The recurrence risk of genetic complex diseases

Mahdi Bijanzadeh[1,2]

[1]Health Research Institute, Thalassemia and Hemoglobinopathy Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz,
[2]Department of Medical Genetics, School of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

Complex inherited diseases affected by an interaction between collective effects of the genotype at one or multiple loci either to increase or to lower susceptibility to disease, combined with a variety of environmental exposures that may trigger, accelerate, exacerbate, or protect against the disease process. The new aspects of genetic techniques have been opened for diagnosis and analysis of inherited disorders. While appropriate Mendelian laws is applied to estimate the recurrence risk of single gene diseases, using empirical recurrence risks are the most important and available method to evaluate pedigree of complex (multifactorial), chromosomal, and unknown etiology disorders. Although, generally, empirical recurrent risks are not accurate, either because of the difference of gene frequencies and environmental factors among populations or heterogeneity of disease; using results of plenty family population studies, computerized estimating programs, genotyping technologies, and Genome-wide association studies (GWASs) of single nucleotide polymorphisms (SNPs), can make it possible nowadays to estimate these risks. The specific family situation and importance recurrence risks of some common complex genetic diseases will be presented in this review and some important multifactorial disorders' recurrence risks will be summarized to help genetic counselors for supporting families and representing better view of genetic disorders.

Key words: Genetics counseling, pedigree, recurrence

INTRODUCTION

Recent valuable advances in medical genetics have resulted in an increase of interest in genetic counseling.[1] The central question usually asked and one of the most important aspects of genetic counseling is the probability of recurrence of a particular disease that has already occurred in a family, in specified relatives, called recurrence risk.[2]

When the counselor classifies the disease as Mendelian, the appropriate Mendelian law can be applied to the specific family situation and estimate the recurrence risk. For chromosomal, multifactorial, and unknown etiology diseases, usually empirical risk can be applied.[1]

Complex, common or multifactorial diseases affected by an interaction between collective effects of the genotype at one or multiple loci either to raise or to lower susceptibility to disease, combined with a variety of environmental exposures that may trigger, accelerate, exacerbate, or protect against the disease process.[1]

Several criteria have been commonly accepted to define the inheritance in multifactorial diseases: the recurrence risk becomes higher when (1) there are more than one affected family members, (2) the disease expression in the proband is more severe, and (3) the proband is of the less commonly affected gender. The fourth criteria said that the recurrence risk usually decreases rapidly in more far relatives. Finally, if the disease prevalence in a population is f, the risk for offspring and siblings of proband is around $\sqrt{f}$.[1]

The parameter λ is used to estimate the risk ratio for a relative of an affected individual when compared with the general population prevalence.[2] For measurement of the relative risk λ_R (R for first-degree relatives), the disease prevalence in the relatives of an affected person is divided to disease prevalence in the general population.[3]

Address for correspondence: Dr. Mahdi Bijanzadeh, Department of Medical Genetics, School of Medicine, Ahvaz Jundishapur University of Medical Sciences, Golestan Boulevard, Ahvaz 61355-33118, Khuzestan, Iran. E-mail: mbijanz@yahoo.com

The early case–control linkage studies based on candidate genes in medium-sized samples have been replaced by genome-wide association studies (GWASs). This progress was the establishment of the Welcome Trust Case–control Consortium focusing on research on multifactorial diseases and the development of DNA microarrays.[3] This consortium was formed to describe studies of 2000 cases and 3000 controls for seven complex human diseases: bipolar disorder, coronary artery disease (CAD), Crohn's disease (CD), hypertension, rheumatoid arthritis (RA), type 1 diabetes (T1D), and type 2 diabetes (T2D).[4]

Despite above methods in risk detection, empirical recurrence risk that updated by new tools and knowledge, is the most important outcome for counselors and can help them for supporting families to explain characteristics of genetic disorders, which is the main aim of this article.

MEDLINE and PubMed were the main databases in present review by the search term "recurrence risk," in combination with the keywords "multifactorial," "common diseases," "genetics counseling," "pedigree," and selected disease. After the evaluation of 270 articles, aside three references that mentioned the usage history of risk calculation, related data of 101 articles published between 1980 and 2016 were analyzed and used.

Congenital heart disease

Congenital heart disease (CHD), gross structural anomalies of the heart or intra thoracic great vessels that are actually or potentially functional significance, are the most common birth defect, presenting in around seven in 1000 live births. A clinical study in Iran between 1998 and 2007, showed a mean prevalence of 12.30/1000 live births.[5] One-quarter of them are associated with chromosome abnormalities (e.g., micro deletions of chromosome 22q11) and teratogens exposure (e.g., maternal insulin-dependent diabetes, rubella infection, and drug consumption). Although majority of the isolated CHD do not show single underlying cause, sometime it presents a feature suggesting a syndromic diagnosis that may show monogenic inheritance.[6] Excess mutations have a role in 10% of CHD cases and led to the estimate that around 400 genes underlie these multifactorial diseases.[7]

Nora and Nora after the review of eight studies involving 3996 offspring of parents who have CHD, reported risk ratio from a high 6.39 for aortic stenosis to a low 1.48 for patent ductus arteriosus.[8]

In 1998, a multicenter and prospective study in UK revealed that if the affected parent of a CHD patient was the mother, recurrence risk was significantly higher. Gill reported the recurrence risk for first-degree relatives of CHD between 2% and 5%.[6]

Cleft lip with or without cleft palate

Oral clefts (OCs) are a heterogeneous group of congenital defects, including syndromic and nonsyndromic cleft lip (CL), cleft palate (CP), and cleft lip and palate (CLP).[9] Nonsyndromic CL with or without CP or CP alone (CL/P), is the most common facial congenital defect[10] with incidence from 1/200-1/2500 births depending on the race and socioeconomic status.[11,12] Pooled incidence of CL and CP from 11 studies in Iran was reported 1/1000.[13] The baby with CL/P is likely to suffer from difficulty feeding, conductive hearing loss, speech problems, dental anomalies and also may result in social and psychological problems. 80–85% of CLs are unilateral and 33% of them have left-sided clefts. Globally, CL/P is more common in males, whereas CP is more common in females. In general, males with CL/P are inclined to a more severe than females and familial CL/P is less severe than sporadic cases. The frequency in females is higher when the father is >40 years.[14] de Araujo *et al*. reported 24 SNPs in 16 genes had significant association with nonsyndromic CL and palate.[15]

