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Severe infectious diseases of childhood as monogenic inborn errors of immunity

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ABSTRACT
The pathophysiology of juvenile infectious illnesses, as well as more broadly clinical disorders during initial infection, is a major issue. Building on elegant findings in plants and animals, a credible and testable human genetic explanation of primary infectious illnesses has recently emerged. There have been three cases of monogenic resistance to common illnesses found. Furthermore, a rising number of monogenic single-gene inborn defects of immunity, both Mendelian (full clinical penetrance) and non-Mendelian (incomplete penetrance), have been shown to underpin serious infectious illnesses that affect otherwise healthy infants during initial infection. These discoveries give a paradigm for understanding hereditary and infectious illnesses, as well as inborn and environmental factors in general.
Keywords: human genetics, immunology, infectious diseases, pediatrics, primary immunodeficiency

I. INTRODUCTION

From the second part of the twentieth century to the present, advances in the field of human genetics of infectious illnesses have been made. It emphasises and explains the significance of the recently identified monogenic inborn immune defects that underpin resistance or susceptibility to certain illnesses. The genetic theory's monogenic component offers a credible explanation for the emergence of severe infectious illnesses during initial infection. Single-gene inborn defects of immunity have been blamed for an increasing number of life-threatening infectious illnesses that have struck otherwise healthy children, adolescents, and even young adults in the last 20 years. These researches were sparked by key but underappreciated discoveries in plant and animal diseases. Because human genotypes frequently exhibit imperfect penetrance (most genetically predisposed people stay healthy) and variable expressivity, infectious illnesses generally emerge as sporadic features (different infections can be allelic at the same locus). Childhood infectious disorders, traditionally assumed to be prototypical environmental diseases, may really be among mankind's most genetically determined ailments. The medical and biological ramifications of this emerging and tested concept are intriguing.

This article reviews the monogenic inborn defects of immunity that have been linked to human infectious disease resistance or vulnerability. These investigations, which began in the 1970s, acquired traction in the mid-1990s. The study of Mendelian characteristics was followed by a study of non-Mendelian monogenic traits, which are characterised by fluctuating expressivity and inadequate clinical penetrance.

Mendelian Resistance to Malaria

The finding of Mendelian resistance to Plasmodium vivax provides an example of infection changing the human genome (1, 2). It's vital to note that these research focused on infection itself rather than its symptoms. Only a tiny percentage of infected people acquire clinical illness, and an even lower percentage develop life-threatening disease during initial infection, as explained in the companion study (3). Furthermore, not everyone who is exposed to the virus becomes sick. Because of a well-defined monogenic genotype for a microbial receptor or coreceptor, this phenomenon has been established to be a Mendelian trait in at least three examples. Louis Miller was a pioneer in this field, conducting groundbreaking research. In 1976, he showed that in erythrocytes, an autosomal recessive absence of the Duffy antigen and receptor for chemokines (DARC) inhibited Plasmodium vivax infection in vitro and infection of humans in vivo (1). A sophisticated set of follow-up studies revealed that the resistance was caused by a single nucleotide mutation in the DARC promoter, which prevented the transcription factor GATA-binding protein 1 (GATA1) from binding to the DARC promoter,

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which is required for DARC expression in the erythrocyte lineage (4). In other cells, those who are affected express DARC properly. Infections with P. vivax are seldom fatal nowadays, but the parasite's selective pressure may have encouraged the development of this gene, which is more prevalent in infected regions and is fixed in some African groups. These findings do not explain the pathophysiology of P. vivax malaria, but they do explain why some people do not become sick despite being exposed to the parasite on several occasions. They also show that a disease can promote the transmission of a human gene that confers Mendelian resistance to the pathogen in question.

