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The Development of Human Genetics at the National Research Centre, Cairo, Egypt: A Story of 50 Years

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Abstract

This article describes my experiences over more than 50 years in initiating and maintaining research on human genetics and genomics at the National Research Centre in Cairo, Egypt, from its beginnings in a small unit of human genetics to the creation of the Center of Excellence for Human Genetics. This was also the subject of a lecture I gave at the 10th Conference of the African Society of Human Genetics, held in Cairo in November 2017, after which Professor Michèle Ramsay, president of the society, suggested that I write an autobiographical article for the *Annual Review of Genomics and Human Genetics*. I hope that I succeeded in the difficult assignment of summarizing the efforts of a researcher from a developing country to initiate and maintain the rapidly advancing science of human genetics and genomics in my own country and make contributions to the worldwide scientific community.

BACKGROUND

I was born in Damanhur, Egypt, the capital city of Beheira Governorate. I was the third child in my family, with an older brother and sister and two younger sisters. I enjoyed being the middle child, and I always thought that the best things are the middle (an Arabic proverb). My parents encouraged knowledge and always told us that education was the best guarantee of our future. This advice proved fruitful: Three of us became medical doctors, and one became a chemical engineer. The physicians were my older brother, a consultant ophthalmologist in Kuwait; one of my younger sisters, a consultant clinical pathologist in the United Kingdom; and myself in the middle.

I was almost always the first in my class in school, with a large difference in grades between myself and my peers. I enjoyed knowledge and used to spend my leisure time reading—mostly scientific works, but occasionally detective stories. I loved to spend time reading dictionaries in both English and French that I found in my father's library. At the end of first grade in primary school, our main class teacher made the following remark in my school certificate: "This child is a rare gem of the finest water. If taken care of, she will be unique, and we congratulate ourselves with her."

I have wanted to be a physician since I was 10 years old. I was sick with typhoid fever at a time where the only available medicine was sulfadiazine, which I took for three months under the supervision of our very kind doctor, Dr. Ibrahim Nagui. I admired his personality and the way he managed my case, which made me keen to become a physician like him.

During my secondary-school studies, I was happy solving difficult geometric problems rather than simple ones. So I discovered that I like challenges.

When my older brother went to medical school, two years ahead of me, I used to enjoy reading his medical textbooks, which further convinced me that I should go to medical school. As a medical student, I enjoyed reading textbooks of anatomy, physiology, and biochemistry written by international scientists. While reading those impressive works, I was dreaming of one day being the author of a similar international textbook.

I graduated from the Faculty of Medicine at Cairo University in December 1957 as the first of the female graduates and among the first 15 of the class (of around 200). I obtained my graduation certificate from Gamal Abdel Nasser, the president of Egypt at that time, during the first Science Festival of Egypt in 1961 (**Figure 1**). This gave me a great push, as if the entire country of Egypt were greeting me. The most famous figure in Egypt from my class is Sir Magdi Yacoub, the cardiac surgeon.

After graduation, I spent one year as an intern at Cairo University Hospitals, followed by two years as a pediatric resident at Cairo University Children Hospital, where I obtained my diploma in child health in October 1960. I discovered my love for children and that they are the most vulnerable in terms of the medical need to keep them healthy. My driving force to study medical genetics was children with chronic diseases and malformations whose etiology was largely unknown at that time and that consequently had no cure. My main pediatrics textbook was the *Nelson Textbook of Pediatrics* (32), and my favorite chapter was written by Josef Warkany on congenital malformations. When I was a resident of pediatrics, it was usual practice to treat children with infectious or nutritional disorders, but studying children with various birth defects was intriguing to me. I used to keep records of such patients and photograph them to have more chances for detailed studies and investigations. This was the wealth of material that I presented to Dr. Victor McKusick when I had the splendid chance to meet him at Johns Hopkins University.

Near the end of my pediatric residency, I thought about my career—whether to continue at the hospital as an instructor, teaching pediatrics to medical students, or to move into research.

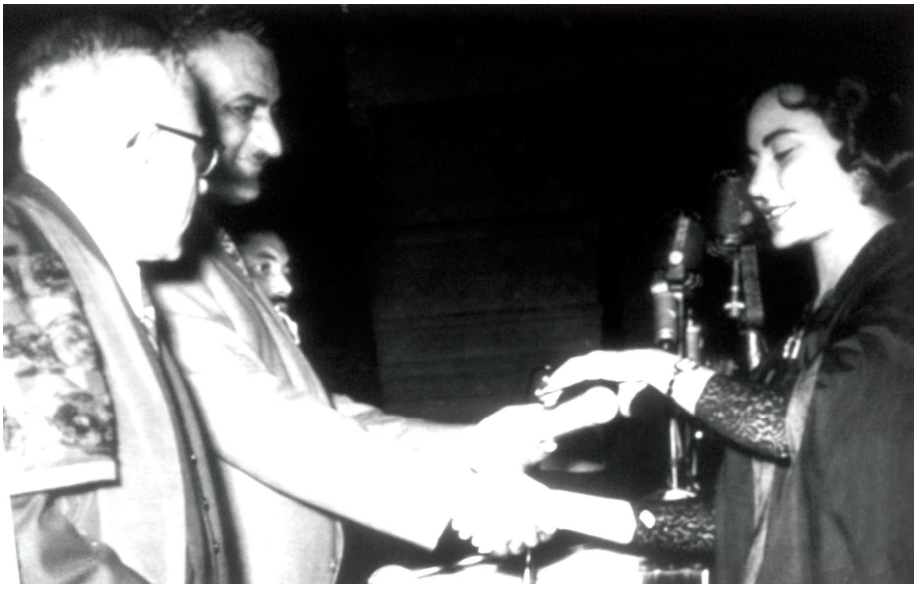

Figure 1

President Gamal Abdel Nasser giving me my medical graduation certificate in December 1957.

I discovered that I was more interested in the depth of solving problematic, intriguing, difficult cases. During that time, I was lucky to meet an eminent professor of pediatrics, Dr. El Nabawy El Mohandes, who had established a unit for medical research at the National Research Centre (NRC) in Cairo; he appreciated my research potential and accepted me as a fellow on his team.