Around 20% of the affected babies have a positive family history; therefore genetic factors are thought to be important in its etiology. Although some of the nonsyndromic and familial cases appear to have a Mendelian inheritance, it is more inherited in a multifactorial pattern.[16]

Having an affected child when the mother or another sibling is affected, both occur at birth prevalence more than population frequencies. Although clefts have a high familial recurrence and estimated ~ 4%, recurrence rates may vary between different races and exceed 4%.[12] The recurrence risk between the first degree relatives of patients with OCs is ~32 times greater than the general population risk for CL/P and 56 times greater for CP.[17]

Silva-Lope suggested a greater genetic impact in the etiology of CL based on the counting of an excess individual with CL over CL/P in the children of consanguineous parents.[9]

Neural tube defects

Neural tube defects (NTDs) are complex congenital abnormalities of the central nervous system resulting from neural tube closure failure during embryogenesis. NTD is one of the most frequent congenital malformations and its prevalence varies between 1 and 10/1000 births, depending on geographic and ethnical conditions.[18] It is estimated that more than 300,000 NTDs are born each year globally, that vast majority of these are in low-income countries.[19] The prevalence of NTDs in Iran reported as 2.97/1000.[20] NTDs can be classified in "open" and "closed" depending on

exposure or covered neural tissue. "Open" NTDs include craniorachischisis due to a total failure of neurulation with most of the brain and the entire spinal cord that remaining open, anencephaly in which the defect occurs in the cranial region and spina bifida cystic that the defect is localized in the lumbo sacral area. In spina bifida cystica, if meninges and cerebrospinal fluid herniated through the defect, it is called meningocele, and when spinal cord and/or nerve roots directly involves, a myelomeningocele is created. "Closed" NTDs, include encephalocele, a bony skull defect in which part of the brain herniates and spina bifida occulta that results from a gap in vertebral arches in the lumbosacral area, but the spinal cord and meninges remain entirely within the vertebral canal.[18] According to Lei and Finnell since more than 300 genes have been reported to be involved in murine neural tube closure, it is likely that more genes contribute to the expression of human NTDs will be discovered.[21]

Janerich after evaluation of 628 NTD cases born during 1956–1972, reported the full sib recurrence rate (1.8%) to be higher than the half sib recurrence rate (0.8%).[22] After that, researchers showed if the proband was the first affected child in the family, the recurrence in the subsequent siblings was 3.15%, and if it was the second affected child, the recurrence was 10–11.76%.[23,24] Teckie et al. showed more significant risk in female infants and also in the first and last children of a mother.[25]

Clubfoot

Congenital Talipes Equinovarus (CTEV) or Clubfoot is a congenital foot anomaly including cavus (plantarflexion of the forefoot on the hindfoot), adduction of the forefoot on the midfoot, varus (inversion of the subtalar joint), and Equinus of the hindfoot. There are controversies about its etiology, including primary muscle, nerve, bone or vascular pathology, retracting fibrosis, and developmental arrest. Some studies supported the hypothesis that a single Mendelian gene (SMG) explains the idiopathic Talipes Equinovarus in families.[26] Yang et al. showed that its etiology could be explained by segregation of SMG and polygenes, while Wang et al. explained autosomal dominant segregation of an SMG with incomplete penetrance.[27] Yong et al. after a systemic review analysis of 21 studies that have examined the genetic variants related to idiopathic CTEV, reported positive association with Hox family genes, collagen family genes, GLI3, N-acetylation genes, T-box family genes, apoptotic pathway genes, and muscle contractile family genes.[28]

The boys' chance in Europe was estimated with twice of girls. In families with one clubfoot offspring, the occurrence of the subsequent siblings is thirty times more than in the general population (7.3%).[29,30]

Honein et al. explained the family history of smoking as an environmental factor of this multifactorial disease.[31]

Mental retardation

Although definition of mental retardation (MR) is a controversy, classification on the basis of intelligence quotients (IQs) has been commonly used. IQ in the general population was distributed in the average of 100 and lesser than 70 were classified as MR. Mild MR is classified based on IQ as mild (50–70), moderate (35–49), severe (20–34), and profound (<20).[32] Mental sub-normality is defined by an IQ between 50 and 70.[33]

The considerable variations reported in the prevalence of MR in countries and regions from 2 to 85/1000, may be due to the variations in definitions and methodologies of studies and classification methods.[34] Maulik meta-analysis reported the prevalence of intellectual disability across 52 studies 10.37/1000 population.[35] The prevalence of mental disorders in Iran reported 21.3% in rural areas and 20.9% in urban areas.[36]

Idiopathic or undetermined MR occurs where there is no cause identified. The nonspecific MR refers to a subgroup that have no distinguishing physical or neurological causes, generally well grown, nondysmorphic, usually male children who have no other problems aside moderate or severe mental subnormality.[32] Grozeva et al. to identify genetic causes of MR screened a cohort of around 1000 individuals with moderate to severe MR and reported 113 pathogenic loss-of-function and 29 pathogenic missense variants.[37]

Bundey et al. reported that the recurrence of MR in the siblings of families with one or both parents affected was 37%. In contrast, for the index patients with no affected parent, the recurrence in siblings was 14.9%. According to the occurrence of MR in the relatives, they found that 13.3% of parents, 6.5% of aunts, 4.5% of uncles, and 2.2% of cousins went to schools for children with moderate learning difficulties.[33] Crow and Tolmie reported that recurrence risks to all siblings of a male proband with severe MR ranged between 3.55 and 14% in commonly quoted series. Following them, Turner and Partington reported the same risk around 3.5% and 17.8%. Knight et al. by telomeric probes of FISH showed that nonvisible chromosomal rearrangements by routine light microscope may account for up to 7% of undiagnosed MR.[38]

Rasic et al. reported that offspring of parents with severe mental illness, including schizophrenia, bipolar disorder, and major depressive disorder had 32% probability of developing these illness by adulthood.[39,40]

Diabetes mellitus

Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia due to defects in secretion and/or action of insulin.[41] It is one of the most common diseases in the world and fifth reason of global death per year (3,000,000 death/year). Diabetes will be explained in two types:

Type 1 diabetes (T1D), previously called Insulin Dependent DM (IDDM) primarily affects young people. GWASs have identified over 40 T1D risk loci.[42] The patients' siblings are at higher risk of developing the same disease when compared with the general population.[43]

Tillil and Köbberling said that regardless of age at onset, offspring of diabetic fathers always had an increased risk than offspring of mothers. They revealed lower age at onset (<25 years) was not associated with a higher risk to siblings.[44] Harjutsalo reported that a younger age at diagnosis, young-onset diabetes of parents, male gender, and older parental age at delivery increased the risk in siblings.[43] Observed risk ratio for monozygote twins of this type of probands is $\lambda m = 100$, for second-degree relatives is $\lambda 2 = 3$, equal with maximum and minimum risk ratio for relatives of type 1, respectively.[2]

Type 2 diabetes (T2D), previously called non-IDDM, is a major cause of morbidity and mortality in developed countries and also taking hold rapidly in the developing world. Around 90% of diabetic individuals have T2D, therefore no more than 10% can be accounted for monogenic forms such as maturity-onset diabetes of the young and mitochondrial diabetes.[45] The International Diabetes Federation estimates that in 2003, 194 million people had DM, and until 2025, 333 million people will have this disease.[46] Thomsen et al. identified a total of 45 genes involved in β-cell function of T2D, pointing to possible causal mechanisms at 37 related loci.[47]

Busfield et al. suggested a general population prevalence of 20%–30% and a sibling recurrence ratio of 1.8–2.5 using disease-gene frequency model and the community based prevalence data.[48]

The life-time risk of developing the disease in offspring of one parent with T2D is around 40%, greater if the mother is affected, and the risk reaching 70% if both parents have diabetes.[49]

Observed risk ratio for monozygote twins of T2D probands is $\lambda m = 10$, for first-degree and second-degree relatives are $\lambda 1 = 3.5$ and $\lambda 2 = 1.5$, respectively.[2] Jorde believed that the empirical recurrence risks for first-degree relatives of T2D are higher than those for T1D and are ranging from 15% to 40%.[1]

Asthma

Asthma is one of the most serious allergic diseases and the most common clinical syndrome due to environmental interaction and genetic factors.[50] According to Global Initiative for Asthma, asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role and it is characterized by increased responsiveness of the tracheobronchial tree to a multiplicity of stimuli and consequently difficulty in breathing.[51,52] More than 30 GWASs have been published on asthma and have identified 49 interesting genes playing the functionally relevant role.[53]

Worldwide, asthma cases are increasing at a rate of 50% every decade and according to the World Health Organization, by the year 2020, asthma, along with chronic obstructive pulmonary disease will become the third global leading cause of death.[54] The overall prevalence of asthma in the first degree relatives of asthmatic patients and the controls were 13% and 4% respectively.[54] Asthma prevalence rates reported by a wide variation: low prevalence in Asian countries (especially China and India: 2%–4%) and high prevalence in the United Kingdom, Canada, Australia, New Zealand, and other developed countries: 15%–20%.[55] Entezari et al. estimated overall prevalence of asthma symptoms in Iran as 13.14%.[56]

Ball et al. as part of the Tucson Children's Respiratory Study, concluded that exposure of young children to older children at home or other children at day care centers protects them against the development of clinical and frequent asthma in the future.[57]

Litonjua documented that maternal asthma strongly associated with asthma in offspring over all ages, while paternal asthma showed to be weakly associated. An additive effect was found on the risk of development of offspring's asthma when both parents were asthmatic.[55]

Coronary artery disease

Coronary artery disease (CAD) is the most common mortality cause in industrial countries and its prevalence is increasing fast in developing countries. Based on the Tehran Lipid and Glucose Study, the aged-adjusted prevalence of CAD in Iran was 21.8%.[58] The unstable angina and myocardial infarction (MI), two important shapes of this common disease resulted from atherosclerosis that is a degenerative condition by deposition of lipid and fibrous matrix in arterial vessel walls, and formation of atheromatous plaques.[59] Several risk factors, such as smoking, diabetes, and hypertension, abdominal obesity, the ApoB/ApoA1 ratio, a psychosocial index, fruit and vegetable intake, exercise, and regular alcohol consumption have been identified as traditional risk factors. The novel risk factors that are contributors to a hostile cardiovascular environment include air pollution,

climate change, HIV infection, psychosocial and economic stressors.[60] LeBlanc *et al*. identified 67 novel loci associated with CAD and 53 loci with significant effects in both CAD and at least 1 of low-density lipoprotein, high-density lipoprotein, triglycerides, type 2 DM, C-reactive protein, systolic blood pressure, and type 1 DM.[61]

Familial aggregation of disease has long been established. Studies in the 1960s showed that the first-degree relatives of patients have around 2–6-fold higher risk of the disease than those of matched controls. The familial aggregation increases with decreasing the age of the affected patients. While women have a lower frequency of CAD than men, the first-degree relatives of index women run a higher risk than those of the affected index men.[62] Fischer reported that siblings of MI patients presented a slightly more severe morphological manifestation of CAD than index cases.[63] Rissanen reported that the relative risks of CAD in brothers of probands in Southern Finland by age 55 years were 11.4, 8.3, and 1.3 depending on whether the diagnosis of MI in these siblings was made before 46 years, at 46–50 years, or 51–55 years of age, respectively.[64]

In a large-scale study on the selected polymorphisms on 4152 Japanese subjects, it has been shown that the risk of MI is significantly associated with the polymorphism in the connexin 37 gene in men and plasminogen-activator inhibitor type 1 and the stromelysin-1 genes polymorphisms in women.[65]

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic and systemic inflammatory disease with autoimmune feature and complex etiology characterized by joint swelling and tenderness, and synovial joints destruction, resulting to severe disability and premature mortality.[66,67] The most common manifestation of the RA is destructive inflammatory arthritis; and in particular, there is a substantial excess of infection and vascular disease; 50% of its mortality is referred to as cardiovascular disease.[68] Genome wide association studies using SNP have characterized more than a hundred loci associated with RA risk, most of which implicate immune mechanisms and some of which shared with other chronic inflammatory diseases.[69]

