

The recurrence risk of genetic complex diseases

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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

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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]

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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 Wellcome 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 cystica 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 λ s. Some difficulties with disease definition and widely variation of λ s 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 λ s 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 Immuchip genotype data from an extended cohort of European individuals and Immuchip 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.

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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	-					
Coarctation 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 Wellcome 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 ductus arteriosus; PS = Pulmonary stenosis; TOF = Tetralogy of Fallot; 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.

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