At the same time, my husband, Dr. Mostafa Raafat, who had finished his obstetrics and gynecology residency at Cairo University Hospitals, won a Fulbright fellowship to travel to the United States; he was among the first candidates from the National Cancer Institute of Cairo to win such an award to be trained abroad in the field of cancer research. His fellowship was to study for a doctorate in pathobiology, specifically in cell and tissue culture, at the School of Public Health under the supervision of Professor George O. Gey at Johns Hopkins University in Baltimore, Maryland.

Knowing that Johns Hopkins was one of the leading scientific universities in the world, I was happy to accompany my husband, and I was hoping I would also have the chance to establish my scientific career there. I carried with me letters of recommendation from Professor Mostafa El Diwani, chairman of pediatrics at Cairo University Children Hospital, where I had spent my pediatric residency. He told me not to worry and assured me that I would be able to handle any scientific setting in the United States.

Full of hope and enthusiasm, when I first met Professor Gey, I asked him to introduce me to Dr. McKusick, and I was very happy that I was able to get an interview appointment with him. When I met Dr. McKusick, I talked to him about my deep interest in the genetic etiology of the puzzling patients I saw during my pediatric residency, and showed him photographs of interesting rare cases for whom I suggested correct diagnoses. He was impressed and told me about the new PhD program in human genetics that he had recently established, in 1960. He arranged interviews for me with other members of the Committee of Human Genetics, including Professors Bernice Cohen (who became the supervisor of my courses), Helen Abbey, Wilma Bias, Edmund Murphy, Bentley Glass, and Charles Boyer. After the interviews, I was accepted as a candidate to study human genetics in the Division of Medical Genetics at Johns Hopkins.

In 1961 and 1962, I took many basic courses both at the Johns Hopkins campus and in the School of Hygiene and Public Health. I passed all the required courses in two years, including both winter and summer courses. The courses were mainly basic genetics and cytogenetics, cell physiology and biochemistry, biostatistics, developmental genetics, and calculus and differential equations. In the summer courses, I had to study the German language, which was helpful in reading the German scientific literature on hand malformations, the subject of my PhD thesis. The second foreign language to satisfy the PhD requirements was French, which I had mastered during my school education in Egypt. I passed all my exams with flying colors, as Dr. McKusick told me.

During that time, I was a fellow in medicine in the Division of Medical Genetics, regularly attending the Moore Clinic meetings held every Tuesday morning, where all of the fellows met with Dr. McKusick to discuss the patients before offering them diagnoses and genetic counseling. Those clinic meetings and seminars were inspiring to me and stimulated me to read more of the literature, which was always available at the splendid Welch Medical Library—a facility that I appreciated very much.

After passing all the course requirements and realizing that my main interest in genetic diseases was congenital anomalies, mainly skeletal dysplasias, it was time to choose the subject of my PhD thesis. At that time, nosology or classification of genetic diseases was highly appreciated; Dr. McKusick gave me access to his files for patients with limb anomalies, which stimulated me to read the available literature to study their genetics. I was happy with the subject because I thought that by performing further investigations, I could add to our understanding of limb development and malformations as well as their genetic etiology. Therefore, we chose the subject of the genetics of hand malformations for my PhD thesis research, which proved to be highly successful. In my thesis, I proposed a classification that for the first time differentiated as a first step whether a hand malformation is an isolated anomaly or is associated with anomalies of other organs as part of a syndrome. The classification was also based on the anatomical site of hand anomalies (preaxial, axial, or postaxial) and their morphology [reduction or absence anomalies, short digits (brachydactyly), fused or nonseparated digits (syndactyly), extra digits (polydactyly), contracted digits (camptodactyly), enlarged digits (macrodactyly), associated with congenital constriction rings or amniotic bands, etc.]. While my classification of certain digital anomalies was based on previous publications, particularly Julia Bell's classification of brachydactyly (3), I made additions and modifications of classifications based on patterns of their inheritance and my personal observations. I proposed a new classification of polydactylies that is still used in OMIM (**https://www.omim.org**).

The research for my PhD thesis was based on extensive review of the world literature concerned with hand malformations and on some of the patients from Dr. McKusick's files, whom I was able to trace with the help of the efficient Moore Clinic staff: Mrs. Margaret Hawkins Abbott, Mrs. Barbara Latrobe, and Mrs. Dorothy Chilcoat, the last of whom accompanied me on visits to the patients' homes. Through this work, I obtained a complete clinical evaluation of the patients accompanied by photographic documentation and radiological evaluations, as well as dermatoglyphic studies of their hands and feet and complete three-generation pedigree studies; I also examined all available family members, regardless of whether they were known to be affected, to look for minor manifestations. I was very happy visiting many families at their homes, mainly in Maryland and other neighboring states. I also studied many patients with hand malformations who came to the Moore Clinic during my fellowship in the Division of Medical Genetics from 1963 to 1965.

In addition to my proposed classification during my thesis work, through both the review of the world literature and the study of my patients I was able to discover new syndromes and suggest

eponyms for some of them. During the 1960s, when Dr. McKusick was convinced of the identity of any new syndrome, regardless of whether I published it separately or not, he would add it to his *Mendelian Inheritance in Man*. When my thesis was finished, Dr. McKusick invited international top scientists in the fields of dysmorphology, genetics, and embryology to evaluate the thesis and attend my defense. I was happy that the examiners appreciated my original hard work; I passed with flying colors, and the examining committee recommended that my thesis be published as a book. I am proud that Dr. McKusick mentioned my work as among "the notable nosologic output from the Moore Clinic" (28, p. 9). The nosology of hand malformations was a very proper choice at that time [Dr. McKusick later wrote, "Nosology, study of the classification of disease, is a science in terms of the definition of science attributed to Einstein: 'an attempt to make the chaotic diversity of our sense experience correspond to a logically uniform system of thought'" (27, p. 23)] and coincided with my interests and pediatric background. I am also grateful that, with the efforts of Dr. McKusick and through a second fellowship at the Moore Clinic (from the March of Dimes, 1973–1974), my PhD thesis was updated and new patients were added whom I studied in Egypt after my return there during that second fellowship. The monograph, coauthored by myself and Dr. McKusick, was published in 1978 (**Figure 2**) with support from the March of Dimes, and I dedicated it to "the malformed and those who care for them" (59).

