**REVIEW OF SELECTED COMMON DISEASES FOR NONSYNDROMIC MENDELIAN SUSCEPTIBILITY LOCI**

**(ORGANIZED BY AGE OF ONSET AND WHO-ICD10 CLASSIFICATION)**

**I. Certain infections and parasitic diseases**

**Early and late onset**

Human body is exposed to infectious diseases starting in early childhood years. Infectious diseases such as respiratory syncytial virus, croup, scarlet fever, pertussis, pneumonia, malaria, measles, meningococcal disease and tuberculosis are responsible for significant childhood mortality and morbidity in the world. For example, pneumonia and diarrhea accounted for one-third of all under five year old child deaths in 2008 (World Health Organization). Although infectious diseases are clearly caused by external biological agents, it is increasingly recognized that genetic susceptibility also plays a role in their pathogenesis. Recently, Mendelian disorders of infectious disease susceptibility predisposing to specific infections have been described. However, these Mendelian diseases either predispose to several different infectious agents or have phenotypic findings dissimilar to common infections or have low penetrance.

For example, pneumococcal disease predisposition by *IRAK4* and *MyD88* deficiencies also predispose to *Staphylococcus aureus* and *Pseudomonas aeruginosa* infections and, in contrast to sporadic invasive bacterial diseases, systemic inflammatory signs are weak in these Mendelian diseases (Picard et al., 2010). Herpes simplex encephalitis associated genes (*TRIF*, *TLR3*, *TRAF3*, *UNC-93B*) are described in a limited number of cases. However, the penetrance of these gene mutations appears very low (for example, only two of seven *TLR3* mutation carriers developed herpes encephalitis) (Alcais et al., 2010). Mendelian susceptibility to mycobacterial diseases is a rare syndrome characterized by predisposition to infections caused by weakly virulent mycobacteria, such as BCG vaccines and nontuberculous environmental mycobacteria in addition to the more virulent mycobacterial species *Mycobacterium tuberculosis*. Systemic salmonellosis, either typhoidal or, more commonly, nontyphoidal, is observed in about 50% of the cases, including in subset who has no signs of mycobacterial disease before the diagnosis of salmonellosis (Al-Muhsen & Casanova 2008). Mendelian susceptibility to isolated tuberculosis is not recognized.

Epidermodysplasia Verruciformis (EV), a rare disorder characterized by predisposition to human papillomavirus (HPV) infection, is caused by *EVER1* and *EVER2* mutations. The physical findings are limited to the skin and rarely occur on the mucosa. The skin lesions, especially in the sun-exposed areas often transform to squamous cell carcinoma. In contrast, the common skin warts are benign conditions. HPV types 16 and 18 are high-risk types of HPV responsible for most high-grade intraepithelial lesions that may progress to carcinomas, particularly in the anogenital and/or mucosal locations. These HPV types are not described in EV. Thus, EV does not appear to represent a Mendelian phenocopy neither for common skin warts nor for the common HPV-related malignancies (Medscape). Similarly, X-linked lymphoproliferative disorder leads to fatal consequences after Epstein-Barr virus (EBV) infection. In contrast, EBV-related infectious mononucleosis is a benign condition.

Either X-linked properdin deficiency or autosomal recessive defects in the terminal components of the complement cascade (C5–C9), which form the membrane attack complex, selectively predispose to invasive meningococcal disease. However, meningoccal disease occurs in less than 53% of those with properdin deficiency. When the probands are removed, the risk is even smaller (18%). Similarly late complement component deficiency causes meningoccal disease in 57-71% when probands are included and in 38% when probands are excluded. (Fijen et al., 1999)

In summary, although variations in certain genes play an important role in determining susceptibility for common infections, including malaria and HIV, and although Mendelian susceptibility to certain infections are documented, currently there is no definitive evidence for a gene mutation that selectively predisposes to a single common infectious disease in a highly penetrant fashion.

**II. Neoplasms**

Malignant neoplasms account for more than 10% of all deaths worldwide. Age is a major risk factor for common malignancies. Most carcinomas affect people over 55 years old. Both genetic and environmental factors play a significant role in pathogenesis of malignant neoplasms. Tobacco use and such viruses as human papillomavirus and hepatitis B virus account for significant fraction of preventable malignancies in developing countries. A small fraction of malignancies is caused by germ line mutations.

**Early onset**

Cancer is uncommon in younger ages. For example, approximately 0.5% of all cancer occurs in children aged 15 or younger in industrialized countries (Stiller 2004). However, cancer related deaths account for more than 10% of all deaths in this age group. Acute lymphoblastic leukemia (ALL) accounts for majority of all childhood cancer in many populations. Other common childhood malignant neoplasms include lymphoma, CNS tumors, neuroblastoma, retinoblastoma, Wilms’ tumor, hepatic tumors, osteosarcoma, Ewing sarcoma, soft tissue sarcomas and germ cell tumors.

Many somatic alterations (translocations, mutations) are discovered in ALL and acute myeloid leukemia (AML), though nonsyndromic germ line predisposition genes are unknown. Down syndrome and such Mendelian diseases as Li-Fraumeni syndrome, neurofibromatosis type 1 (NF1), ataxia telangiectasia (AT), Fanconi anemia and hereditary immunodeficiencies increase childhood leukemia risk. However, these diseases predispose to multiple malignancies and/or are associated with syndromic features. Other tumor susceptibility syndromes that predispose to certain common childhood tumors include Gorlin syndrome (medulloblastoma), NF1 and NF2 (pilocytic astrocytoma, meningioma), hereditary non-polyposis colorectal cancer (HNPCC) (glioma), Dennys-Drash syndrome and WAGR (Wilms tumor).

Familial juvenile polyposis syndrome is characterized by development of multiple polyps in the gastrointestinal tract. Juvenile polyposis carries a high risk of malignant transformation. Common juvenile polyps, however, are usually solitary hamartomatous polyps that carry no significant risk of malignant transformation, indicating different biological behavior. In addition, up to 20% of juvenile polyposis patients have congenital abnormalities. Therefore, familial juvenile polyposis and sporadic hamartamatous polyps are considered distinct disorders (Calva & Howe 2008).

Recently, activating mutations in *ALK* are associated with familial and sporadic neuroblastoma, a neuroectodermal tumor that often develops in the adrenal gland, mostly in children below 10 years old. Mutation analysis of the *ALK* gene in extended families reveal that the penetrance is approximately 50% (Devoto et al., 2011), suggesting that environment or modifier loci play an important role in determining which carrier develops neuroblastoma. Furthermore, syndromic consequences of germ line activating *ALK* mutations is recently described suggesting that neuroblastoma susceptibility may not be the only phenotypic consequence (de Pontual et al., 2011). Similarly, mutations in *SUFU* predispose to isolated desmoplastic medulloblastomas with a low-penetrance (30%) (Brugieres et al., 2010). In summary, there is no evidence for a Mendelian mutation that selectively predisposes to a common childhood malignancy in a nonsyndromic and highly penetrant fashion.

**Late onset**

Cancer is the primary cause of death among women aged 40-79 and among men aged 60-79. The most common malignancies are prostate, lung and colorectal cancers in men and breast, lung and colorectal cancers in women (World Health Organization). Other common malignant neoplasms include melanoma of skin, hematologic neoplasms, oral cancer, pancreatic cancer, kidney cancer, ovarian cancer, uterine cancer, thyroid cancer and urinary bladder cancer. Several rare autosomal dominant cancer predisposition syndromes are associated with increased risk of malignancies in multiple organ sites. Li-Fraumeni syndrome, familial melanoma, familial adenomatous polyposis, Von-Hippel Lindau syndrome, inherited breast and ovarian cancers, multiple endocrine neoplasia type I and type II, Gorlin syndrome, Cowden syndrome, familial diffuse type gastric cancer, Peutz-Jeghers syndrome, hereditary non-polyposis colorectal cancer syndromes are all characterized by development of multiple organ site malignancies (Scriver et al., 2001). For example, Li-Fraumeni syndrome, caused by germ line *TP53* gene mutations, increases breast cancer risk as well as many other tumors including brain tumors, leukemias and sarcomas.

Two inherited cancer syndromes primarily cause a common malignancy involving one organ with lower frequency of a second unrelated cancer. Familial melanoma syndrome, caused by *CDKN2A* germ line mutations, also increases risk of pancreatic cancer in certain individuals. Familial diffuse type gastric cancer, caused by *CDH1* germ line mutations, also increases risk of lobular breast cancer.