Although Jones *et al*. reported that there was no significant data for increasing familial risk of RA; "immune-genetic" studies showed weak association between HLA and community RA.[70] According to its relatively low familial aggregation, the genetic component has also been calculated by computing the value of λs. Some difficulties with disease definition and widely variation of λs resulted in its range from 2 to 17 by Seldin research and 5-10 by Jawaheer *et al*. study, although in total it has as 8.[68,71]

Lawrence believed that recurrence risk of excess sibling (Ks) was restricted to families of the probands who had severe disease, sero positive or erosive RA, but when the proband had mild disease, Ks was barely higher than the general population risk. In accordance, he reported the value for λs to be ~ 3 where the proband was seropositive and ~ 7 where the proband had seropositive, erosive RA, in keeping with polygenic susceptibility.[72]

Inflammatory bowel diseases

Inflammatory bowel disease (IBD) contains the chronic relapsing inflammation disorders of any part of the gastrointestinal tract and colon, respectively called Crohn's disease (CD) and ulcerative colitis (UC). They are common inflammatory disorders of the intestines characterized by a nonregulated mucosal immune response. Family history is a risk factor, with a maximum incidence in early adult life. Khor *et al*. offered insight into its mechanisms in mucosal immunity, including genetic factors interacting with microbial and environmental causes and biological checkpoints.[73] It accepted that disease occurs in the interaction between candidate genes, antigenic stimulus, and the cells of immune system.[74]

Liu *et al*. reported the trans-ancestry association study of IBD, with genome-wide or Immunochip genotype data from an extended cohort of European individuals and Immunochip data from individuals of East Asian, Indian or Iranian descent and implicated 38 loci in IBD risk for the first time.[75]

In the study by Yang *et al*. from Southern California in the first degree relatives of non-Jewish probands, the life time risks were 5.2% and 1.6% when probands had CD and UC, respectively.[76]

It has been reported that 75% of affected families with IBD are concordant for disease type, with the remaining 25% being mixed (one member with CD and another with UC). These data show a model of disease pathogenesis resulting from multiple susceptibility genes that some genes common to both CD and UC, and some separately were linked to one disease.[77]

Bridger *et al*. reported that smoking at diagnosis was associated with development of CD in all of the familial patients, with increases when analyzed for ileocaecal disease, fibrostenosis, and intestinal resection.[78]

Schizophrenia

Psychiatric disorders are considered as models for risk assessment of multifactorial disorders, because they are

common, complex and heterogeneous etiology, and involve complicated risk calculations. Schizophrenia characterized by around 1–2.5 standard deviation decline in the range of cognitive domains, including memory, executive function, verbal fluency, and attention/information processing.[79] It is perhaps the best studied of the psychiatric disorders and affects ~1% of the population. According to its frequency, general practitioners, psychiatrists, and other medical professionals may make referrals for genetics consultations to address a case of schizophrenia. Schizophrenia Working Group of the Psychiatric Genomics Consortium reported a multi-stage schizophrenia GWAS and identified 128 independent associations spanning 108 conservatively defined loci that meet genome-wide significance, 83 of them have not been previously reported.[80]

Although, empiric recurrence risks for schizophrenia are reasonably well established; these risks that take into account multiple different diagnoses within a family are generally not available. In addition, it is relatively a common several individuals within a three-generation family affected by mental illnesses, but empiric recurrence risks for schizophrenia are not available for more than a combination of two or more affected family members. Little empiric data are available to guide recurrence risk calculation where individuals on both sides of the family are affected. On the other hand, schizophrenia is clinically heterogeneous; thought to be in part, a result of underlying genetic heterogeneity, so when both sides of a family are affected, vulnerabilities conferred by each side may be different.[81]

A first-degree relative risk of a schizophrenic individual is about ten times the population risk. The discrepancies suggesting the use of an empiric risk range rather than a single risk number resulted from one study; for example, for an individual with a parent affected with schizophrenia, different studies have demonstrated empiric recurrence risks between 6% and 16%.[81]

Gershon and Alliey-Rodriguez reported that new structural mutations (*de novo* copy number variants (CNVs): Chromosomal microdeletions and microduplications) present in 4%–7% of patients with bipolar disorder, schizophrenia, or autism spectrum disorder and can occur almost anywhere in the genome.[82] For a person with this type of CNV, the absolute risk of these three mentioned diseases is 14% much higher than the general population risk. Rare CNVs have also been identified, that are generally not new mutations, but constitute very high effective risk factors, sometime up to 82%. The first rare CNV associated with schizophrenia on chromosome 22 was discovered at 1995 and then became apparent that rare CNVs were associated with many diseases, especially CNS diseases.[82]

Several of these rare CNVs with higher effects on disorder risk than common SNPs, are associated with some of the three psychiatric diseases mentioned here. Gershon and Alliey-Rodriguez introduced the bunch of rare CNV locus by higher effects on these three illness, including: 1q21.1, 3q29, 7q11.23, 15q11.2, 15q11.2-13.1, 15q13.3, 16p11.2, 17p12, 22q11.21, and 22q11.2.[82]

Cancers

Cancer traditionally introduced as a disease driven by the accumulation of genetic mutations and environment triggers that first ones have been considered the major causes of neoplasia and now expanded to incorporate the disruption of epigenetic regulatory mechanisms that are prevalent in cancer.[83] Different researches reported bunch of associated loci for each type of cancers.[84-86]

Cancer genetic consultations reached a recent development, in terms of information-giving data and counseling. Reasons given for the assessment and communication of different cancer risks include to guide decisions about the use of diagnosis methods, use of drug chemo prevention and to help decisions about hormone replacement therapy, prophylactic, and curative surgery. The assessment of cancer risk is based on the knowledge of the average risk of cancer for the general population; among the risk factors studied, the family history and its correlate, the genetic risk, have the highest impact on the onset of breast/ovarian/colorectal cancers.[87]

Healthcare providers have been encouraged to collect and systematically analyze the family history of cancer in families, so as to facilitate prevention efforts and screening of relatives. This goal usually at first, involves obtaining a cancer family history; then, determining whether a hereditary susceptibility exists; and finally, communicating this risk assessment to patients and their families.[88]