The book required an extraordinary amount of hard work, which was completed in four years: three years during the work on my PhD thesis and one year of my postdoctoral fellowship at the Moore Clinic, along with some additional work to add illustrative cases that I studied in Egypt.

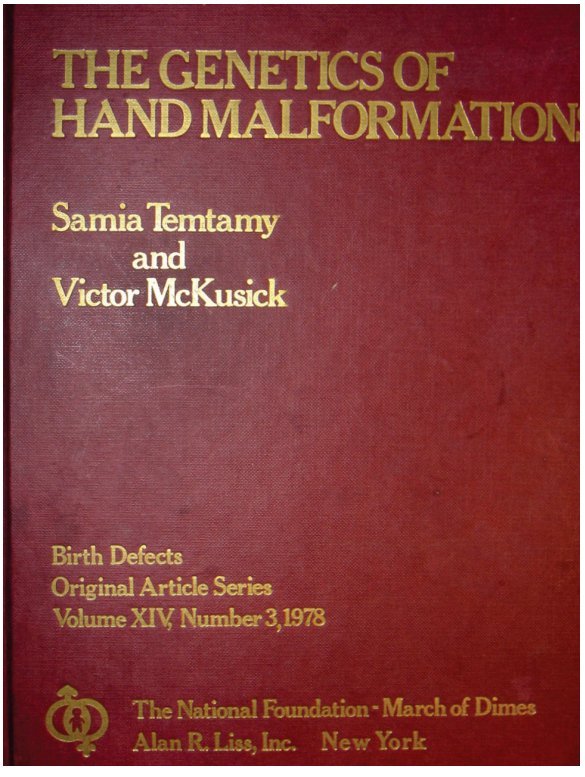

Figure 2

The 619-page monograph by Temtamy & McKusick (59).

I used to spend many nights until dawn in the Welch Medical Library finding documents for the book. Throughout the years following its publication, I have been frequently asked whether I will publish another edition, but my answer has always been negative. To do that in a way that would satisfy me, I would need to have enough time to update all the literature and add new observations, which would be a full-time job for one or more years, one I cannot fulfill among all my responsibilities at the NRC.

THE ALEXANDRIA PROPHECY: MY BOOK IS MY SON!

One day during our honeymoon, which we spent in Alexandria, Egypt, while sitting at the seashore, a Bedouin palm reader looked at my palm and told me, "You are going to have three daughters and one son. This son will make you famous in the whole world." In fact, I had only two daughters and no sons. However, when I think it over, I always consider my book with Dr. McKusick (59) to be my son that made me famous!

I am happy when I meet scientists or receive emails from colleagues or even patients from different parts of the world who consult me or are reading the book. Even some scientists have told me or mentioned to my students that they find it indispensable.

In the summer of 2002, I enjoyed a memorable visit when a Danish PhD student, Klaus Kjaer, wrote to me an email as "a great admirer" of my classification of limb malformations. He wanted to learn from my clinical experience since he was planning to be a clinical geneticist focusing on limb defects, and to his knowledge no one in Denmark had focused on this field. He visited my clinic at the NRC to meet me in person and learn my approach to patients with malformations. When I looked up his publications in PubMed recently (August 2018), I found that he now has 38 publications in clinical molecular genetics, including work on limb and other organ malformations.

I AM USUALLY A SPLITTER BUT OCCASIONALLY A LUMPER

According to Dr. McKusick (27), medical geneticists can be divided into splitters or lumpers. A remarkable story of the former is my discovery of Carpenter syndrome (**Figure 3**). One day, after having lunch in the staff cafeteria at Johns Hopkins, I saw a young girl accompanied by her

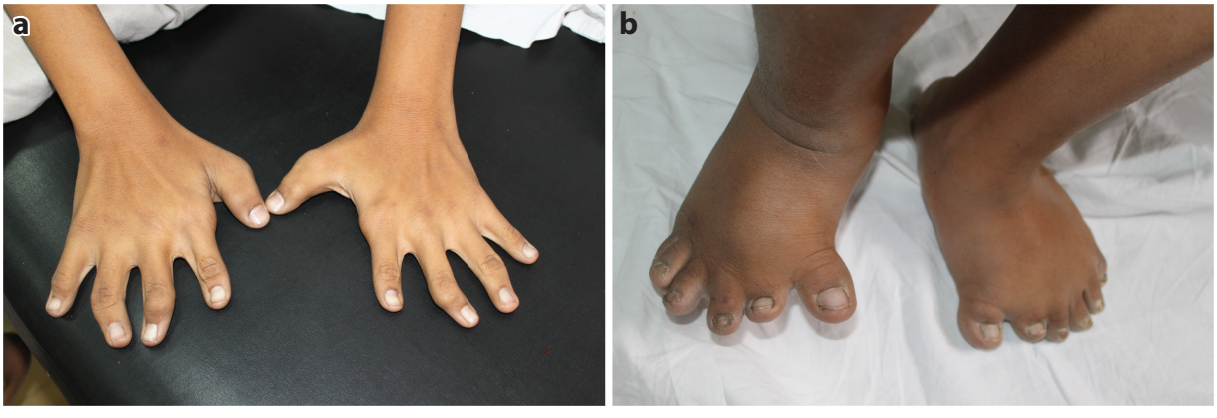

Figure 3

(*a*) The hands of an Egyptian patient with Carpenter syndrome; note the specific brachydactyly and mild soft tissue syndactyly. (*b*) The feet of the same patient, showing preaxial polydactyly and syndactyly (polysyndactyly).