Other forms of Mendelian Resistance to Infection

A series of identical investigations published in 1996 revealed why HIV does not infect uncommon persons in vivo despite repeated sexual encounter. In vitro, these people's CD4+ T cells were found to be resistant to infection. These individuals (5–7) were found to have an autosomal recessive chemokine (C-C motif) receptor 5 (CCR5) deficiency. The most prevalent mutation underlying this trait is thought to have originated in Scandinavia, but the evolutionary mechanisms driving its expansion to Southern Europe are unknown. The autosomal recessive fucosyltransferase 2 (FUT2) defect, which was found in 2003, is the third and last example we'll look at. Individuals who have this deficit are naturally resistant to norovirus-induced diarrhoea (8, 9). This illness is largely benign in affluent nations now, but it was potentially life-threatening in ancient times and remains so in impoverished countries today. With these three cases, we have real autosomal recessive genetic determinism with entire or almost total penetrance. Through a causative mechanism, the monogenic lesions inhibit infection (i.e., lack of cell infection by a specific microbe). These findings apply to a huge number of people, and they clearly demonstrate the population-level influence of Mendelian genetics. Because these three studies show the importance of a single unique gene for each infection, these discoveries have substantial biological consequences. The therapeutic implications are also critical, because inhibiting these chemicals in other people is a sensible strategy to prevention or treatment. It's amazing that this field hasn't taken off yet. Seronegativity has been recorded in at least a tiny percentage of the population for practically all prevalent bacteria, implying that naturally and maybe genetically resistant individuals exist. It would not be unexpected if other types of autosomal recessive resistance to infection by other microbes, particularly common and aggressive diseases, were discovered.

Mendelian susceptibility to Mycobacterial Diseases

We may now talk about the key subject of single-gene variations causing clinical outcome heterogeneity in infected people. Our effort was divided into two stages. We started with Mendelian infectious illnesses, which are the polar opposite of the aforementioned Mendelian resistance. Indeed, doctors have documented uncommon viral illnesses with full Mendelian segregation since the 1940s. These disorders were not deemed primary immunodeficiencies since there were no obvious immunological abnormalities (10, 11). The examples of "idiopathic" sickness produced by live bacillus Calmette–Guérin vaccines, which were apparently published initially in 1951 (12–14), drew our quick attention. When these mycobacterial species arose as opportunistic agents in various environments, patients who were preferentially prone to clinical illness caused by environmental mycobacteria were observed (15). Patients are more vulnerable to mildly pathogenic mycobacteria and, less frequently, other intramacrophagic infections, such as Salmonella (16). The clinical relationship of sickness induced by a weakly pathogenic Mycobacterium and Salmonella is nearly pathognomonic for this illness. Multiplex and/or consanguineous afflicted families were shown to have Mendelian susceptibility to mycobacterial disease (MSMD) (15). MSMD is a set of really Mendelian illnesses—monogenic disorders with total or near-perfect clinical penetrance. As a result, the percentage of family instances against sporadic cases is significant, at least in big kinships and kindreds. Despite Mendelian inheritance, these individuals were long thought to have idiopathic infections rather than primary immunodeficiencies since there was no immunological profile that segregated with illness.

Inborn Errors of IFN Immunity

We used a mix of positional cloning and candidate gene techniques to look for the genetic basis of MSMD. In London, Michael Levin took a similar technique. We published the initial genetic aetiology of MSMD in 1996: autosomal recessive