The 2002 update of the Swedish Family Cancer Database included 754 165 first invasive cancers in parents (diagnosed between 1961 and 2000) and 112 216 in offspring (diagnosed at the ages below 68 years between 1991 and 2000) and reported that when a parent is a proband, the overall standardized incidence ratio (SIR) is 2.02 for specific cancer. From 24 site specific familial cancer risks were significantly increased, Hodgkin's disease showed the highest SIR of 4.88, followed by testicular (4.26), and nonmedullary thyroid cancer (3.26). Esophageal cancer, ovarian cancer, and multiple myeloma had SIRs in excess of 3.00. Among the common cancers, SIRs were increased for female breast cancer (1.84), prostate cancer (2.45), colorectal adenocarcinomas (1.86), and the number of familial pairs ranged between 681 and 1779 for each. Among siblings, 20 of the 21 sites had a significant effect and testicular cancer showed the highest SIR of 9.28, followed by Hodgkin's disease (5.94), kidney (4.74), prostate (4.46), and ovarian

cancer (4.25). Also, age is an important risk factor for cancer and the cumulative risk will increase markedly at greater ages.[89]

Oncogenes and tumor suppressor genes are two important examples of mutations represented as molecular genetics causes of cancers.[90] Sukhai *et al*. designed an assessment protocol and classification system for somatic variants identified through next-generation sequencing molecular profiling of tumor-derived samples and applied these to a pilot dataset of somatic variants profiling of 158 tumor samples derived from their cancer center.[91]

Implementation of a unified management plan for familial cancers will be a challenge to the involved professionals and to the other involved parties.[89]

Table 1 shows the application details about some congenital and most common post child multifactorial disorders' recurrence risks.

CONCLUSION

Still, recurrence risk detection is one of the most important pensions of genetic counselor; and consultant will not be satisfied even though when they are informed about the disorder repetition risk in family. Although, new aspects of genetic techniques have been opened for diagnosis and analysis of inherited disorders; using empirical recurrence risks are the most important and available methods to evaluate pedigree of multifactorial, chromosomal, and unknown etiology disorders and predict relapsing of current disorder in the future. The recurrence risks of some common multifactorial genetic diseases which manifested due to interaction of genetic background and environmental causes are presented in the article.

Acknowledgments

Financial support and sponsorship

Conflicts of interest
The authors have no conflicts of interest.

Table 1: The recurrence risks of some common multifactorial genetic diseases

Multifactorial disease	Affected family member (%)					GP%	λs WTCCC, 2007	References
	Father	Mother	Sibs	Second degree	Third degree			
CHD								
AS	3	13-18	2			1		[15]
ASD	1.5	4-4.5	2.5					
AV	1	14	–					
Coaretation of aorta	2	4	2					
PDA	2.5	3.5-4	3					
PS	2	4-6.5	2					
TOF	1.5	2.5	2.5					
VSD	2	6-10	3					
Cleft lip/plate		4		0.7	0.3	0.1		[92]
Club foot		2.5		0.5	0.2	0.1		[1]
Autism		4				0.07-1.8		[93,94]
Hirschsprung		4		4.5		0.02		[95]
Mental retardation	37.4		18.8	6.4	2.2	0.2-8.5		[33,34,38]
DM								
Type 1	4-6	1-3	1-6	1.93	1.74	0.3-0.5	15	[1,2,4,96]
Type 2	7-13		10-15	1.36	1.14	0.2-5	3	[4,96-98]
Asthma	13		13	N/A	N/A	2-20		[54,55,99]
CAD	6	2	2.75			5	2-7	[4,62]
Rheumatoid arthritis	2-12 (4.9-7.6)					0.2-1	5-10	[3,4,100]
IBD								
Crohn's disease		5.2				0.003-0.043	17-35	[4,76,77]
UC		1.6				0.007-0.012		
Schizophrenia	6	6	9	2-6	2	1		[81,101,102]
Bipolar disorder		7-10				1		[103]
Cancer		2.48				0.93		[104]

GP = General population; λs WTCCC, 2007 = Estimated sibling recurrence risk reported by the Welcome Trust Case Control Consortium reported at 2007; CHD = Congenital heart diseases; AS = Aortic stenosis; ASD = Atrial septal defect; AV = Atrioventricular canal or dextroversion; PDA = Patent ductusarteriosus; PS = Pulmonary stenosis; TOF = Tetralogy of Fallott; VSD = Ventricular septal defect; DM = Diabetes mellitus; CAD = Coronary artery diseases; IBD = Inflammatory bowel diseases; UC = Ulcerative colitis; N/A = Not applicable

AUTHOR'S CONTRIBUTION

MB contribution in the conception of the work, conducting the study, revising the draft and approval of the final version of the manuscript.