Activating germ line mutations in the *MET* gene predispose only to papillary renal carcinoma without a consistently increased risk of other cancers or syndromic manifestations (Schmidt et al., 1999). Approximately13% of renal cancers, which primarily affect older individuals with an median age of 64 years (Medscape), are papilllary type (Cheville et al., 2003). Multiple *MET* mutations are linked to development of familial papillary renal cancer in a highly penetrant fashion (over 90%) (Schmidt et al., 1998). Thus, *MET* gene mutations represent a Mendelian phenocopy for papillary type renal carcinoma.

**III. Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism**

These diseases primarily include nutritional, hemolytic, aplastic and other anemias; coagulation and other hemorrhagic conditions; and other diseases of blood and blood forming organs. Most diseases in this category become apparent in early ages. This general category includes many primarily genetic and individually uncommon disorders such as hemoglobinopathies, coagulation defects and congenital and acquired abnormalities of platelets. Nutritional anemias could result from primary dietary deficiencies of iron, vitamin B12 and folate or are secondary to blood loss, congenital factor deficiencies, malabsorption or drugs. Acquired hemolytic anemias can be caused by drugs, autoimmunity, hemolytic uremic syndrome, paroxysmal nocturnal hemoglobinuria and non-autoimmune hemolytic anemias.

**Early onset**

*Hemolytic uremic syndrome (HUS):* HUS is generally diagnosed in infancy and early childhood and is typically characterized by microangiopathic hemolytic anemia, thrombocytopenia and acute renal failure. Two forms of HUS are present. The typical HUS involves diarrhea; while atypical HUS does not. HUS with diarrhea is the common form, accounting for 95% of cases in children. The typical HUS is preceded by a prodrome of diarrhea, most commonly caused by a shiga-toxin producing *Escherichia coli* infection (Medscape). There is no evidence for a Mendelian phenocopy for the typical HUS.

Atypical HUS can occur at any age and represents 5 -10% of HUS in children, but the majority of aHUS patients are adults. aHUS is a disease of complement alternative pathway. Mutations in certain genes in complement alternative pathway are implicated in atypical HUS with a low penetrance (less than 60%). (Sullivan et al., 2011,Loirat & Fremeaux-Bacchi 2011)

**Late onset**

*Paroxysmal nocturnal hemoglobinuria (PNH):* PNH is clinically characterized by hemolytic anemia, thrombosis and pancytopenia. PNH can be diagnosed in any age but most often in adults with a median age of 42 years (Medscape). The disease is caused by inactivating somatic mutations of the *PIGA* gene leading to abnormal glycosylphosphatidylinositol (GPI) biosynthesis and loss of certain membrane associated antigens. No highly penetrant genes predisposing to nonsyndromic PNH is described (Johnston et al., 2012).

**IV. Endocrine, nutritional and metabolic diseases**

These diseases primarily include diabetes mellitus; thyroid and other endocrine gland disorders; obesity and metabolic disorders. Obesity and diabetes mellitus are major contributors to chronic disease and disability in the world.

**Early onset**

*Type 1 diabetes mellitus (DM1)*: DM1 is a chronic multisystem metabolic disorder that results from autoimmune destruction of the pancreatic beta cells leading to insulin deficiency. It is distinguished from type 2 diabetes by a tendency to develop ketosis and ketoacidosis, if insulin is withdrawn (Medscape). There are strong genetic influences on susceptibility to DM1 with a major role played by HLA class II genes. In addition, more than 40 non-HLA genes modify risk of DM1 (Steck & Rewers 2011). Despite extensive genetic studies, non-syndromic Mendelian loci have yet to be described for DM1 (Pociot et al., 2010).

*Polycystic ovary syndrome (PCOS):* PCOS is a common chronic disease involving 5-10% of reproductive age women and is characterized by anovulation, hyperandrogenism and infertility. There is a strong association between PCOS and obesity, insulin resistance, type 2 diabetes mellitus and cardiovascular disease. Despite evidence for a genetic contribution to PCOS, no Mendelian gene has ever been identified (Ewens et al., 2010). Genes involved in steroidogenesis, steroid hormone action, gonadotropin, insulin pathways, energy homeostasis and chronic inflammation were implicated, though no single predisposition gene for PCOS is universally replicated (Prapas et al., 2009).

**Late onset**

*Obesity:* Obesity, a worldwide epidemic, is a major risk factor for type 2 diabetes, hypertension, stroke and cardiovascular disease. Although energy intake and physical activity are key factors for obesity, genes clearly play a role in modifying risk. Approximately 20-25% of children and 30-35% of adults older than 19 years of age are currently overweight or obese. Obesity rate is higher among Black, Hispanic and women. Obesity prevalence increases with increased age until 64 years of age. For example, while obesity rate is 18.2% among 18-29 year olds, it increases to 30.8% among 45-64 year olds (Mendes). Heredity plays an important role in susceptibility to common forms of obesity and mostly involves multiple interacting loci (Chung 2012).

A few examples of monogenic susceptibility to obesity are discovered in recent years. The genes underlying rare human monogenic forms of obesity include leptin (*LEP*), leptin receptor (*LEPR*), pro-opiomelanocortin (*POMC*), proconvertase 1 (*PC1*) and melanocortin 4 receptor (*MC4R*). Mutations in these genes, except *MC4R*, have been rarely described in human and often result in syndromic features such as delayed puberty (*LEP*, *LEPR*), short stature (*LEPR*) and adrenal insufficiency and red hair (*POMC*). Multiple mutations in *MC4R* were described in non-syndromic early onset obesity associated with hyperphagia, increased fat mass, increased lean mass, increased bone mineral density, increased linear growth and hyperinsulinemia. Analysis of multiple extended families with obesity and *MC4R* mutations demonstrate high but sometimes incomplete penetrance (above 80%; often 100% in many families) (Sina et al., 1999,Farooqi et al., 2003,Vaisse et al., 2000). Thus, *MC4R* mutations define a Mendelian phenocopy for obesity.

*Type 2 diabetes mellitus (DM2):* DM2 is a common complex disorder, characterized by combination of defects in insulin secretion and peripheral resistance to insulin action. Frequency of DM2 is expected to increase further in the near future with aging trends. Genetic factors play an important role in determining DM2 susceptibility (Imamura & Maeda 2011,Ahlqvist,Ahluwalia & Groop 2011). For example, monozygotic twin concordance rate is about 70%, whereas dizygotic twin concordance rate is about 20-30%. The genetics of DM2 is also influenced by multiple susceptibility loci. Recent genome-wide association studies have identified over 40 loci influencing risk of DM2.

Monogenic forms of diabetes include maturity onset diabetes of the young (*MODY*) and those caused by mutations leading to abnormal insulin processing and defective ATP-sensitive potassium channels. In addition, mutations in *WFS1* and mitochondrial DNA cause diabetes with extra-pancreatic features. MODY mutations primarily reduce pancreatic beta cell function and involve genes for glucokinase and various transcription factors (Murphy, Ellard & Hattersley, 2008). MODY differs from DM1 by nonketosis and lack of islet autoantibodies and from DM2 by normal insulin sensitivity, insulinopenia and leanness of patients. Thus, clinical and laboratory characteristics of MODY and other predisposing Mendelian loci appear to be distinct from DM1 and DM2.

**V. Mental and behavioral disorders**

Substance abuse, psychosis, mood disorders, autism and other behavioral disorders are common. They often have early age at onset and bring tremendous costs to societies throughout the world (Kessler et al., 2009). This category involves certain diseases including autism, schizophrenia, bipolar disorder, major depression, neurotic disorders and substance abuse that have been extensively studied to identify the underlying susceptibility genes.

**Early onset**

*Schizophrenia:* Genetic contribution to schizophrenia is substantial, complex and has been intensively studied for decades. Recent genome-wide association studies implicate several loci including MHC regions, *NRGN* and *TCF4*. In addition, copy number variations (CNVs) are increased in schizophrenia. The CNVs were identified in multiple chromosomal regions and were also linked to other neurodevelopmental or psychiatric diseases (e.g. autism and mental retardation) (Girard et al., 2011). More recently, large scale sequencing studies found mutations in certain candidate genes (*MAOB* and *SHANK3*) in isolated cases or small multiplex families. Altogether, however, no evidence exists for a highly penetrant Mendelian susceptibility gene in schizophrenia.