mother coming out of the plastic surgery clinic. I noted that she had tower skull (craniosynostosis) and distinctive facies and limb anomalies. I asked her mother to let us see her daughter at the Moore Clinic. Immediately after I examined her, I remembered a photograph of a patient published in Josef Warkany's chapter on congenital malformations in the *Nelson Textbook of Pediatrics* (32). Warkany commented on the photograph that the patient had both Apert syndrome and Laurence–Moon–Bardet–Biedl (LMBB) syndrome. The girl I met in the corridor—I called her "my angel"—had identical craniofacial features, mainly craniosynostosis and hypertelorism, limb malformations, partial soft-tissue syndactyly, brachydactyly of the hands, and preaxial polydactyly and syndactyly of the feet. I was sure that this patient and the patient shown in Warkany's chapter had the same syndrome, which is neither Apert syndrome nor LMBB syndrome: The syndactyly was not complete in the hands and feet (characteristic of Apert syndrome), and the foot malformation was preaxial rather than postaxial polydactyly (which occurs in LMBB syndrome). I looked in the world literature in almost all languages and was happy to find some previously published cases with similar features; the first report in sisters was by a British surgeon named Carpenter in 1901. I wrote a paper and had it published in the *Journal of Pediatrics* in 1966 as my first scientific publication in an international journal (41), and I was the sole author. I asked Dr. McKusick to join the authorship, but he refused completely, emphasizing that it was all my efforts. This success encouraged me to be a splitter, since I had already acquired the capability of identifying similarities and differences. As a splitter, I identified many syndromes both during my PhD thesis work and after it, when I returned to Egypt.

I was a lumper only once, and this also has a story. When I was at the Moore Clinic as a fellow in medical genetics in 1973, I had the chance to study an interesting family who was referred to us with mucopolysaccharidosis. I was consulted because of the characteristic appearance of pudgy hands of affected family members. On examining the family in detail and reviewing the literature, I found two syndromes that could fit, which had been published by Dr. Grange Coffin and Dr. Robert Lowry. When I presented my paper on this at a birth defects conference in Newport Beach, California, Dr. McKusick asked Drs. Coffin and Lowry, who were attending the conference, whether they would agree to combine their syndromes under one name, Coffin–Lowry syndrome, as I suggested. They both agreed, as witnessed by the conference audience, and the paper was published (62).

New syndrome identification is a talent and an art. It requires a meticulous observer with a strong memory that stores the features of reported syndromes and their characteristic gestalt, along with an analytical ability to identify similarities and differences. The main value of new syndrome identification is accurate molecular characterization followed by proper genetic counseling.

MY "NEW" SYNDROMES

As frequently stated by my mentor, Dr. McKusick, "treasure your exceptions." I used to keep photos of published cases with different dysmorphic features in the back of my mind and recall them when I found a similar case. I identified new syndromes during various stages of my career: during preparation of my PhD thesis, during preparation of my monograph with Dr. McKusick, while holding a fellowship in the Division of Medical Genetics at Johns Hopkins, and throughout the rest of my scientific career. **Table 1** gives examples of syndromes that I identified, in collaboration with my coworkers; I named them based on either the author who first reported them in the literature or the main organ presenting the anomalies. Dr. McKusick included my name for two syndromes (60, 64) in his *Mendelian Inheritance in Man*. The molecular bases, including mutation identification, of most of these syndromes have been revealed by international efforts that

Table 1 Syndromes that I identified in collaboration with my coworkers

Syndrome	OMIM number	Reference
Syndromes with limb reduction defects		
Duane/radial dysplasia syndrome (also sometimes called Okihiro syndrome)	607323	66
Autosomal recessive variant of Adams–Oliver syndrome	100300	50
Baller–Gerold syndrome (craniosynostosis and radial defect)	218600	42
Roberts syndrome	268300	42
Nager acrofacial dysostosis	154400	59
Schinzel ulnar-mammary syndrome	181450	59
Miller postaxial acrofacial dysostosis [called fifth digit syndrome and Genee–Weidemann syndrome in our monograph (59)]	263750	59
Syndromes with brachydactyly		
Temtamy-type brachydactyly (A4)	112800	42
Temtamy preaxial brachydactyly syndrome	605282	60
Du Pan syndrome	228900	42
Coffin–Lowry syndrome	303600	62
Syndromes with syndactyly		
Synpolydactyly (type II syndactyly)	186000	42
Skeletal dysplasia with soft-tissue syndactyly tumors and ocular, dental, and digital anomalies	—	31
Saethre–Chotzen syndrome	186000	42
Pfeiffer syndrome	101600	42
Cenani–Lenz syndrome	212780	42
Syndromes with polysyndactyly		
Carpenter syndrome	201000	41
Mohr–Majewski syndrome (type IV orofaciodigital syndrome)	258860	59
Greig cephalopolysyndactyly syndrome (polysyndactyly with abnormal skull shape)	175700	42
Postaxial polydactyly dental vertebral anomalies	263540	36
Syndromes with macrodactyly		
Macrodactyly, hemihypertrophy, and connective tissue nevi (later called Proteus syndrome)	176920	63
Syndromes with contracture deformities of the hands		
Ter Haar syndrome (megalocornea mental retardation type 2)	249420	47
FGFR3 homozygous mutation, camptodactyly, tall stature, and hearing loss	610474	23
Syndromes with eye anomalies		
Congenital cataract, microphthalmia, and nystagmus	212550	65
Congenital lipoid proteinosis, congenital cataract, and characteristic facies	—	2
Cataract, hypertrichosis, and mental retardation (CAHMR) syndrome	211770	67
Temtamy syndrome (agenesis of the corpus callosum, craniofacial dysmorphism, mental retardation, and ocular colobomas)	218340	64
Skeletal dysplasias		
Metaphyseal dysplasia, anetoderma, and optic atrophy	250450	54
New syndrome of bone fragility and dwarfism	—	56
3-M syndrome	273750	30
Brachydactyly, syndactyly, short stature, microcephaly, and intellectual disability	—	35