REFERENCES

1. McCance KL, Huether SE. Pathophysiology: The Biologic Basis for Disease in Adults and Children. 5th ed. St. Louis, MO: Elsevier/Mosby; 2006. p. xxiv, 1780.
2. Rich SS. Mapping genes in diabetes. Genetic epidemiological perspective. Diabetes 1990;39:1315-9.
3. Dieudé P. Rheumatic diseases: Environment and genetics. Joint Bone Spine 2009;76:602-7.
4. Wellcome Trust Case Control Consortium. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature 2007;447:661-78.
5. Naghavi-Behzad M, Alizadeh M, Azami S, Foroughifar S, Ghasempour-Dabbaghi K, Karzad N, et al. Risk factors of congenital heart diseases: A case-control study inNorthwest Iran. J Cardiovasc Thorac Res 2013;5:5-9.
6. Gill HK, Splitt M, Sharland GK, Simpson JM. Patterns of recurrence of congenital heart disease: An analysis of 6,640 consecutive pregnancies evaluated by detailed fetal echocardiography. J Am Coll Cardiol 2003;42:923-9.
7. Edwards JJ, Gelb BD. Genetics of congenital heart disease. Curr Opin Cardiol 2016;31:235-41.
8. Nora JJ, Nora AH. Maternal transmission of congenital heart diseases: New recurrence risk figures and the questions of cytoplasmic inheritance and vulnerability to teratogens. Am J Cardiol 1987;59:459-63.
9. Gil-da-Silva-Lopes VL, Monlleo IL. Risk factors and the prevention of oral clefts. Braz Oral Res 2014;28:1-5.
10. Klotz CM, Wang X, Desensi RS, Grubs RE, Costello BJ, Marazita ML. Revisiting the recurrence risk of nonsyndromic cleft lip with or without cleft palate. Am J Med Genet A 2010;152A: 2697-702.
11. Mossey PA, Little J, Munger RG, Dixon MJ, Shaw WC. Cleft lip and palate. Lancet 2009;374:1773-85.
12. Wehby GL, Nyarko KA, Murray JC. Oral cleft recurrence risk and subsequent maternal fertility preferences and behavior in Brazil. Birth Defects Res A Clin Mol Teratol 2014;100:48-56.
13. Khazaei S, Shirani AM, Khazaei M, Najafi F. Incidence of cleft lip and palate in Iran. A meta-analysis. Saudi Med J 2011;32:390-3.
14. Setó-Salvia N, Stanier P. Genetics of cleft lip and/or cleft palate: Association with other common anomalies. Eur J Med Genet 2014;57:381-93.
15. de Araujo TK, Secolin R, Félix TM, de Souza LT, Fontes MÍ, Monlleó IL, et al. A multicentric association study between 39 genes and nonsyndromic cleft lip and palate in a Brazilian population. J Craniomaxillofac Surg 2016;44:16-20.
16. Chenevix-Trench G, Jones K, Green AC, Duffy DL, Martin NG. Cleft lip with or without cleft palate: Associations with transforming growth factor alpha and retinoic acid receptor loci. Am J Hum Genet 1992;51:1377-85.
17. Younkin SG, Scharpf RB, Schwender H, Parker MM, Scott AF, Marazita ML, et al. A genome-wide study of de novo deletions identifies a candidate locus for non-syndromic isolated cleft lip/palate risk. BMC Genet 2014;15:24.
18. Imbard A, Benoist JF, Blom HJ. Neural tube defects, folic acid and methylation. Int J Environ Res Public Health 2013;10:4352-89.
19. Fonseca EB, Raskin S, Zugaib M. Folic acid for the prevention of neural tube defects. Rev Bras Ginecol Obstet 2013;35:287-9.
20. Afshar M, Golalipour MJ, Farhud D. Epidemiologic aspects of neural tube defects in South East Iran. Neurosciences (Riyadh) 2006;11:289-92.
21. Lei Y, Finnell RH. New techniques for the study of neural tube defects. Adv Tech Biol Med 2016;4. pii: 157.
22. Janerich DT, Piper J. Shifting genetic patterns in anencephaly and spina bifida. J Med Genet 1978;15:101-5.
23. Seller MJ. Recurrence risks for neural tube defects in a genetic counseling clinic population. J Med Genet 1981;18:245-8.
24. Copp AJ, Stanier P, Greene ND. Neural tube defects: Recent advances, unsolved questions, and controversies. Lancet Neurol 2013;12:799-810.
25. Teckie G, Krause A, Kromberg JG. Neural tube defects in Gauteng, South Africa: Recurrence risks and associated factors. S Afr Med J 2013;103 12 Suppl 1:973-7.
26. Palmer RM. The genetics of talipes equinovarus. J Bone Joint Surg Am 1964;46:542-56.
27. Chapman C, Stott NS, Port RV, Nicol RO. Genetics of club foot in Maori and Pacific people. J Med Genet 2000;37:680-3.
28. Yong BC, Xun FX, Zhao LJ, Deng HW, Xu HW. A systematic review of association studies of common variants associated with idiopathic congenital talipes equinovarus (ictev) in humans in the past 30 years. Springerplus 2016;5:896.
29. Cooper A, Jones S. Foot disorders in childhood. Surgery (Oxford) 2014;32:46-9.
30. Lie RT, Wilcox AJ, Skjaerven R. A population-based study of the risk of recurrence of birth defects. N Engl J Med 1994;331:1-4.
31. Honein MA, Paulozzi LJ, Moore CA. Family history, maternal smoking, and clubfoot: An indication of a gene-environment interaction. Am J Epidemiol 2000;152:658-65.
32. Crow YJ, Tolmie JL. Recurrence risks in mental retardation. J Med Genet 1998;35:177-82.
33. Bundey S, Thake A, Todd J. The recurrence risks for mild idiopathic mental retardation. J Med Genet 1989;26:260-6.
34. Roeleveld N, Zielhuis GA, Gabreëls F. The prevalence of mental retardation: A critical review of recent literature. Dev Med Child Neurol 1997;39:125-32.
35. Maulik PK, Mascarenhas MN, Mathers CD, Dua T, Saxena S. Prevalence of intellectual disability: A meta-analysis of population-based studies. Res Dev Disabil 2011;32:419-36.
36. Noorbala AA, Bagheri Yazdi SA, Yasamy MT, Mohammad K. Mental health survey of the adult population in Iran. Br J Psychiatry 2004;184:70-3.
37. Grozeva D, Carss K, Spasic-Boskovic O, Tejada MI, Gecz J, Shaw M, et al. Targeted next-generation sequencing analysis of 1,000 individuals with intellectual disability. Hum Mutat 2015;36:1197-204.
38. Turner G, Partington M. Recurrence risks in undiagnosed mental retardation. J Med Genet 2000;37:E45.
39. Rasic D, Hajek T, Alda M, Uher R. Risk of mental illness in offspring of parents with schizophrenia, bipolar disorder, and major depressive disorder: A meta-analysis of family high-risk studies. Schizophr Bull 2014;40:28-38.
40. Costain G, Bassett AS. Individualizing recurrence risks for severe mental illness: Epidemiologic and molecular genetic approaches. Schizophr Bull 2014;40:21-3.
41. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2004;27 Suppl 1:S5-10.
42. Brorsson CA, Nielsen LB, Andersen ML, Kaur S, Bergholdt R, Hansen L, et al. Genetic risk score modelling for disease progression in new-onset type 1 diabetes patients: Increased genetic load of islet-expressed and cytokine-regulated candidate genes predicts poorer glycemic control. J Diabetes Res 2016;2016:9570424.

43. Harjutsalo V, Podar T, Tuomilehto J. Cumulative incidence of type 1 diabetes in 10,168 siblings of Finnish young-onset type 1 diabetic patients. Diabetes 2005;54:563-9.