The *DISC1* gene broken by a balanced chromosomal translocation breakpoint, t(1;11), in a large Scottish family has been identified as a candidate for mental illness. The penetrance of the translocation is close to 0.5 (Blackwood et al., 2001). The translocation co-segregates with multiple diseases including schizophrenia, bipolar disorder and major depression, indicating that disruption of *DISC1* does not cause a Mendelian phenocopy for any specific psychiatric disorder but is associated with several clinical phenotypes that cross the traditional diagnostic boundaries (Chubb et al., 2008). Additional highly penetrant *DISC1* mutations have yet to be discovered in other families, but rare variants were observed in a bipolar study sample (in five of 504 cases) (Song et al., 2010).

*Bipolar disorder:* Several genome wide association studies are performed and certain genes including *ANK3* and *CACNA1C* are implicated. Highly penetrant gene mutations predisposing to bipolar disorder have yet to be described (O'Donovan, Craddock & Owen 2009; Nothen et al., 2010).

*Autism spectrum disorders (ASD):* Heritability of ASD is high with an MZ twin concordance rate of up to 60%. Many interacting genetic loci likely underlie the genetic susceptibility. Over the years, linkage, candidate gene, whole genome association studies and recently exome sequencing efforts have implicated hundreds of loci. However, no single highly-penetrant gene has ever been identified. For example, *SHANK3* gene mutations are implicated in one *de novo* case and in one affected sibling pair. Notably, multiple rare *SHANK3* nonsynonymous variants, which were transmitted from the healthy parents, were also identified in the affected individuals. (Durand et al., 2007). Similarly, a *de novo* mutation is considered pathogenic, but nine other nonsynonymous variants transmitted from healthy parents were considered non-pathogenic in another study (Moessner et al., 2007). These findings highlight the difficulties in understanding the phenotypic consequences of extremely rare variants. Even though some of the implicated rare variants may increase ASD susceptibility, no single *SHANK3* variant has been shown to segregate in an extended family in a highly penetrant fashion.

*Obsessive compulsive* disorder (OCD): OCD and the associated disorders such as trichotillomania, Tourette syndrome and body dysmorphic disorder are prevalent chronic disabling disorders that belong to a broad WHO diagnostic subcategory of neurotic, stress-related and somatoform disorders. Genetics of OCD is complex involving multiple loci. Recently, rare *SAPAP3* gene variants are implicated in increased susceptibility to OCD and trichtillomania. There is no evidence that these rare variants in *SAPAP3* or other genes co-segregate with disease in extended families (Zuchner et al., 2009).

*Tourette Syndrome (TS):* Family and twin studies indicate strong genetic component to TS. The *SLITRK1* gene is implicated by its proximity to a translocation breakpoint and by identification of two rare variants in TS patients (Abelson et al., 2005). Subsequent studies failed to confirm the association of these rare variants with TS (O'Rourke et al., 2009). Currently, there is no evidence for a highly penetrant susceptibility gene for TS.

*Anorexia Nervosa (AN):* AN, an eating disorder characterized by a weight loss of at least 15% of expected body weight associated with a pathologic fear of weight gain, carries an increased risk of morbidity and mortality. Although family and twin studies show increased heritability of AN, no major genes have ever been implicated (Pinheiro, Root & Bulik 2009).

*Stuttering:* Stuttering, a common disorder of speech fluency, is characterized by pathologic repetition and prolongation of speech elements (Fisher 2010). Family and twin studies indicate a strong and complex genetic component to susceptibility to stuttering. Recently, mutations in certain lysosomal enzyme genes were shown to be enriched among stutterers. However, these mutations do not show a Mendelian transmission. The only extended family described thus far (Kang et al., 2010)) shows partial co-segregation of a mutation in *GNPTAB* with the stuttering phenotype. In this family, several affected individuals do not have the gene mutation while some homozygous mutation carriers are phenotypically normal. Overall, 25/36 carriers of at least one *GNPTAB* mutation have stuttering (68% penetrance). Three affected individuals have no *GNPTAB* mutation. Thus, these variants are incompletely penetrant and probably act in concert with other variants to develop stuttering.

*Specific language impairment (SLI):* SLI is characterized by delayed and sometimes incomprehensible language skills in children who have no hearing loss or other developmental delays. *FOXP2* gene is first implicated by discovery of a missense mutation in a three generation family whose members had problems with speech, language and in controlling movement and sequencing of orofacial muscles (verbal dyspraxia). In some members, a decline in nonverbal intelligence is also noted (Newbury, Fisher & Monaco 2010). A second small family is also described when a heterozygous *FOXP2* mutation was discovered among cases of verbal dyspraxia (Fisher & Scharff 2009). Importantly, dyspraxia is not seen in most sporadic SLI cases (Fisher & Scharff 2009). Altogether, the phenotypic abnormalities cross boundaries of multiple diagnostic categories and indicate that *FOXP2* mutations predispose to a complex syndrome involving speech impairment rather than to nonsyndromic SLI. Accordingly, no *FOXP2* mutations were discovered among SLI cases (Newbury et al., 2002). A major gene that predisposes to SLI in a nonsyndromic fashion has yet to be described.

*Developmental Dyslexia:* DD is characterized by specific impairment of reading ability significantly below the expectation compared to similar age, intelligence and education levels. DD is highly heritable. Although many loci and some genes were implicated, no major gene for DD is ever identified (Scerri & Schulte-Korne 2010).

**Early and late onset**

*Substance abuse disorders (SUDs)*: Alcohol and substance abuse primarily affects the young but they can be present both in the young and in older individuals. Substance dependence to both legal (e.g. nicotine, caffeine, alcohol, over the counter drugs) and illicit substances (e.g. cocaine, hallucinogens) has strong genetic influences. The heritability estimates for SUDs are 40-55%, although environmental exposure modifies these genetic influences substantially. Many susceptibility loci have been implicated by candidate gene and genome wide association studies. No major gene that predisposes to SUDs in a highly penetrant fashion has ever been described (Kendler et al., 2012).

**VI. Diseases of the nervous system**

This category includes many common neurological disorders including epilepsy, Alzheimer disease, Parkinson's disease, multiple sclerosis, migraine and cerebrovascular disease that significantly contribute to global health burden. Genetics of these disorders are extensively studied.

**Early onset**

*Migraine:* Migraine is a common episodic neurovascular disorder with age at onset peaking at 5-17 years. Two main subtypes are characterized by the absence or presence of an aura, transient neurological symptoms that occur prior to or during a migraine attack. Epidemiological studies support a significant role for heredity, which likely involves multiple genetic loci. Highly penetrant gene mutations for common subtypes of migraine have yet to be identified.

Familial hemiplegic migraine (FHM) is a genetic form of migraine characterized by migraine with aura and motor weakness (hemiplegia). Both familial and sporadic forms are thought to be caused by mutations in various genes. (de Vries et al., 2009). The presence of hemiplegia distinguishes FHM from the common forms of migraine. In contrast to common migraine which affects more than 10% of population, the migraine with hemiplegia is a rare condition with an estimated prevalence of 0.01%. (Lykke Thomsen et al., 2002). In addition, the consequences of FHM gene mutations appear to be pleiotropic: mutations in *CACNA1A*, the most commonly mutated FHM locus, are also associated with episodic ataxia; mutations in *ATP1A2* can cause epilepsy, coma, ataxia and mental retardation and *SCN1A* is also a causative locus for epilepsy. Finally, mutations involved in FHM loci could not be clearly linked to common migraine subtypes (Maher & Griffiths 2011). Thus, mutations in FHM loci are associated with unusual clinical features not encountered in common migraine and thus they likely do not represent Mendelian phenocopies for common migraines.

*Epilepsy:* Epilepsy is characterized by recurrent unprovoked seizures and has a lifetime prevalence of approximately 3%. Epilepsy is clinically highly heterogeneous and classified either as primary/idiopathic epilepsy (no gross neuropathological abnormalities) or as symptomatic epilepsy (associated with gross pathologic abnormalities). The classification schemes for epilepsy have changed over time and the phenotype definitions are not always straightforward. Idiopathic generalized epilepsy (IGE) is believed to have a strong genetic basis. IGE has several major subtypes including childhood absence epilepsy, juvenile myoclonic epilepsy, generalized epilepsy with febrile seizures plus (GEFS+) and tonic–clonic seizures. GEFS+ is largely genetic in origin and defines a broad range of epileptic phenotypes ranging from febrile seizures to severe myoclonic epilepsy of childhood (Dravet syndrome) (Pandolfo 2011). Germ line mutations in ions channels are identified in IGE but the predisposed phenotypes span multiple clinical forms for most genes.