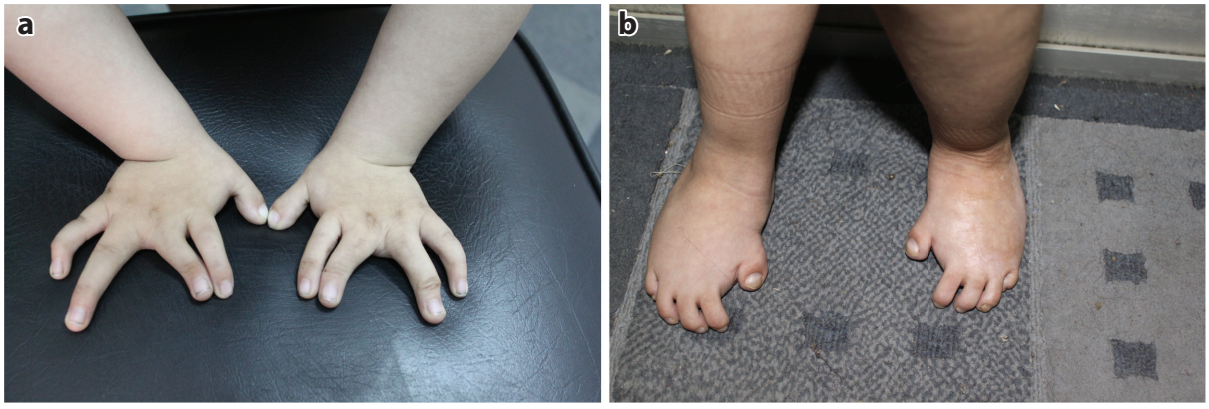

Figure 4

(*a*) The hands of an Egyptian patient with Temtamy preaxial brachydactyly syndrome due to a *CHSY1* mutation, showing preaxial brachydactyly and camptodactyly of fingers. (*b*) The feet of the same patient, showing severe preaxial brachydactyly of toes.

determined their genetic identity, thus justifying their splitting, as indicated by their different OMIM numbers.

The process of new syndrome identification consists of an endless stream of international knowledge that only begins with the report of a new syndrome. The following are examples of some of our "new" syndromes and the subsequent publications that reported their molecular bases or further defined their phenotypic spectra: Carpenter syndrome (29) (**Figure 3**), Greig syndrome (24), Cenani–Lenz syndrome (20, 57), Baller–Gerold syndrome (51), Temtamy preaxial brachydactyly syndrome (1, 19, 45, 46, 52) (**Figure 4**), Roberts syndrome (15, 56), 3-M syndrome (11, 12, 49), the autosomal recessive variant of Adams–Oliver syndrome (38), and Nager acrofacial dysostosis (16).

MY RETURN TO EGYPT

I obtained my PhD in human genetics from Johns Hopkins on February 9, 1966, preceded by Alan H. Emery and David Rimoin. I returned to Egypt on the cruise boat *Constitution*, and after a tour of the Mediterranean area that included Casablanca, Gibraltar, and Naples, we reached Alexandria in March. My main aim after my return was to establish on scientific grounds the modern medical specialty of human genetics at the NRC, as I had learned it during my five years in the United States. I was keen to be surrounded by researchers with whom I could discuss different basic and advanced aspects of this fascinating scientific field. I always thought that human genetics is the main basis for medical knowledge. This proved to be true, especially after the completion of the Human Genome Project and the initiation of personalized medicine.

Introducing human genetics at the NRC in 1966 was not easy. Some human genetics units had been created, especially in the pediatric departments of Ain Shams University and Cairo University, headed by the late Professors Nemat Hashem and Ekram Abdel-Salam, respectively, and one was started later at the Alexandria University Medical Research Institute by Dr. Suzan Roushdy Ismail, who had obtained her PhD in human genetics in the United Kingdom. I was determined to transfer the knowledge that I had gained in the United States to promote various health advantages by the early and accurate diagnosis, prevention, and management of genetic diseases in the Egyptian population, in whom genetic diseases have been recorded since antiquity (55). I started by collaborating with the Department of Pediatric Surgery at the Cairo University Children

Hospital, headed by the late Professor Adel Lotfy, because most patients with congenital anomalies were referred to that department. Since cytogenetic studies were greatly appreciated at that time, I started by initiating a small tissue culture room and a cytogenetics laboratory, with one technician assisting me. Dr. Lotfy was impressed when I diagnosed the first child who presented with bilateral inguinal hernia and palpable gonads as having complete androgen insensitivity syndrome, since she had female external genitalia, a negative Barr body, a positive Y body, and a 46,XY karyotype. Colleagues from different hospitals started to refer their patients with congenital anomalies or mental subnormality to me for chromosomal studies. I succeeded in increasing the appointments of my coworkers and started the Human Genetics Unit in the Medical Research Division of the NRC's Basic Medical Sciences Department. I was also the first to start a clinic to receive patients within the premises of the NRC.

The Division of Medical Genetics at Johns Hopkins comprised mainly the specialties of clinical genetics, cytogenetics, biochemical genetics, and immune genetics. My main goal was to initiate human genetics at the NRC. First, I had to find staff and train them in the main medical genetics specialties. I succeeded in convincing medical school graduates to join me, especially pediatricians. I was also able to convince a physician interested in biochemistry to start biochemical genetics work, and she became the head of the Department of Biochemical Genetics. I also appreciated the orodental manifestations of genetic disease and initiated the Department of Orodental Genetics. At Johns Hopkins, prenatal diagnosis was part of obstetrics and gynecology, but I preferred to have a separate Department of Prenatal Diagnosis and Fetal Medicine. As molecular genetics became one of the important pillars of genetic diagnosis, I started a Department of Medical Molecular Genetics to include graduates from the Faculty of Science and Faculty of Pharmacy. We are also incorporating bioinformatics in our group, which is practiced now mainly by cytogeneticists and molecular geneticists.

The Human Genetics Unit formed in 1966. The decision to form the Human Genetics Department was made in 1977 after we increased the facilities offered by this unit. In 2003, the Human Genetics Department became the Human Genetics and Genome Research Division, which is the foundation of the Center of Excellence for Human Genetics that formed in 2014. The division includes eight departments working in collaboration: the Departments of Clinical Genetics, Orodental Genetics, Cytogenetics, Prenatal Diagnosis and Fetal Medicine, Biochemical Genetics, Immunogenetics, Medical Molecular Genetics, and Molecular Genetics and Enzymology. The division includes 229 researchers in different fields of genetics and is considered the largest such division in Egypt, and probably in the region. The division and the Center of Excellence for Human Genetics also include multiple specialized teams comprising clinical geneticists as well as members from the other laboratory departments as needed; these teams cover autism and behavioral disorders, blood disorders and genodermatosis, bone and limb anomalies (skeletal dysplasias), brain malformations, neurogenetics, congenital heart diseases, Down syndrome and early intervention, disorders of sex development and genetic endocrinology, microcephaly and epilepsy, neuromuscular disorders, and phenylketonuria (PKU) and other metabolic disorders.