44. Tillil H, Köbberling J. Age-corrected empirical genetic risk estimates for first-degree relatives of IDDM patients. Diabetes 1987;36:93-9.

45. Stumvoll M, Goldstein BJ, van Haeften TW. Type 2 diabetes: Principles of pathogenesis and therapy. Lancet 2005;365:1333-46.

46. Yoon KH, Lee JH, Kim JW, Cho JH, Choi YH, Ko SH, et al. Epidemic obesity and type 2 diabetes in Asia. Lancet 2006;368:1681-8.

47. Thomsen SK, Ceroni A, van de Bunt M, Burrows C, Barrett A, Scharfmann R, et al. Systematic functional characterization of candidate causal genes for type 2 diabetes risk variants. Diabetes 2016;65:3805-11.

48. Busfield F, Duffy DL, Kesting JB, Walker SM, Lovelock PK, Good D, et al. A genomewide search for type 2 diabetes-susceptibility genes in indigenous Australians. Am J Hum Genet 2002;70:349-57.

49. Ridderstråle M, Groop L. Genetic dissection of type 2 diabetes. Mol Cell Endocrinol 2009;297:10-7.

50. Bijanzadeh M, Ramachandra NB, Mahesh PA, Mysore RS, Kumar P, Manjunath BS, et al. Association of IL-4 and ADAM33 gene polymorphisms with asthma in an Indian population. Lung 2010;188:415-22.

51. Bijanzadeh M, Ramachandra NB, Mahesh PA, Savitha MR, Manjunath BS, Jayaraj BS. Lack of association between asthma and ABO blood group. Lung 2009;187:389-92.

52. Hargreave FE, Nair P. The definition and diagnosis of asthma. Clin Exp Allergy 2009;39:1652-8.

53. Sanz-Lozano CS, García-Solaesa V, Davila I, Isidoro-García M. Applications of molecular genetics to the study of asthma. Methods Mol Biol 2016;1434:1-13.

54. Bijanzadeh M, Mahesh PA, Ramachandra NB. An understanding of the genetic basis of asthma. Indian J Med Res 2011;134:149-61.

55. Subbarao P, Mandhane PJ, Sears MR. Asthma: Epidemiology, etiology and risk factors. CMAJ 2009;181:E181-90.

56. Entezari A, Mehrabi Y, Varesvazirian M, Pourpak Z, Moin M. A systematic review of recent asthma symptom surveys in Iranian children. Chron Respir Dis 2009;6:109-14.

57. Ball TM, Castro-Rodriguez JA, Griffith KA, Holberg CJ, Martinez FD, Wright AL. Siblings, day-care attendance, and the risk of asthma and wheezing during childhood. N Engl J Med 2000;343:538-43.

58. Hadaegh F, Harati H, Ghanbarian A, Azizi F. Prevalence of coronary heart disease among Tehran adults: Tehran Lipid and Glucose Study. East Mediterr Health J 2009;15:157-66.

59. Farrall M, Green FR, Peden JF, Olsson PG, Clarke R, Hellenius ML, et al. Genome-wide mapping of susceptibility to coronary artery disease identifies a novel replicated locus on chromosome 17. PLoS Genet 2006;2:e72.

60. Gersh BJ, Sliwa K, Mayosi BM, Yusuf S. Novel therapeutic concepts: The epidemic of cardiovascular disease in the developing world: Global implications. Eur Heart J 2010;31:642-8.

61. LeBlanc M, Zuber V, Andreassen BK, Witoelar A, Zeng L, Bettella F, et al. Identifying novel gene variants in coronary artery disease and shared genes with several cardiovascular risk factors. Circ Res 2016;118:83-94.

62. Sankaranarayanan K, Chakraborty R, Boerwinkle EA. Ionizing radiation and genetic risks. VI. Chronic multifactorial diseases: A review of epidemiological and genetical aspects of coronary heart disease, essential hypertension and diabetes mellitus. Mutat Res 1999;436:21-57.

63. Fischer M, Broeckel U, Holmer S, Baessler A, Hengstenberg C, Mayer B, et al. Distinct heritable patterns of angiographic coronary artery disease in families with myocardial infarction. Circulation 2005;111:855-62.

64. Hauser ER, Mooser V, Crossman DC, Haines JL, Jones CH, Winkelmann BR, et al. Design of the genetics of early onset cardiovascular disease (GENECARD) study. Am Heart J 2003;145:602-13.

65. Yamada Y, Izawa H, Ichihara S, Takatsu F, Ishihara H, Hirayama H, et al. Prediction of the risk of myocardial infarction from polymorphisms in candidate genes. N Engl J Med 2002;347:1916-23.

66. Jawaheer D, Seldin MF, Amos CI, Chen WV, Shigeta R, Monteiro J, et al. A genomewide screen in multiplex rheumatoid arthritis families suggests genetic overlap with other autoimmune diseases. Am J Hum Genet 2001;68:927-36.

67. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO 3rd, et al. 2010 Rheumatoid arthritis classification criteria: An American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010;62:2569-81.

68. Harney S, Wordsworth BP. Genetic epidemiology of rheumatoid arthritis. Tissue Antigens 2002;60:465-73.

69. Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. Lancet 2016;388:2023-2038.

70. Jones MA, Silman AJ, Whiting S, Barrett EM, Symmons DP. Occurrence of rheumatoid arthritis is not increased in the first degree relatives of a population based inception cohort of inflammatory polyarthritis. Ann Rheum Dis 1996;55:89-93.

71. Jawaheer D, Li W, Graham RR, Chen W, Damle A, Xiao X, et al. Dissecting the genetic complexity of the association between human leukocyte antigens and rheumatoid arthritis. Am J Hum Genet 2002;71:585-94.

72. Wordsworth P, Bell J. Polygenic susceptibility in rheumatoid arthritis. Ann Rheum Dis 1991;50:343-6.

73. Khor B, Gardet A, Xavier RJ. Genetics and pathogenesis of inflammatory bowel disease. Nature 2011;474:307-17.

74. Satsangi J, Jewell DP, Rosenberg WM, Bell JI. Genetics of inflammatory bowel disease. Gut 1994;35:696-700.

75. Liu JZ, van Sommeren S, Huang H, Ng SC, Alberts R, Takahashi A, et al. Association analyses identify 38 susceptibility loci for inflammatory bowel disease and highlight shared genetic risk across populations. Nat Genet 2015;47:979-86.