Because of the clinical and genetic heterogeneity of epilepsy syndromes, here the evaluation for Mendelian phenocopies is confined to childhood and juvenile absence epilepsy and juvenile myoclonic epilepsy (JME), the most common and clinically well-defined forms of childhood epilepsy. These two forms appear clinically and genetically distinct with minimal overlap (Crunelli & Leresche 2002; Winawer et al., 2003). No gene has yet been implicated that faithfully predisposes to only JME or idiopathic absence epilepsies. Recently, mutations in *EFHC1* are identified in a subset of JME families. When clinical seizures or electrophysiological abnormalities are considered, the penetrance was 78% in an extended family. However, clinical penetrance was less than 65% in two extended families (Suzuki et al., 2004). There is also evidence that *EFHC1* mutations may also predispose to other epilepsy subtypes (Stogmann et al., 2006).

Rare variants enriched in the *CACNA1H* gene are implicated in idiopathic absence seizures, but penetrance appears low and the predisposition involves multiple epilepsy types (Heron et al., 2007). Mutations in *GLUT1*/*SLC2A1*, which encodes the glucose transporter type 1, are implicated in 10% of absence seizures but the phenotype is pleiotropic and includes paroxysmal exertional dyspnea, ataxia, movement disorders and intellectual disability (Valente & Albanese 2011) . In summary, there is no definitive evidence that mutations in any gene recapitulate the common idiopathic epilepsies in a nonsyndromic, nonpleiotropic and highly penetrant fashion, although marked clinical and genetic heterogeneity warrants further evaluation for Mendelian phenocopies with accumulation of new genetic and clinical data.

*Multiple sclerosis (MS):* MS is an immune-mediated demyelinating disorder characterized by waxing and waning neurological deficits. MS is more common in women who have an average disease onset of 29 years of age. Both genetic and environmental factors play an important role in etiology of MS. Single genes with a large effect size have yet to be identified, although recent genome-wise association studies identified many susceptibility regions including replicated HLA loci (Baranzini, 2011).

**Late onset**

*Alzheimer disease (AD):* AD is the primary cause of dementia in the elderly and is characterized by progressive loss of cognitive functions, behavioral impairment and memory deterioration. The incidence of AD has been increasing throughout the world and is expected to reach epidemic proportions as the world population ages. Majority of the patients are over 65 years old. Genetic causation has been established in early onset AD, which tends to be more severe but is clinically indistinguishable from later onset AD. Thus far, mutations in *APP*, *PSEN1* and *PSEN2* are linked to the development of early onset AD in a highly penetrant (>85%) and non-syndromic fashion. Allelic variation in *APOE* also plays an important role in modifying risk of AD. Many other susceptibility loci have been implicated as a result of recent genome-wide association studies (Reitz, Brayne & Mayeux 2011). Thus, mutations in *APP*, *PSEN1* and *PSEN2* represent Mendelian phenocopies for AD.

*Parkinson disease (PD):* PD is the second most common neurodegenerative disease with a high prevalence in older individuals (4% of population affected by the age of 85 years). PD is typically characterized by tremor, rigidity, bradykinesia, and postural instability, although nonmotor features including depression, autonomic insufficiency, cognitive impairment, olfactory deficits, psychosis, and sleep disturbance are also very common. PD risk is multifactorial with approximately 20% of patients reporting a family history (Bekris, Mata & Zabetian 2010). There are several rare monogenic forms of PD.

Mutations in *SNCA (PARK1)* and *LRRK2 (PARK8)* cause autosomal dominant PD; while mutations in Parkin *(PARK2)*, *PINK1 (PARK6)*, and *DJ-1 (PARK7)* lead to autosomal recessive PD in a non-syndromic fashion, closely resembling idiopathic PD (Klein & Westenberger 2012). At least 10 other PD risk loci are implicated, subset of which is linked to PD with complex/syndromic phenotypes. Mutations in nonsyndromic genes cause either early onset PD (*SNCA, Parkin, PINK1* and *DJ-1*) or classical PD (*LRRK2*). The age-dependent penetrance is over 80% for mutations in *SNCA*, *Parkin*, *PINK1* and *DJ-1*; while more variable for *LRRK2* (Bekris, Mata & Zabetian 2010,Pankratz & Foroud 2007). Thus, mutations in *SNCA, Parkin, PINK1* and *DJ-1* represent Mendelian phenocopies for PD*.*

*Frontotemporal Dementia (FTD)*: FTD (formerly Pick's disease) is predominantly a presenile disorder characterized by behavioral changes and cognitive impairment, especially involving language and executive functions, and is associated with neurodegeneration in the frontal and/or temporal lobe cortices.

Several clinical variants including behavioral, semantic dementia, progressive and non-fluent aphasia define a heterogeneous spectrum of FTD. There is evidence that corticobasal degeneration and supranuclear palsy may also belong to the FTD complex (Kertesz 2003). FTD has two main pathological subtypes: frontotemporal lobar degeneration (FTLD) with tau inclusions (FTLD-tau); and FTLD with neuronal inclusions that are positive for ubiquitin and TAR-DNA binding protein of 43 kDA (FTLD-TDP) (Seelaar et al., 2011). A positive family history is present in up to 50% of cases, but an autosomal dominant transmission pattern is seen 10-27% of all FTD patients.

Mutations in *MAPT*, the gene encoding the microtubule associated protein tau cause autosomal dominant FTD in a highly penetrant fashion (>90%). The inclusions associated with *MAPT* mutations are predominantly Tau-positive. Mutations in *GRN* gene, which encodes progranulin, also cause FTD in an autosomal dominant highly penetrant (>90%) fashion. The inclusions associated with *GRN* mutations are tau-negative and ubiquitine and TDP-43 positive. Mutations in *MAPT* and *GRN* cause FTD that is clinically similar to sporadic cases. Parkinsonism may or may not be associated with *MAPT* and *GRN* mutations (Boeve & Hutton 2008). Notably, parkinsonism and other extrapyramidal signs are common in FTD, especially in the tauopathy subgroup, and are observed in 82% of all patients with disease progression (Forman et al., 2006). Thus, mutations in *MAPT* and *GRN* represent Mendelian phenocopies for FTD.

*Amyotrophic lateral sclerosis (ALS):* ALS is a common and fatal degenerative motor neuron disease. ALS is characterized by insidious, painless progressive muscle weakness affecting one or more body regions without loss of sensory abilities. ALS is a sporadic disease in approximately 90% of the cases. Familial forms, often with an autosomal dominant transmission pattern, account for up to 10%.

Clinical features of sporadic and familial forms are similar except for an earlier age at onset in familial cases. Features observed in familial cases including extrapyramidal, cerebellar and cognitive findings are also seen in sporadic cases (Andersen & Al-Chalabi 2011).

Hereditary ALS is most commonly associated with autosomal dominant mutations in *SOD1*, *FUS* and *TARDBP* genes. Highly penetrant mutations in each gene are described in extended families (de Belleroche, Orrell & King 1995; Aggarwal & Nicholson 2005; Suzuki et al., 2010). While mutations in *SOD1* selectively predisposes to early onset ALS; those in *FUS* and *TARDBP* may also predispose to frontotemporal dementia (Millecamps et al., 2010). *SOD1* carriers have an 80% risk of developing ALS by age 85 years (Valdmanis & Rouleau 2008). Thus, mutations in *SOD1* represent a Mendelian phenocopy for ALS.

**VII. Diseases of the eye and adnexa**

Eye diseases represent an important public health problem throughout the world. While communicable eye diseases such as river blindness and trachoma are common in less developed countries; glaucoma, cataract, age-related macular degeneration and diabetic retinopathy are major causes of visual deficiencies in industrialized countries.

**Early onset**

*Strabismus:* Strabismus, misalignment of the eyes, is a very common childhood disorder involving up to 4% of population. Strabismus has concomitant and incomitant forms. Concomitant strabismus occurs when the angle of deviation of the eyes remains constant, regardless of the position of gaze, and includes the common forms of strabismus, such as esotropia, exotropia, hyperopia, microstrabismus, and monofixation syndrome. Concomitant strabismus accounts for approximately 95% of all cases (Engle, 2007). Most cases of nonsyndromic strabismus are sporadic, although epidemiologic, twin and family studies support a significant hereditary component. The genetics of concomitant strabismus in the absence of obvious structural abnormalities of the eye or brain remains poorly understood. A locus on 7p (STBMS1) is implicated but the underlying gene remains unknown (Rice et al., 2009). Currently, no Mendelian phenocopy has been identified for concomitant strabismus.