To initiate the different specialties in our division, in other divisions at the NRC and at different universities in Egypt I have supervised more than 100 PhD, MD, and MS theses in medicine and science in the fields of human genetics, experimental mutagenesis, zoology, forensic medicine, pediatrics, ophthalmology, pathology, andrology, internal medicine, gynecology and obstetrics, biochemistry, dentistry, clinical pathology, psychiatry, and orthopedics (hand surgery). I have even supervised degrees in social sciences and higher education and in the police academy; in these three fields, the dissertations were written in the Arabic language!

My research, ideas, and publications and the dissemination of my knowledge to the public and media have created an important awareness among physicians, scientists, decision makers, and the

public about the importance of human genetics as a medical science in Egypt. This led to the initiation of neonatal screening in 2003, a program that began with a population screening project funded by the Academy of Scientific Research and Technology. I was the principal investigator of that project; the collaborating centers were the Human Genetics Department at the NRC, the Pediatric Genetics Unit at Cairo University, Ain Shams University, Mansoura University, and the Human Genetics Department in the Medical Research Institute at Alexandria University. Each team studied 3,000 newborns at maternal and child health centers for the presence of any congenital anomalies, screening them for hypothyroidism, PKU, galactosemia, and biotinidase deficiency using blood spots collected on Guthrie cards. The results of this neonatal screening of 15,000 newborns showed a high frequency of hypothyroidism and PKU (44), which convinced the health authorities in Egypt to start neonatal screening for hypothyroidism in all Egyptian governorates in 2003; screening for PKU was later added as well.

My team also conducted valuable epidemiological studies on the frequency of congenital malformations in newborns (61) and the frequency of mental subnormality in Assiut Governorate, Egypt (58). All of our epidemiological studies confirmed a relative high frequency of autosomal recessive disorders because of high parental consanguinity rates (48).

My main research interests—initiated by my studies at Johns Hopkins in the early 1960s and perpetuated by my continuous evaluation of referred patients with suspected genetic disorders, reading of the world literature, sharing in the publication of different articles, and international interactions with colleagues, either by meeting them in person at conferences or during mutual scientific visits or by contacting them over the Internet—have been clinical genetics, dysmorphology, syndrome identification, limb malformations, and skeletal dysplasias.

THE CENTER OF EXCELLENCE FOR HUMAN GENETICS

We succeeded in obtaining a grant from the Science and Technology Development Fund, part of the Egyptian Ministry of Higher Education and Research, on a competitive basis to initiate a Center of Excellence for Human Genetics with a fund of 10 million Egyptian pounds. The center is composed of the departments of the NRC Human Genetics and Genome Research Division, and its main project is to advance the diagnosis and management of genetic diseases. The project started in 2014, and through it we acquired the modern research equipment and fine chemicals necessary for genetic and genomic technologies. Through the center, we plan to (*a*) reach accurate diagnoses for different genetic diseases using modern technologies (e.g., next-generation sequencing, proteomics, microarrays, and laser dissection microscopy); (*b*) identify gene mutations prevalent among Egyptians as an essential requirement for their early diagnosis, prevention, and management; (*c*) study rare genetic diseases that may lead to the discovery of new diseases or genes and genetic pathways, thus paving the way for novel therapeutic or preventive strategies; and (*d*) enable national and international collaboration to allow the mutual exchange of expertise and twinning agreements between related centers of excellence worldwide. At present, we are concentrating our studies on patients with disorders within the four most common categories at our clinics: skeletal disorders and limb malformations, neurogenetic disorders, hereditary blood disorders, and multiple congenital anomalies.

CONFERENCES, WORKSHOPS, AND TRAINING COURSES

I have participated in more than 50 conferences, mainly international, and as an invited speaker, mostly in plenary sessions. Among the significant conferences was our first International Conference of Human Genetics and Physical Anthropology, held at the Cairo Hilton Hotel in December

Figure 5

Dr. Victor McKusick and myself as cochairs of the opening session at the first International Conference of Human Genetics and Physical Anthropology in Cairo, Egypt, in December 1989.

1989. Many human genetics colleagues participated as invited speakers, headed by my mentor, Dr. McKusick, with whom I shared the opening session (**Figure 5**). Dr. McKusick and his lovely wife, Anne, very much enjoyed their visit and described it as memorable. The proceedings of this conference were published as a supplement to Volume 66 of the *Journal of the Egyptian Public Health Association*.

The African Society of Human Genetics and the National Society of Human Genetics–Egypt are two forums for scientists interested in human genetics in Africa to meet, interact, network, and collaborate. They aim to equip the African scientific community and policy makers with the information and practical knowledge needed to contribute to the field of human genetics and to attract global attention to the efforts of African scientists in this rapidly evolving scientific field. Another major goal is to ensure that Africa is not left out of the genomic revolution.

In November 2007, we held the fifth Conference of the African Society of Human Genetics in conjunction with the National Society of Human Genetics–Egypt at the Pyramisa Hotel in Cairo. Many international human geneticists were invited speakers, headed by Dr. Francis Collins (director of the US National Institutes of Health) and Dr. Charles Rotimi (founding president of the African Society of Human Genetics). We also had the pleasure and honor of holding the 10th Conference of the African Society of Human Genetics at the Nile Ritz-Carlton Hotel in Cairo in November 2017 with many participants and invited speakers, headed by Professor Michèle Ramsay (current president of the African Society of Human Genetics) and Dr. Maximilian Muenke (from the National Human Genome Research Institute in Bethesda, Maryland, USA). Such meetings were of the utmost importance to update our young researchers in Egypt and other African countries with the rapidly advancing knowledge in the fields of human genetics and genomics.