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full IFN-γ receptor 1 (IFN-R1) deficiency (17, 18). We and others continued similar forward genetic method for the following 20 years, discovering a collection of 17 inborn IFN-γ immunity defects involving nine genes (19–23). Some MSMD-causing genes regulate IFN-γ production while others regulate its effect. There is a lot of allelic variability in these nine MSMD-causing genes. However, because all of these impairments affect IFN-γ immunity, they show physiological homogeneity. Furthermore, human IFN-γ immunity governs host defence against mycobacteria as a quantitative feature. MSMD's clinical manifestations are largely influenced by IFN-γ immunity levels, with total IFN-γ deficiency being the most severe (24). This research has clear clinical implications. The genetic abnormalities underlying these Mendelian infections were uncovered in these research, providing molecular genetic confirmation that mycobacterial illness might be Mendelian. When the receptor is fully nonfunctional, the patients are treated with IFN-γ and antibiotics, or hematopoietic stem cell transplantation. The immunological ramifications are significant: These findings back with Carl Nathan's theory that IFN-γ is more of a macrophage activator than an antiviral agent (25). They also discovered that the Th1 arm of CD4+ T cells (IL-12 is the Th1-inducing signature cytokine, and IFN-γ is the Th1 effector signature cytokine), which had been shown to control intracellular microbe infections in inbred mice, had a narrower spectrum of action in outbred humans in natural infection (with environmental mycobacteria) or iatrogenic infection (with the bacillus Calmette–Guérin vaccine). Which genes are required for the regulation of other microorganisms if IL-12 and IFN-γ are required for the control of such a limited number of germs? MSMD was the first investigation of Mendelian predisposition to a restricted, particular population of microorganisms, and it continues to be the most thorough of its kind. Because genetic etiologies for only approximately half of the known MSMD cases have been found, this research is still ongoing.

A Neglected Connection: Neisseria and Complement

Before moving on to additional examples of Mendelian infections, I'd want to talk about complement, because it's fascinating to attempt to figure out why it didn't play a bigger part in the field. Between 1993 and 1998, mutations in genes encoding complement's terminal components (C5–C9) or its activation protein properdin (encoded by the X chromosome) were reported (26–31). In 2001, a mutation in a gene encoding factor D, another activating protein, was discovered (32). Surprisingly, these recessive abnormalities are at the root of Neisseria meningitidis' selective, late-onset, recurring, and invasive illness (typically meningococcal meningitis). However, unlike MSMD, these impairments were not discovered as a result of the discovery of a family propensity to Neisseria in the absence of overt immunological abnormalities. Instead, decreased global complement activity in a random instance of Neisseria meningitis led to the discovery of C6 and C8 activity deficiencies in 1976 (33, 34) and the identification of C6, C8B, and C8A gene mutations two decades later. In a spontaneous instance of meningitis in 1989 (35), deficient factor D activity was initially recorded, and the first causative mutation for this illness was published a decade later. C5 and C9 deficiencies were originally discovered in a lupus patient and a healthy person in 1976 and 1981, respectively (36, 37). In occasional cases of Neisseria illness in 1979 and 1989 (38, 39), such deficiencies were discovered, leading to the identification of C5 and C9 mutations. In 1978 and 1982, only C7, properdin, and factor D deficits were detected in multiplex kindreds with Neisseria illness (40, 41). Other patients with Neisseria infections were studied as a result of these research. In other words, kindreds with Neisseria infections have never been described as idiopathic or as having a Mendelian predisposition to Neisseria meningitis in the medical literature, most likely because Neisseria was regarded to be sufficiently pathogenic to produce illness on its own (despite the presence of this microbe in the nostrils of almost all children). These breakthroughs were accomplished without using a genome-wide genetic method or even a candidate gene technique to test a genetic hypothesis. Instead, they were predicated on the chance discovery of decreased total complement activity. However, the faults of properdin, factor D, and complement's terminal components are intriguing in retrospect. These results show unequivocally that mutations in any of multiple genes affecting a shared component of a main arm of immunity can result in invasive illnesses caused by a specific type of common pathogen. Furthermore, one or both of these complement abnormalities have been discovered in a considerable number of children with invasive meningococcal illness (42). These findings,

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however, did not have the same influence on the definition of candidate genetic architectures for infectious illnesses as the MSMD study, presumably due to the method through which they were gathered.