In contrast, several Mendelian forms of the less common incomitant strabismus, where ocular misalignment changes upon gaze position, have been recognized including congenital fibrosis of the extraocular muscles, horizontal gaze palsy with progressive scoliosis, and familial Duane retraction syndrome. Mendelian forms of the incomitant strabismus result from mutations in genes crucial for the development of ocular motor neurons and their axonal connections. These congenital incomitant strabismus syndromes are now referred to as the congenital cranial dysinnervation disorders.

**Late onset**

*Glaucoma:* Glaucoma is a leading cause of blindness in the world and is characterized by loss of retinal ganglion cells. Elevated intraocular pressure is the most important risk factor for glaucoma. Glaucoma affects 4-10% of the population older than 40 years in USA. Primary open-angle glaucoma (POAG), in which the iridocorneal angle is unobstructed and normal in appearance but aqueous outflow is impaired, is the most prevalent form of glaucoma (Kwon et al., 2009). Age older than 40 years is a risk factor for development of POAG (Medscape), whereas juvenile POAG is rare. Black race and positive family history of POAG is also a risk factor for POAG, although the heritability is complex.

Analysis of extended families with autosomal dominant juvenile POAG led to identification of mutations in the myocilin (*MYOC*) gene, which account for approximately 4% of adult and 10% of juvenile POAG. *MYOC* mutations are associated with greater elevations in intraocular pressure relative to adult-onset POAG. Age dependent penetrance of *MYOC* mutations is close to 100% (Adam et al., 1997; de Vasconcellos et al., 2003). Thus, *MYOC* mutations represent a Mendelian phenocopy for POAG*.*

**VIII. Diseases of the ear and mastoid process**

**Early onset**

*Otitis media (OM*): OM, the second most common disease of childhood, is often a recurrent disease. One third of children experience 6 or more episodes of OM by age 7. In less developed nations, OM is extremely common and leads to major mortality because of intracranial complications (World Health Organization). Although heritability plays an important role in OM susceptibility, the underlying genetics is complex and no Mendelian phenocopy is ever described (Rye et al., 2011).

**Late onset**

*Age related hearing loss (ARHL, presbycusis):* ARHL is a sensorineural hearing impairment in the elderly characterized by bilateral high-frequency hearing loss resulting in impairment in speech discrimination. ARHL is an age related common disorder. The disease starts between age 50 and 60 and approximately 25-30% of people aged 65-74 years may have impaired hearing (Zahnert, 2011).

Mutations in the *DFNA5* cause exon skipping and lead to autosomal dominant non-syndromic hearing impairment in a sensorineural, progressive, nonsyndromic and highly-penetrant fashion (van Camp et al., 1995). The hearing impairment starts in high frequencies between 5 and 15 years of age. Thus, mutations in *DFNA5* cause Mendelian phenocopies by leading to development of hearing loss that closely resembles the most typical type of ARHL (Uchida et al., 2011).

**IX. Diseases of the circulatory system**

Cardiovascular diseases, including heart disease and stroke, are among the major causes of death and disability around the world. This broad diagnostic category includes rheumatic fever, hypertensive diseases, ischemic heart diseases, pulmonary heart disease and diseases of pulmonary circulation, cerebrovascular diseases or stroke, diseases of arteries, arterioles and capillaries, and congenital malformations or birth defects of the circulatory system.

**Early onset**

*Acute Rheumatic Fever (ARF):* ARF is an inflammatory disorder that may develop after a Streptococcus infection (such as strep throat or scarlet fever) and can involve heart, joints, skin, and brain. The peak age of ARF is 6-20 years. ARF rarely occurs after 30 years of age. The incidence and mortality from rheumatic heart disease (RHD) has declined substantially through public health and sanitary improvements. However, RHD still accounts for 25-50% of all cardiac admissions internationally and continues to be a major public health concern in Middle East, India, parts of Africa and South America (Medscape). Significant heritability is implicated through twin studies but little is known about the susceptibility genes. Several susceptibility loci are considered but no Mendelian phenocopy is ever described (Guilherme, Ramasawmy & Kalil, 2007).

**Late onset**

*Hypertension (HT):* HT, sustained increase in blood pressure, is one of the most common diseases with major public health impact. HT often is seen in 30-50 year olds; while complicated HT is seen in even older subjects (40-60 year olds) (Medscape). Family and twin studies estimate 30-40% heritabilities. More than 20 monogenic forms of hypertension are discovered and highlighted the important role of renal salt metabolism in pathogenesis of HT. In contrast, essential HT reflects aberrancies in multiple regulatory systems including kidney, central and sympathetic nervous systems and contractile processes of vasculature. Possible contributions are also made by immune and inflammatory response pathways and skin microenvironment related to sodium excretion. Thus, it is unclear whether the rare Mendelian forms of HT can be considered Mendelian phenocopies for the common essential HT (Coffman, 2011).

*Coronary artery disease (CAD):* Atherosclerosis is significantly associated with CAD. CAD or atherosclerotic heart disease, the major form of ischemic heart disease, is the leading cause of death in many countries. An increase in total to high-density lipoprotein cholesterol ratio, hypertension, cigarette smoking, excess weight, elevated blood sugar levels, lack of exercise, stress, electrocardiographic abnormalities, and other factors are associated with the development of CAD (Castelli, 1984). Although atherosclerosis begins in early ages, clinical manifestations of CAD become apparent often in fifth decade or in older ages.

Familial hypercholesterolemia (FH) is primarily an autosomal dominant disorder characterized by increased low-density lipoprotein (LDL) cholesterol levels and premature CAD as a result of germ line mutations affecting lipoprotein metabolism. Thus far, loss-of-function mutations in LDL receptor (*LDLR*) and apolipoprotein B-100 genes and gain-of-function mutations in proprotein convertase subtilisin/kexin type 9 (*PCSK9*) gene are linked to accelerated atherosclerosis and premature CAD in a nonsyndromic fashion. Penetrance of *LDLR* mutations for hypercholesterolemia is approximately 1, while penetrance for development of CAD by age 65 is 0.85 for men and 0.5 for women (Civeira & International Panel on Management of Familial Hypercholesterolemia 2004). Penetrance of *PCSK9* mutations for the development of CAD is even higher than the penetrance of *LDLR* mutations (Humphries et al., 2006) and approaches 1 in certain families (Timms et al., 2004). Thus, mutations in *LDLR* and *PCSK9* represent Mendelian phenocopies for CAD.

*Stroke:* Cerebrovascular disease and stroke, a major cause of disability, are strongly associated with dementia, age-related cognitive decline and late onset epilepsy. Atherosclerosis, cardioembolism and small-vessel disease are the major underlying causes of stroke. A significant genetic component, including major gene effects, exists in predisposition to stroke (Chabriat et al., 2009).

Small vessel disease results from either arteriolar occlusion or widespread incomplete infarction of the white matter caused by critical stenosis of medullary arterioles and hypoperfusion (Binswanger's disease) (Roman et al., 2002), leading to lacunar infarcts and deep white matter changes. Since lacunar infarcts represent 20-30% of symptomatic strokes, small vessel disease is considered as an important subtype of cerebrovascular disease (Chui, 2007).

Mutations in the *NOTCH3* gene predispose to a heritable small-vessel disease known as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). CADASIL is characterized by recurrent strokes and ischemic attacks, progressive cognitive decline and psychiatric disturbances. It appears that no cognitive feature in CADASIL uniquely distinguish it from sporadic small vessel disease (Charlton et al., 2006). Cerebral small vessel disease-related brain lesions such as white matter lesions and lacunes are common findings by magnetic resonance imaging in the elderly. For example, white matter lesions, leukoencephalopathy or leukoaraiosis are seen in up to 44% of patients with stroke in general (Leys et al., 1999). Overall, the radiological, histopathologic and clinical phenotypes of the age-related cerebral small vessel disease remarkably resemble CADASIL (Schmidt et al., 2011). The penetrance of *NOTCH3* mutations is very high and approaches 1 by age 30-40 when carriers are evaluated by magnetic resonance imaging (MRI) (Chabriat et al., 1995). Thus, *NOTCH3* mutations represent aMendelian phenocopyfor small-vessel type stroke.