We participated in many of the Asian–European Workshops on Inborn Errors of Metabolism and hosted three of them in Cairo, in 1995, 2005, and 2015. I also had the splendid chance to participate in international genetic conferences held at the Kuwait Medical Genetics Center in 2012 and 2014, and I was invited by Professors Sadika Al-Awady and Laila Bastaki to see patients as a consultant during these conferences.

Another memorable meeting was the Human Genome Organization (HUGO) meeting held in February 2017 in Barcelona, Spain, where I was honored with the HUGO African Prize for lifetime contributions in human genetics and presented a plenary award lecture. The prize was funded by the South African company Inqaba Biotec, which supported my travel to attend the meeting and provided funding for some biotechnology reagents for genomic research. Professor Stylianos Antonarakis was the head of HUGO, and I also had the pleasure of meeting international colleagues such as Professors Ada Hamosh, David Valle, and Nara Sobreira from Johns Hopkins, with whom we developed our collaboration with the Baylor-Hopkins Center for Mendelian Genomics

(see below). I also met Professor Stefan Mundlos from Charité and the Max Planck Institute for Molecular Genetics in Berlin, Germany, who sent me his recent book on limb malformations and wrote to me in an accompanying letter that my book with Dr. McKusick on the genetics of hand malformation (59) had "somewhat started [his] career."

INTERNATIONAL COLLABORATIONS

I owe the maintenance and continued upgrades of our diagnostic and research activities to our international collaborations. After the tremendous push I had from being a fellow for about seven years in the Division of Medical Genetics at Johns Hopkins, which gave me contact with distinguished fellows and visitors from all over the world and later with scientists with mutual interests at conferences, the following are notable examples of scientific agreements, conferences, fellowships, and training courses:

- I attended the March of Dimes meetings in Baltimore, Maryland, USA, in 1967, 1972, 1973, and 1974. During these meetings, I had the chance to become acquainted with several eminent human geneticists and dysmorphologists, including John Opitz, Robert Gorlin, David Smith, and Widukind Lenz.
- I received a Fulbright fellowship to attend the Salzburg Seminar in American Studies in Salzburg, Austria, in 1979.
- I received a German Academic Exchange Service fellowship to participate in the European Conference for Genetic Counseling in Essen, Germany, in 1982.
- I set up a scientific agreement between the NRC Human Genetics Department and the Essen University Institute of Human Genetics from 1982 to 1985. Two of our staff members from the Department of Cytogenetics received training on chromosomal banding techniques under the supervision of Professor Eberhard Passarge of the Institute of Human Genetics, and one staff member from the Department of Orodental Genetics received training on ultrastructural studies of gingival biopsy with Professor Manfred Blank from the Essen University Institute of Anatomy.
- The Japanese Teratology Society invited me to deliver the opening lecture at their 24th annual meeting in Tokyo, Japan, in July 1984 (43). I was also offered a memorable 15-day tour of various human genetics centers in Tokyo, Kyoto, and Nagoya.
- We collaborated on a project on the molecular genetics of the intersex problem with Professor Marc Fellous of the Pasteur Institute in Paris, France, from 1990 to 1992. Through this project, we acquired our first PCR machine, our first transilluminator, and a Polaroid camera to start molecular genetic studies of the *SRY* gene at the NRC (26).
- As a result of my recommendation, one of my young staff members won a Fulbright fellowship to be trained for six months by Professor Haig Kazazian at Johns Hopkins in 1992. The molecular techniques at that time were mainly reverse dot blot, denaturing gradient gel electrophoresis, and Sanger sequencing (14).
- One of my students did the practical part of her PhD thesis under combined supervision with Professor Jörg Schmidtke of the Faculty of Medicine at Leibniz University Hannover, Germany, in 1992, on molecular genetic diagnosis of fragile X syndrome (9).
- One of my students, Dr. Laila Effat, who had done her PhD thesis on PKU mutations, received a three-month postdoctoral Fulbright fellowship, supervised by Professor Savio Woo of Baylor College of Medicine in Houston, Texas, USA. This fellowship resulted in a publication (8) and subsequent initiation of PKU molecular identification as a service and research area in our division.

- We participated in a project with Professor Giovanni Romeo of the University of Genoa, Italy, on new DNA techniques for identifying mutations in the beta-globin gene in Egyptian beta-thalassemia patients. This was the first project in Egypt to be funded by the International Centre for Genetic Engineering and Biotechnology in Trieste, Italy. Through this project, two of our staff received training on DNA technology in Genova from 1993 to 1997, and the collaboration also resulted in two publications (13, 34).
- We participated in the European Union FP7 project Euro-Mediterranean Network for Genetic Services (MedGeNET) from 2006 to 2008, with myself and Professor Giovanni Romeo as the principal investigators.
- We also participated in the Medicina Genetica per i Paesi del Mediterraneo (MedGenMed) project under principal investigator Professor Giovanni Romeo from 2006 to 2008. Through this project, we started hybrid courses webcasted from Bertinoro, Italy; these courses were offered for free during the two years of the project, and we are still enjoying them thanks to the efforts of the European School of Genetic Medicine and the European Society of Human Genetics and the support of the National Society of Human Genetics–Egypt and the NRC.
- We participated in a project on the biochemical diagnosis of mucopolysaccharidosis under principal investigator Professor Ed Wraith of Manchester University, United Kingdom, from 2000 to 2002, funded by the British Council. Through this project, we had mutual exchange visits between our biochemical genetics team and Manchester University experts. We are at present the main reference center in Egypt to diagnose mucopolysaccharidosis and treat it by enzyme replacement therapy.
- Our Department of Biochemical Genetics has an ongoing collaboration with Professor Yoon S. Shin-Podskarbi of Munich University, Germany. This collaboration began in 1990 with the training of our staff on screening for inborn errors of metabolism.
- We participated in a research project on identifying the genomic causes of rare genetic disorders in consanguineous families under principal investigators Professor Stylianos Antonarakis and Professor Hanan Hamamy of the University of Geneva, Switzerland, from 2012 to 2015. This project was supported mainly by Gebert Rüf Stiftung and other Swiss agencies following the successful Geneva International Consanguinity Workshop in 2011. This collaboration resulted in three important publications (10, 22, 23).
- We have been collaborating with Professor Victor Luis Ruiz Pérez of the Instituto de Investigaciones Biomédicas "Alberto Sols" in Madrid, Spain, for about 10 years on various projects, supported mainly by the Spanish Ministry of Economy and Competitiveness and the Centro de Investigación Biomédica en Red de Enfermedades Raras. Other than Dr. Ruiz Pérez, the principal investigators include Professors Valérie Cormier-Daire, Bernd Wollnik, and Pablo Lapunzina. Our collaboration began with Dr. Ruiz Pérez's interest in a family with Ellis–van Creveld syndrome about whom we had written a paper (53); affected members had associated unusual orodental anomalies and intellectual disability, and molecular investigations revealed unusual findings. We continued our collaboration with his team by investigating molecular and clinical aspects of other patients with Ellis–van Creveld syndrome and bone fragility disorders, with particular emphasis on identifying new genes in autosomal recessive variants of osteogenesis imperfecta, which we frequently see in our clinic and is probably relatively common in our community given the high consanguinity rate (4–7, 17, 18, 25, 33, 68–70).
- Dr. Maximilian Muenke has been organizing an annual, one-month-long International Summit in Human Genetics and Genomics hosted by the National Human Genome Research Institute at the National Institutes of Health in Bethesda, Maryland, USA. This