76. Yang H, McElree C, Roth MP, Shanahan F, Targan SR, Rotter JI. Familial empirical risks for inflammatory bowel disease: Differences between Jews and non-Jews. Gut 1993;34:517-24.

77. Bonen DK, Cho JH. The genetics of inflammatory bowel disease. Gastroenterology 2003;124:521-36.

78. Bridger S, Lee JC, Bjarnason I, Jones JE, Macpherson AJ. In siblings with similar genetic susceptibility for inflammatory bowel disease, smokers tend to develop crohn's disease and non-smokers develop ulcerative colitis. Gut 2002;51:21-5.

79. Stuchlik A, Sumiyoshi T. Cognitive deficits in schizophrenia and other neuropsychiatric disorders: Convergence of preclinical and clinical evidence. Front Behav Neurosci 2014;8:444.

80. Schizophrenia Working Group of the Psychiatric Genomics Consortium. Biological insights from 108 schizophrenia-associated genetic loci. Nature 2014;511:421-7.

81. Austin JC, Peay HL. Applications and limitations of empiric data in provision of recurrence risks for schizophrenia: A practical review for healthcare professionals providing clinical psychiatric genetics consultations. Clin Genet 2006;70:177-87.

82. Gershon ES, Alliey-Rodriguez N. New ethical issues for genetic counseling in common mental disorders. Am J Psychiatry 2013;170:968-76.

83. You JS, Jones PA. Cancer genetics and epigenetics: Two sides of the same coin? Cancer Cell 2012;22:9-20.

84. Wang Z, Seow WJ, Shiraishi K, Hsiung CA, Matsuo K, Liu J, et al. Meta-analysis of genome-wide association studies identifies multiple lung cancer susceptibility loci in never-smoking Asian women. Hum Mol Genet 2016;25:620-9.

85. Kar SP, Beesley J, Amin Al Olama A, Michailidou K, Tyrer J, Kote-Jarai Z, *et al.* Genome-wide meta-analyses of breast, ovarian, and prostate cancer association studies identify multiple new susceptibility loci shared by at least two cancer types. Cancer Discov 2016;6:1052-67.

86. Lesseur C, Diergaarde B, Olshan AF, Wünsch-Filho V, Ness AR, Liu G, *et al.* Genome-wide association analyses identify new susceptibility loci for oral cavity and pharyngeal cancer. Nat Genet 2016;48:1544-50.

87. Julian-Reynier C, Welkenhuysen M, Hagoel L, Decruyenaere M, Hopwood P; CRISCOM Working Group. Risk communication strategies: State of the art and effectiveness in the context of cancer genetic services. Eur J Hum Genet 2003;11:725-36.

88. Hampel H, Sweet K, Westman JA, Offit K, Eng C. Referral for cancer genetics consultation: A review and compilation of risk assessment criteria. J Med Genet 2004;41:81-91.

89. Hemminki K, Eng C. Clinical genetic counselling for familial cancers requires reliable data on familial cancer risks and general action plans. J Med Genet 2004;41:801-7.

90. Turnpenny PD, Ellard S. Emery's Elements of Medical Genetics. 14th ed. Philadelphia, PA: Elsevier/Churchill Livingstone; 2012. p. xiii, 445.

91. Sukhai MA, Craddock KJ, Thomas M, Hansen AR, Zhang T, Siu L, *et al.* A classification system for clinical relevance of somatic variants identified in molecular profiling of cancer. Genet Med 2016;18:128-36.

92. Nussbaum RL, McInnes RR, Willard HF, Thompson MW, Hamosh A. Thompson and Thompson Genetics in Medicine. 7th ed. Philadelphia: Saunders/Elsevier; 2007. p. xi, 585.

93. Pickles A, Bolton P, Macdonald H, Bailey A, Le Couteur A, Sim CH, *et al.* Latent-class analysis of recurrence risks for complex phenotypes with selection and measurement error: A twin and family history study of autism. Am J Hum Genet 1995;57:717-26.

94. Neggers YH. Increasing prevalence, changes in diagnostic criteria, and nutritional risk factors for autism spectrum disorders. ISRN Nutr 2014;2014:514026.

95. Badner JA, Sieber WK, Garver KL, Chakravarti A. A genetic study of Hirschsprung disease. Am J Hum Genet 1990;46:568-80.

96. Weires MB, Tausch B, Haug PJ, Edwards CQ, Wetter T, Cannon-Albright LA. Familiality of diabetes mellitus. Exp Clin Endocrinol Diabetes 2007;115:634-40.

97. Chern MM, Anderson VE, Barbosa J. Empirical risk for insulin-dependent diabetes (IDD) in sibs. Further definition of genetic heterogeneity. Diabetes 1982;31:1115-8.

98. Fagot-Campagna A, Pettitt DJ, Engelgau MM, Burrows NR, Geiss LS, Valdez R, *et al.* Type 2 diabetes among North American children and adolescents: An epidemiologic review and a public health perspective. J Pediatr 2000;136:664-72.

99. Burke W, Fesinmeyer M, Reed K, Hampson L, Carlsten C. Family history as a predictor of asthma risk. Am J Prev Med 2003;24:160-9.

100. Deighton CM, Walker DJ. The familial nature of rheumatoid arthritis. Ann Rheum Dis 1991;50:62-5.

101. Kirov G, Grozeva D, Norton N, Ivanov D, Mantripragada KK, Holmans P; International Schizophrenia Consortium; Wellcome Trust Case Control Consortium, *et al.* Support for the involvement of large copy number variants in the pathogenesis of schizophrenia. Hum Mol Genet 2009;18:1497-503.

102. Kim Y, Zerwas S, Trace SE, Sullivan PF. Schizophrenia genetics: Where next? Schizophr Bull 2011;37:456-63.

103. Smith EN, Bloss CS, Badner JA, Barrett T, Belmonte PL, Berrettini W, *et al.* Genome-wide association study of bipolar disorder in European American and African American individuals. Mol Psychiatry 2009;14:755-63.

104. Draper GJ, Heaf MM, Kinnier Wilson LM. Occurrence of childhood cancers among sibs and estimation of familial risks. J Med Genet 1977;14:81-90.