**X. Diseases of the respiratory system**

Respiratory system diseases significantly impact mortality and morbidity in all age groups. This category includes respiratory infections including upper and lower respiratory tract infections, influenza, and pneumonia; chronic lower respiratory diseases including bronchitis, emphysema, asthma and bronchiectasis; lung diseases caused by external agents; interstitial lung diseases; and pleural diseases.

**Early onset**

*Asthma:* Asthma is one of the most common childhood chronic diseases. Asthma has significant genetic contributions, with heritability estimates ranging from 35% to 95%. However, identification of specific genetic variations contributing to risk has been challenging. Thus far no Mendelian asthma susceptibility gene has been identified (Ober & Yao, 2011).

**Late onset**

*Chronic lower respiratory diseases:* Emphysema and chronic bronchitis (chronic obstructive pulmonary disease (COPD)) significantly contribute to adult morbidity. Genetic contribution is thought to play an important role in pathogenesis of lower respiratory diseases. However, Mendelian susceptibility genes have yet to be identified. The only gene confirmed to influence COPD susceptibility is *SERPINA1*, which encodes alpha1-antitrypsin. Several other loci are implicated by recent genome wide association studies (Silverman et al., 2011).

**XI. Diseases of the digestive system**

Diseases of the digestive system cover a wide spectrum of disorders involving oropharynx, gastrointestinal tract, liver, biliary system and pancreas. Collectively, these disorders represent a major public health burden. Especially, peptic ulcer disease, pancreatitis, diverticular disease, abdominal wall hernia, gastroesophageal reflux disease, gallstones, inflammatory bowel disease, appendicitis are common diseases of major public health concern.

**Early onset**

*Caries:* Dental caries is the most common chronic disease of childhood. Although dental caries is not generally a life threatening disease, spread of odontogenic infection can lead to sepsis, deep abscesses and airway compromise. Multiple factors are involved in etiology of caries, including nutrition, tooth morphology, oral hygiene and other factors, although twin studies also reveal a strong genetic component. No mendelian predisposition locus has ever been identified for isolated dental caries. However, association studies implicate some susceptibility variants (Wendell et al., 2010).

*Small Bowel Malrotation* (SBM): SBM results from failure of normal rotation of the small intestines during embryonic development and poses a great risk for midgut volvulus. Most cases are diagnosed by 1 year of age. Multiple identical twins concordant for SBM is reported suggesting a role for hereditary factors (Smith,Long & Nwomeh 2006). Most malrotations are reported in syndromic associations. Isolated SBM occurs in ~30% of cases (Ford et al., 1992). There have been a few reports of familial segregation of non-syndromic SBM but no major gene has been identified. (Martin & Shaw-Smith 2010)

*Appendicitis*: Appendicitis, acute inflammation of the appendix, is a common and potentially life threatening condition mostly affecting pediatric and young adult populations. There is evidence of genetic contribution to the etiology of appendicitis, possibly more prominent in females than in males, as evidenced by complex segregation analysis and twin studies. However, limited genetic research has been undertaken to identify the underlying susceptibility genes (Oldmeadow et al., 2009).

**Late onset**

*Pancreatitis*: Acute pancreatitis (AP) is characterized by autodigestion of pancreas caused by abnormal secretion of zymogen granules leading to acinar cell injury. The recurrent attacks of AP characterize chronic pancreatitis. AP is most often associated with chronic alcohol use and biliary stones, although the exact cause may not be known in a substantial number of cases. The median age of onset is influenced by the underlying etiology, but often is over 30 years of age (Medscape). Gain of function mutations in the cationic trypsinogen gene (*PRSS1*) lead to premature activation of trypsinogen to trypsin and cause early onset autosomal dominant nonsyndromic pancreatitis with a penetrance of at least 80% (Rebours et al., 2009). Thus, mutations in *PRSS1* represent a Mendelian phenocopyfor pancreatitis.

*Inflammatory bowel disease (IBD):* IBD is a common, idiopathic, possibly autoimmune disease characterized by inflammation involving the gastrointestinal tract. The 2 major types are ulcerative colitis (UC) and Crohn’s disease (CD). Most IBD cases are first diagnosed in young adults, although a secondary peak occurs in older individuals. The mean age at diagnosis is over 33.4 years to 45 years for UC and 5 to 10 years later for UC (Loftus, 2004). IBD has strong genetic and environmental influences. Some genetic susceptibility loci are shared between CD and UC but others appear specific to UC or CD. The most prominent susceptibility gene for IBD is the *NOD2* gene in CD susceptibility. At least of one of three main *NOD2* variants (Arg702Trp, Gly908Arg and Leu1007incC) is found in 25%-45% of CD Caucasian patients and in only 15%-20% of healthy subjects (Nunes et al., 2011). Mendelian predisposition loci for IBD have not been described.

**XII. Diseases of the skin and subcutaneous tissue**

Skin diseases are associated with significant financial burden to society and can cause severe psychological and emotional disturbances and even death. There are approximately 3000 skin diseases that belong to the WHO-defined diagnostic category including infections, bullous disorders, dermatitis and eczema, papulosquamous disorders, urticaria and erythema, radiation-related disorders and skin appendage disorders.

**Early onset**

*Atopic dermatitis (AD):* AD is a common pruritic disease that often starts in early ages and characterized by eczematous lesions, dry skin and thickening of the skin. Pathogenesis of AD is poorly understood but immunological and hereditary factors are suspected to play an important role. Haploinsufficiency of the filaggrin (*FLG*) gene is linked to predisposition to development of moderate to severe AD with or without the compounding phenotype of asthma with an estimated odds ratio of 3.12 (Rodriguez et al., 2009). Significant fraction of moderate to severe eczema cases (45.7–56%) carries one or more *FLG* null mutations. *FLG* homozygous mutations cause ichthyosis vulgaris (IV) with high penetrance. Notably, heterozygous FLG mutations also cause IV in a variably penetrant fashion. IV is a relatively common Mendelian skin disorder characterized by abnormal keratinization. Thus, haploinsufficiency caused by *FLG* null-mutations, that have high population frequency in certain Northern European countries, predispose both to moderate to severe AD and to IV in a variably penetrant fashion, consistent with pleiotropy (Brown & McLean 2009). There is no evidence for a gene that predisposes to AD in a highly penetrant and nonsyndromic, nonpleiotropic fashion.

*Psoriasis:* Psoriasis is a common chronic inflammatory multisystem disease primarily involving skin of elbows, knees and scalp. Although it can start at any age, young adulthood is the most common period of disease onset (Medscape). Variations in several loci such as HLA region and in *IL12B* and *IL23R* genes associate with increased risk. Highly penetrant Mendelian loci have not been discovered

(Roberson & Bowcock 2010).

**Late onset**

Bullous disorders: Common bullous skin disorders including pemphigus vulgaris and bullous pemphigoid usually affect the older people and have complex etiology involving genetic and environmental factors with autoimmunity playing an important role in their pathogenesis (Sinha 2011; Zakka, Reche & Ahmed 2011).

**XIII. Diseases of the muculoskeletal system and connective tissue**

This broad category includes arthropathies, systemic connective tissue disorders, disorders of back/spine (dorsopathies), disorders of muscles and other soft tissues and disorders of bones and cartilage. Musculoskeletal and connective tissue disorders such as arthritis and osteoporosis represent significant disease burden to society in terms of disability and work loss.

**Early onset**

*Ankylosing spondylitis (AS): AS* is a common chronic multisystem inflammatory disorder often involving the axial skeleton but can also have extra-articular and extra-skeletal manifestations such as uveitis and aortitis. AS often affects young males. The average age at disease onset is 26 years, although the diagnosis may be delayed (Medscape). The etiology of AS is obscure but genetics, especially the presence of HLA-B27, plays an important role. Many other non-HLA genes are recently implicated in predisposition to AS, but no Mendelian loci have ever been described (Thomas & Brown, 2010).

*Idiopathic adolescent Scoliosis (IAS):* IAS is a common disorder characterized by pathologic structural curvature of the spine in otherwise healthy children. It is often diagnosed at or around puberty, more commonly in girls. IAS is often seen in multiple members of a family suggesting genetic influence. Etiology is obscure (Weinstein et al., 2008). Linkage analyses have implicated genetic heterogeneity with suggestions of several monogenic loci. However, the underlying genes have yet to be identified (Edery et al., 2011).

