Evolution Canyon, Israel; functional analysis of the entomopathogenic nematode parasitism; genome structure and genomic stability; the role of CCDC26 in human acute myeloid leukemia; and missense mutations and genetic testing.

Chapter 1 - Historically referred to as the “silent killer,” ovarian cancer was believed to have no symptoms at all until the disease had progressed to advanced stages and, approximately 10% of ovarian cancers may be due to an inherited genetic predisposition. It has been estimated that approximately 7% of women with ovarian cancer have a positive family history of the disease. The first-degree relatives of ovarian cancer probands have a threefold to sevenfold increased risk, especially if multiple relatives are affected, including if at an early age at onset. A common goal of molecular techniques is the diagnosis of early-stage ovarian cancer as well as the identification of markers to improve the therapy during all stages of the disease. Risk calculation programs define risks and assist in decision-making in clinical options and genetic testing; they provide information on the risks of the disease, mutation status and the use of genetic testing in the management of high-risk families.

Furthermore, while a large number of surrogate preliminary markers have been identified, there are still limited studies on ovarian cancer genomics. In this chapter, we'll illustrate the possibilities of genoproteomic diagnostic technique in hereditary ovarian cancer, discussing on therapeutic planning, as surveillance, chemoprevention and prophylactic surgery.

Chapter 2 - Gene flow is examined in five major taxa (bacteria, soil fungi, flowering plants, Drosophila, and Acomys rodents) at the “Evolution Canyon” model in Israel vis-à-vis the effects of evolutionary driving forces including mutation, genetic drift, gene flow, and natural selection. The “Evolution Canyon” (EC) model reveals evolution in action across life at a microscale (four ECs are currently explored in Israel) involving interslope biodiversity, adaptation, and incipient sympatric ecological speciation across life from bacteria to mammals (Nevo, 1995, 1997, 2001, 2006, 2009, and Nevo EC link at http://evolution.haifa.ac.il). In all of the five major taxa, it is clearly demonstrated that strong interslope natural microclimatic selection overrides the homogenizing effects of gene flow

despite its constant interslope operation. The effects of strong contrasting interslope microclimatic natural selection against high UV solar radiation, temperature, and drought stresses on the "African" (AS) savannoid south-facing slope (SFS) and against light deprivation (shade) stress on the "European" (ES) forested north-facing slope (NFS) cause dramatic interslope biotic divergence. This involves both adaptive divergence followed by incipient sympatric ecological speciation across life clearly demonstrating how natural selection is the major evolutionary driving force of adaptation and speciation across life locally and probably largely regionally and globally also.

Chapter 3 - Entomopathogenic nematodes (EPNs) from the families of Heterorhabditidae and Steinernematidae are widely used to control a large number of insect pests with a great economical impact. Despite the ability of this nematode to parasitize and kill a large number of insects, the rate of parasitism and mortality that a nematode strain caused is insect- and developmental stage-specific, thus suggesting a differential susceptibility to stress caused by each insect. To enhance the infective efficiency, improvements in traits, especially those related to insect specificity are required. Functional genomic approache can support the understanding of parasitism mechanisms.

Public database searching and comparative analysis identified a series of genes with potential roles in nematode parasitism and stress tolerant. Nematodes resist host immune attacks by immuno-evasion strategies which often involved the parasite body surface that seems to play a key role in the interactions with the host immune reactions. Serine-, aspartic-, cysteine-, and metallo-protease are involved in tissue invasion and extracellular protein digestion. Nematode also secrets protease inhibitors to inhibit both of the host and their own proteases. Heat-shock proteins are particularly important for survival in different tissues of the host and different host species. Secretion of antioxidant proteases is believed to protect the parasite from reactive oxygen species which arise from the infection-stimulated host. Superoxide dismutase, catalase, and glutathione peroxidase, peroxiredoxins are probably the major H2O2-detoxifying enzymes. Late embryonic abundant proteins were also important molecules functioned in stress tolerant. All these genes are potentially useful for increasing nematode efficient parasitism and the abilities to resist environmental stress conditions.

Chapter 4 - Structure is incorporated into the everyday objects, social and genomic networks that surround us providing a delicate balance of flexibility and stability. This chapter will discuss the methods that are currently used to untangle genome structure and the networks of interactions that occur between chromosomes to provide genomic stability. We will concentrate on the recently developed proximity-based ligation approaches which are opening new avenues of investigation into genome architecture. Finally, we will discuss a range of pitfalls that must be avoided when designing and performing these deceptively simple experiments. Although these methods are still in the early stages of development and application, they promise to bring about an explosion in our understanding of genome organization and stability.

Chapter 5 - Acute myeloid leukemia (AML) is often accompanied by genetic alteration, but it remains to be discovered whether any specific genetic alteration, including loss or gain of a certain gene(s), is responsible for the onset and recurrence of AML. On the other hand, several cytological and genetic alterations have been reported to be good criteria for the prognosis of the disease.

Recently, CCDC26 was found to be the gene whose copy number had been increased most frequently in cytogenetically normal pediatric AML patients. Increased gene copy

number in AML cells sometimes occurs in the form of a double minute chromosome (dmin), which consists of a repeat unit originating from a normal chromosome. We have analyzed the structure of gene amplification on dmins and on another form of extra-chromosomal element that is similar to dmins but which is more stable and confers resistance to drug-induced differentiation of a human AML cell line HL-60. CCDC26 is encoded in the amplified unit and is transcribed specifically in undifferentiated HL-60 cells. It is also transcribed in dmin-positive AML and in a similar leukemic disorder, myelodysplastic syndrome. Truncation of CCDC26, resulting in abnormal CCDC26 transcripts, is often observed in AML cells, including HL-60 cells. Knock down of CCDC26 expression promotes retinoic acid-induced differentiation of AML cells. However, the molecular function of CCDC26 remains unclear. Indeed, it is uncertain whether the open reading frame, deduced from the primary sequence, is actually translated. There is a possibility that the CCDC26 transcript functions as a non-coding RNA. Moreover, in mammals, there is a highly conserved region in the intron of CCDC26, suggesting that information is encoded in this region. Some kind of an intronic micro RNA is a strong candidate. Here, I will summarize a possible role of CCDC26 in the AML cells.

Chapter 6 - The presence of missense mutations detected during genetic testing makes it difficult to classify their pathogenic effect. It is possible that the predicted amino acid change affects protein function; however, it is also possible that a missense mutation does not act at the protein level but rather at the nucleotide level by interfering with the correct assembly of the pre-mRNA splicing machinery. In this chapter we describe that short 6 to 9 nucleotides-containing sequence motifs act as exonic splicing regulatory elements. They are specifically recognized by corresponding splicing factors, which then assist in the recognition of the conserved splice site motifs by the spliceosome. Many examples show that a point mutation in these exonic splicing regulatory elements is sufficient to change splicing factor binding, which impairs inclusion of an exon during the splicing reaction. Thus, the molecular consequence of a missense mutation can be exon skipping and thus cause a frameshift in the messenger RNA that results in a premature stop codon and loss of function of the affected allele. Although several bioinformatic tools exist to predict splicing factor binding to mRNA, this effect of a missense mutation on splicing cannot yet be accurately predicted by sequence analysis alone. In order to determine whether a missense mutation has a deleterious effect on splicing of the corresponding mRNA, experimental analysis with either patient RNA or splicing reporter minigenes is required.