summit is for health-care professionals from low- or middle-income countries who are interested in advancing genetics and genomics in research and medicine to resolve health challenges. The summit serves as a forum for participants to interact and train with experts in the field and establish collaborations in genetic research and medicine, which exactly matches our goals. One of our young staff members participated in the first summit in 2016, and two more participated in the second in 2017.

- One of my young collaborators attended the 10th Annual Introductory Course on Skeletal Dysplasias held in Lausanne, Switzerland, in July 2016. The course was organized by Dr. Sheila Unger, Professor Luisa Bonafé, and Professor Andrea Superti-Furga at the Centre Hospitalier Universitaire Vaudois in Lausanne, supervised by Professor Superti-Furga. Our staff was funded by Egyptian Science and Technology Development Fund grant 5253 for the Center of Excellence for Human Genetics.
- We recently started a collaboration with the Baylor-Hopkins Center for Mendelian Genomics chaired by Professors David Valle from Johns Hopkins and James Lupski from Baylor College of Medicine. Johns Hopkins and Baylor have received grant support from the National Human Genome Research Institute for the creation of this center to help solve Mendelian disorders for which the genetic etiology is presently unknown. We started our collaboration by submitting clinical data of rare cases through PhenoDB and by having one of our molecular geneticists trained to interpret the results of whole-exome sequencing. She had this training for two weeks with Dr. Nara Sobreira at the McKusick-Nathans Institute for Genetic Medicine at Johns Hopkins, funded by Egyptian Science and Technology Development Fund grant 5253 for the Center of Excellence for Human Genetics.

I must also mention other valuable collaborations with various eminent international scientists. Examples include Professor Joseph Gleeson (37), who has visited us several times, is actively collaborating with our neurogenetics group, and trained two of our young researchers in his neuroscience laboratory at the University of California, San Diego, USA, for two months each; Professor Bernd Wollnik, who identified the gene mutations for Temtamy preaxial brachydactyly syndrome (19) and Cenani–Lenz syndrome (20); Professor Fowzan Sami Alkuraya, with whom we have done work on skeletal dysplasias (21) and microcephaly (39); and Professors Han Brunner and Stanislav Kmoch, with whom we worked on identifying the causative gene mutation for growth retardation, alopecia, pseudoanodontia, and ocular manifestations (GAPO) syndrome (40).

It is almost impossible to list all of the international collaborations we have had in all of our departments. I greatly appreciate our international collaborations and hope they will continue and flourish. Evidence of such international collaborations can be seen at the National Society of Human Genetics–Egypt website (**http://www.nshg-society.eg.net**), where lists of staff publications are being updated; our international publications are also available on PubMed and Scopus.

Realizing the importance of promoting human genetics as a science, meeting our patients' social needs, and treating our patients ethically, we established the National Society of Human Genetics–Egypt in 2005. Our main objectives were to increase professional and public awareness about the prevention and management of genetic diseases through the mass media and communications through newspapers, television, and radio and to increase public and professional knowledge about the care, rehabilitation, and management of genetically disabled individuals through meetings and leaflets distributed to the public. At the executive committee meeting of the International Federation of Human Genetics Societies, held on November 3, 2010, in Washington, DC, USA, the National Society of Human Genetics–Egypt was accepted as a corresponding member in the federation, becoming the first member from Egypt and from the Arab world to be so honored.

The *Middle East Journal of Medical Genetics*, published since January 2012 by Wolters-Kluwer, is the society's official journal.

IN CONCLUSION

I have tried to summarize my achievements during a half century of my life in human genetics. I hope this has been helpful to my colleagues and students, whom I have always cherished. I love the science of human genetics and look forward to seeing it flourish in Egypt in the coming years. I realize that our progress has been slow; this is mainly because Egypt, like most developing countries, has had infectious diseases as a health priority, and once those are overcome, genetic diseases will become a priority, as is enjoyed in most developed countries.

Finally, I would like to mention my two main mottoes that drive me and maintain my enthusiasm:

> Good, better, best. Never let it rest, till your good is better and your better is best.
>
> —Author unknown

> Make no little plans; they have no magic to stir men's blood and probably themselves will not be realized. Make big plans; aim high in hope and work, remembering that a noble, logical diagram once recorded will never die, but long after we are gone be a living thing, asserting itself with ever-growing insistency.
>
> —Daniel Burnham, American architect

I think I have laid the foundation for the science and practice of human genetics and genomics at the NRC, from shortly after the discovery of the correct number of human chromosomes through to the human genome era. The whole world is aiming to reach the goals of precision medicine and personalized medicine through genomic research. I would like the young generation to realize that, wherever they are in the developed or developing world, they must persevere to achieve their high scientific goals, nothing is impossible, and "where there's a will, there's a way."

DISCLOSURE STATEMENT

The author is not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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I dedicate this article to the soul of my great mentor, Dr. Victor A. McKusick.

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