**Late onset**

*Thrombotic Thrombocytopenic Purpura (TTP):* TTP is closely related to hemolytic uremic syndrome (HUS) with a distinct pathogenesis. TTP is characterized by the pentad of microangiopathic hemolytic anemia, thrombocytopenic purpura, neurologic abnormalities, fever, and renal disease. Renal abnormalities tend to be more severe than in HUS. In contrast to HUS, TTP mostly affects older people with an average age at onset 40 years (Medscape).

TTP patients have unusually large multimers of von Willebrand factor (vWF) in their plasma. Patients with TTP have a defective plasma protease that normally degrades these ultralarge vWF multimers. In hereditary TTP, mutations in the gene encoding a protease known as *ADAMTS13* (a disintegrinlike and metalloprotease with thrombospondin type 1 motif 13), have been described. In the more common sporadic form, an antibody inhibitor can be isolated in most patients. Mutations in the *ADAMTS13* gene cause TTP in an autosomal recessive fashion with a penetrance of %95 (Levy et al., 2001). Thus, *ADAMTS13* mutations represent a Mendelian phenocopy for TTP.

*Systemic lupus erythematosus (SLE):* SLE is a complex multifactorial chronic disease characterized by inflammation of multiple organs including kidneys, joints, blood, skin, serosal surfaces and central nervous system and by the presence of anti-nuclear of antibodies (ANA). SLE primarily affects women in reproductive age, although it can also affect children and older individuals. Although SLE often is diagnosed in black females in reproductive ages, the average age at onset is over 40 years in whites and males (Pons-Estel et al., 2010). Another study estimates the average age at onset of SLE as 31 years (Petri, 2002). Kidney involvement is the most common cause of lupus-associated mortality and morbidity.

SLE has a major heritable component as shown by family and twin studies (Flesher et al., 2010). However, the genetics of SLE is complex. Recent genome wide association studies have implicated many loci affecting the disease risk. In addition, rare gene mutations involving the early components of the classical complement pathway (C1q, C4 and C2) were implicated in pathogenesis of SLE. SLE associated with complement factor deficiencies is often very early onset and is characterized by susceptibility to recurrent bacterial infections. Especially, C1q deficiency is strongly linked to SLE and immune deficiency. C1q deficiency can arise from loss-of-function mutations in any of the three genes (C1qA, C1qB and C1qC) encoding the polypeptide chains which assemble to make the C1q protein. Joint analysis of 63 cases with C1q deficiency demonstrates a high incidence of SLE or SLE-like disease (approximately 88%) suggesting high penetrance of the underlying mutations (Schejbel et al., 2011). Although genetic analysis of extended families would be needed to more accurately define the penetrance and the phenotypic consequences of C1q mutations, results thus far suggest that C1q mutations define Mendelian phenocopies for SLE. More recently, a single fully-penetrant homozygous mutation in the *DNASE1L3* gene is also implicated in extended consanguineous Arab families (Al-Mayouf et al., 2011). Discovery of additional mutations would also qualify *DNASE1L3* as a Mendelian phenocopy for SLE.

*Inclusion body myositis (IBM)*: IBM is an acquired slowly progressive myopathic process characterized by weakness or impairment of muscle function and by the presence of rimmed-vacuoles by muscle pathologic examination. The affected muscles vary but asymmetric involvement of knee and ankle extensors and wrist and finger flexors are common. Eventually diffuse proximal and distal weaknesses develop in most cases (Medscape). Swallowing difficulties contribute to morbidity. IBM is the most common acquired myopathy in patients older than 50 years with a prevalence of up to 35 per million.

Hereditary IBM (hIBM) is an autosomal recessive form caused by highly penetrant (approximately 80%) mutations in the UDP-N-acetylglucosamine 2-epimerase/N-N-acetylmannosamine kinase (*GNE*) gene (Eisenberg et al., 2001). hIBM is also characterized by progressive muscle weakness and muscle pathology including rimmed vacuoles. Unlike sporadic IBM, the quadriceps muscle is often spared. Recent genotype-phenotype analysis indicates, however, that the quadriceps muscle can also be affected in hIBM suggesting a broad phenotypic overlap between hereditary and sporadic IBM (Eisenberg et al., 2003). Thus, *GNE* mutations represent aMendelian phenocopy for IBM.

*Paget’s disease of bone (PDB):* PDB is a common chronic disorder characterized by disorganized bone remodeling with abnormal osteoclastic and osteoblastic activity, pathologically leading to formation of woven (mosaic) bone. These abnormal activities in bone metabolism cause weaker and more vascular bone leading to pain, deformity and secondary complications. Uncommon but significant risk of malignant transformation is also present. PDB is primarily a disease of older individuals and most commonly diagnosed in the sixth decade. Approximately 10% of individuals older than 80 years have PDB (Ralston, Langston & Reid, 2008).

Etiology of PDB is complex but strong influence of genetic predisposition is noted. Multiple mutations in the *SQSTM1* gene, which encodes sequestosome 1/p62, were described in many extended classical autosomal dominant PDB families who have no evidence of other extra-skeletal or syndromic manifestations (Goode & Layfield, 2010). The penetrance of *SQSTM1* is age-dependent and incomplete but high. For example, the penetrance of the common P392L mutation is 79%-87% after age 60 among 109 carriers from 11 PDB families (Morissette, Laurin & Brown, 2006). Thus, *SQSTM1* mutations represent a Mendelian phenocopy for PDB.

**XIV. Diseases of the genitourinary system**

Diseases of the genitourinary system include glomerular, tubulointerstitial diseases, renal failure, urolithiasis, diseases of male genital organs, breast, inflammatory and noninflammatory disorders of female pelvic organs and other genitourinary disorders. In general, most renal diseases can progress into end stage renal disease (ESRD) with dependence on dialysis or kidney transplantation. Among diseases of the genitourinary system, glomerulonephritis (GN), nephrotic syndrome (NS), infections and obstructive uropathy are the major causes of ESRD.

**Early onset**

*IgA nephropathy (IAN):* IAN is the most common primary GN. Clinical picture varies from a benign one to rapidly progressive GN (RPGN). IAN can occur in all ages but most diagnosed patients are 16 years to 35 years of age. The pathogenesis involves deposition of IgA immune complexes. Although genetic contribution to IAN is strongly suspected, and multiple loci are implicated by linkage studies (Kiryluk et al., 2010), thus far no Mendelian gene mutations are identified (Boyd et al., 2012).

*Vesicoureteral reflux (VUR):* VUR is characterized by reverse flow of urine from bladder to ureters and kidney and is associated with increased risk of infection, hydronephrosis and abnormal kidney development. VUR is the most common urological abnormality affecting 1-2% of pediatric population. Although hereditary factors are well-recognized, no single gene has been identified (Puri et al., 2011,Toka et al., 2010).

*Minimal change nephrotic syndrome (MCNS):* MCNS is the most common form of childhood nephrotic syndrome. NS is defined by massive proteinuria, hypoalbuminemia and edema. MCNS is characterized by retraction of epithelial foot processes by electron microscopy and response to corticosteroid treatment in most cases. Thus, MCNS is essentially a steroid-sensitive NS (SSNS). SSNS is a sporadic disease with a weak familial tendency. There are few reported cases of familial clustering (Landau et al., 2007; Motoyama et al., 2009). Although a locus for SSNS was mapped, the underlying gene remains to be identified (Ruf et al., 2003).

**Late onset**

*Nephrolithiasis:* Kidney stones are common findings with significant medical costs but they are not common causes of renal failure. Peak incidence occurs among 35-45 year olds, although renal calculi can be diagnosed in a wider age range (Medscape). Calcium stones are the most common types. Family and twin studies suggest strong genetic influences and several monogenic diseases were described. The mutated genes often encode for ion channels or renal structural proteins and result in hypercalcuric kidney stones associated with multiple reabsorption defects and/or syndromic features (Vezzoli et al., 2011).

*Focal segmental glomerulosclerosis (FSGS):* FSGS is the leading glomerular cause of ESRD, accounting for 7-10% of childhood nephritic syndrome (NS) and 20-30% adult NS. Wehrmann et al. identified an average at onset of 32 year in a group of 250 patients with idiopathic FSGS with an overall 10-year renal survival of 67% (Wehrmann et al., 1990). Chun et al. found that age at onset was 38, 40 and 52 years for common histologic variants of adult FSGS (Chun et al., 2004). In contrast to MCNS, which is often steroid sensitive, most cases of FSGS are steroid resistant. Among children, FSGS is usually found when NS is steroid resistant (Benoit et al., 2010). Many factors (HIV infection, obesity, hypertension, diabetes) can predispose to FSGS, but most cases are idiopathic. The incidence of FSGS appears to be increasing both in children and adults in recent years (Hogg, Middleton & Vehaskari, 2007).

Loss of function mutations affecting podocin (*NPHS2*) and nephrin (*NPHS1*) result in autosomal recessive childhood or early adulthood-onset steroid-resistant FSGS with full penetrance and no associated syndromic features. In addition, autosomal dominant mutations in *ACTN4*, encoding actin-binding protein, alpha-actinin 4 cause proteinuria starting in adolescence or early adulthood and progresses to FSGS and ESRD in adulthood in a highly penetrant (but less than 100%) and non-syndromic fashion (Tryggvason, Patrakka & Wartiovaara, 2006; Machuca, Benoit & Antignac, 2009). Genetic testing reveals mutations in these genes in majority of the infantile FSGS cases and may account for many other cases presenting in early childhood (D'Agati, Kaskel & Falk, 2011), suggesting that truly sporadic FSGS is more common in adults than in children. In summary, mutations in nephrin, podocin and *ACTN4* represent Mendelian phenocopies for steroid-resistant FSGS.

**XV. Pregnancy, childbirth and the puerperium**

Complications of pregnancy, childbirth and puerperium, approximately 6 week period from delivery of placenta, are among the leading causes of death and disability among women of reproductive age in under-developed parts of the world. These diseases include pregnancy with abortive outcome, edema, proteinuria and hypertensive disorders and other disorders related to pregnancy, delivery and puerperium such as hemorrhage, infections, endocrine and psychiatric disorders. In general, bleeding, infections, unsafe abortion, eclampsia and obstructed labor are responsible for most maternal deaths (Gee, 2002). Many factors, both genetic and non-genetic, are involved in susceptibility to these disorders. For example, recurrent spontaneous abortions are associated with antiphospholipid antibodies, uterine malformations, systemic endocrine disorders and constitutional chromosomal abnormalities.

**Early onset**

*Preeclampsia (PE):* PE is a common pregnancy-induced disorder characterized by hypertension and proteinuria with variable presentation of abnormal edema. It is thought that placenta plays a central role in triggering PE, possibly involving abnormal immune relationship between mother and fetus. Genetic susceptibility to PE is well-established, although finding the underlying genes has not been straightforward. Genetics of PE is complex with interactions among multiple loci affecting susceptibility. No mendelian mutations were ever described in predisposition to PE (Williams & Pipkin 2011).

**XVI: Certain conditions originating in the perinatal period**

These disorders primarily involve maternal factors complicating pregnancy, labor and delivery; disorders of abnormal gestational length and abnormal fetal growth; birth trauma; respiratory and cardiovascular diseases specific to the perinatal period; perinatal infections and hematological disorders; digestive system, transient endocrine and cutaneous disorders of the newborn and fetus.

While some of these disorders result from perinatal environmental factors (e.g., infection, trauma), others are characterized by marked etiologic heterogeneity (e.g., intrauterine growth restriction, cerebral palsy). Because of multiplicity of risk factors for perinatal disorders, role of genetic factors in most perinatal disorders are not well studied.

**Early onset**

*Preterm birth (PB):* PB refers to a delivery before 37 weeks of gestation. PB is responsible for majority of neonatal morbidity and mortality. Although environmental factors, including smoking, illicit drug use, deficiencies of iron folate or vitamin D, and African American ethnicity increase risk of PB, epidemiologic studies suggest that genetic factors are also contributory. Influence of genes determining response to infection/inflammation and those regulating extracellular matrix are suspected. Thus far, no single gene is linked to PB risk in a highly penetrant fashion (Anum et al., 2009).

**XVII: Congenital malformations and deformations**

Congenital disorders are common and diverse group of disorders that are responsible for significant childhood mortality throughout the world. Chromosomal disorders also contribute to neonatal disease burden, but here, only disorders with multifactorial complex inheritance are evaluated. The most common conditions are congenital heart defects and neural tube defects, where heredity is strongly implicated. Genetic influence for certain congenital disorders, including esophageal atresia and tracheoesophageal fistula (Genevieve et al., 2011), congenital diaphragmatic hernia (Brady et al., 2011), choanal atresia (Burrow et al., 2009), small bowel malrotation (Martin & Shaw-Smith, 2010), cryptorchidism (Kojima et al., 2009) are suspected. However, highly penetrant nonsyndromic nonpleiotropic predisposition genes have yet to be described for any congenital disorder.

*Neural tube defects (NTDs):* NTDs refer to group of congenital disorders characterized by defective coverings of the nervous system. These disorders range from the mild forms of spina bifida to anencephaly. NTDs are more common in females and in certain ethnic groups. Folic acid supplementation reduces risk of NTDs. The incidence of NTDs seems to be declining in the last several decades. The majority (>90%) of NTDs are sporadic, with recurrence patterns compatible with a multifactorial polygenic or oligogenic pattern, rather than single gene models (Greene, Stanier & Copp, 2009). Although several polymorphisms and rare mutations have been implicated in predisposition to NTD, highly penetrant gene mutations have yet to be identified (Narisawa et al., 2012).

*Congenital heart defects (CHDs):* CHDs are the most common birth defects. The most common types include ventricular septal defect (VSD), atrial septal defect (ASD), bicuspid aortic valve (BAV), pulmonary stenosis (PS), tetralogy of Fallot (TOF) and coarctation of aorta. Most CHD cases occur in isolation, while up to 40% of them occur in a syndromic setting. Approximately, 30% of newborns with chromosomal abnormalities, including trisomy 21, trisomy 13, trisomy 18 and Turner and Klinefelter's syndromes have CHDs. In addition, submicroscopic deletions and duplications such as 22q11 deletion syndrome and Williams-Beuren syndrome have cardiac malformations as part of a syndromic presentation (Richards & Garg, 2010).

Single gene mutations are rarely implicated among non-syndromic CHD cases. Mutations in genes underlying certain developmental syndromes, including *JAG1* (Alagille syndrome) and *TBX1* (Holt-Oram syndrome) are identified in diverse isolated CHDs such as TOF, truncus arteriosis and PS. In addition, mutations in more than 15 genes are linked to the increased risk of CHDs. A notable characteristic of these mutations is pleiotropism and low penetrance. Mutations in a given gene predispose to a multitude of cardiac defects in different carrier individuals. For example, mutations in *NOTCH1* lead to BAV, mitral valve stenosis, TOF and VSD and mutations in *NKX2.5* predispose to ASD, VSD, Aortic stenosis, mitral valve and conduction abnormalities in different subjects.There is no evidence for a highly penetrant gene mutation that exclusively predispose to a single common congenital cardiac abnormality (i.e, without pleiotropism) ( Bruneau, 2008; Joziasse & Roos- Hesselink, 2011)

*Cleft Lip/Palate (CL/P):* Orofacial clefts are common congenital malformations. Approximately 70% of cleft lip with or without cleft palate (CL/P) and 50% of CP only are non-syndromic. Although a strong genetic component to non-syndromic CL/P is evident by twin and family studies, few pedigrees show Mendelian inheritance and no highly penetrant non-syndromic predisposition locus has ever been identified (Dixon et al., 2011).

*Hirschsprung disease (HSCR):* HSCR is a common congenital malformation characterized by absence of enteric neurons within certain regions of the gastrointestinal tract. Influence of genetics in pathogenesis of HSCR is strong but the underlying genetics is often complex and multigenic. HSCR occurs in isolation in 70% of patients, but is associated with a chromosomal abnormality or a syndromic presentation in the remaining 30% of the cases. Isolated HSCR is characterized by multigenic inheritance and influence of environment. At least 10 genes are implicated in predisposition to HSCR. Highly penetrant susceptibility genes for isolated HSCR could not be identified. Most common mutations associated with isolated HSCR involve the *RET* gene. *RET* mutations cause autosomal dominant HSCR with reduced penetrance: 70% in males and 50% in females (Amiel et al., 2008). Other predisposition genes are either described in a few cases or cause syndromic manifestations such as Waardenburg syndrome.

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