Epidermodysplasia Verruciformis

In human genetics, immunology, infectious illnesses, and cancer, Epidermodysplasia verruciformis (EV) is a one-of-a-kind case. EV is a very unusual ailment, as its lack of a widespread term suggests, and most readers are likely unaware of it (43). It is, nevertheless, possibly the most intriguing disease discussed here, at least from a historical standpoint. In the first decade of life, patients with EV acquire flat warts and other skin abnormalities. These lesions likely to deteriorate into nonmelanoma skin malignancies around the age of 20. They are caused by a group of human papillomaviruses (HPV) known as EV-associated oncogenic β-HPV (EV-HPV), which are found in the general population as innocuous commensals. The discovery of HPV-5 in EV tumours was the first indication of a papillomavirus's carcinogenic function in a human cancer (44). The clinical signs of this illness were initially documented in 1922 (45), the disease's genetic basis in 1933 (46), and the viral aetiology in 1946. (47). As a result, EV should have been the first main immunodeficiency identified. However, this was not the case, most likely because EV patients had no discernible immunological profile. Not until 2004, two years after Gérard Orth and colleagues identified the first single-gene inborn errors underlying autosomal recessive EV—mutations of transmembrane channel-like 6 and 8 (TMC6 and TMC8) (48)—was this condition finally included in the international classification of primary immunodeficiencies, albeit reluctantly (49, 50). Mild immunological abnormalities, which were more likely a result rather than a cause of EV, were later detected in these patients (51). Because the activities of TMC6 and TMC8 are mainly unknown, the cellular and molecular mechanism of EV remains a mystery (52). In keratinocytes, one feasible idea is that the TMC complex regulates cell-intrinsic immunity against oncogenic EV-specific HPV. The investigation for novel genetic etiologies of EV in individuals who do not have TMC mutations should aid in the resolution of this critical issue.

X-Linked Lymphoproliferative Disease

In 1974–1977 (53–56), a clinical description of a large kindred with X-linked recessive lymphoproliferative illness (XLP) was published, prompting the diagnosis of this disease as a primary immunodeficiency (57). In maternally related men, three different phenotypes in response to EBV infection were discovered, demonstrating full penetrance with varied expressivity: hemophagocytosis, lymphoma, and hypogammaglobulinemia. The realm of immunology comprised all three phenotypes. However, they were the result of an inborn defect, and in the absence of EBV infection, they did not even correspond to an intermediate phenotype. Despite the absence of acknowledgment of EV, this trio was deemed significant enough to be included in the 1978 worldwide classification of main immunodeficiencies. (57) In 1998, three groups discovered the initial genetic foundation for XLP (58–60). Signaling lymphocytic activation molecule-associating protein (SAP), an intracellular molecule produced in T and natural killer (NK) cells, is encoded by the disease-causing gene. More than a decade later, via somatic genetic investigations of heterozygous female and revertant male patients, the pathophysiology of XLP was eloquently explained (61, 62). This somatic genetic strategy to addressing the cellular foundation of a germline problem proved to be quite successful. SAP-expressing CD8+ T cells were shown to be absolutely necessary for EBV-infected B cells to be controlled. Two of the three B-cell phenotypes, polyclonal B-cell proliferation (precipitating hemophagocytosis via T-cell activation) and B-cell lymphoma, are explained by their absence. XLP, in any case, is a great example of a life-threatening illness or virus-induced malignancy that is also Mendelian. It paved the door for the identification of two more similar recessive syndromes, X-linked inhibitor of apoptosis (XIAP) deficiency and X-linked magnesium transporter 1 (MAGT1) deficiency (64–67).

Chronic Mucocutaneous Candidiasis

We also discovered the genetic foundation for familial chronic mucocutaneous candidiasis (CMC), a Mendelian "hole" in host protection that was initially characterised clinically in the late 1960s and early 1970s (68, 69). Surprisingly, our research into MSMD led to the finding of mutations in another arm of the effector CD4+ T-cell response, Th17 cells, whereas our research into CMC led to the discovery of

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mutations in another arm of the effector CD4+ T-cell response, Th17 cells. Patients with MSMD and IL-12 receptor 1 (IL-12Rβ1) impairment who also have CMC were able to bridge the two disorders (70). Patients with CMC have recurrent or chronic mucocutaneous infections with Candida albicans, a commensal fungus. The disease segregates as a recessive or dominant characteristic in multiplex families. CMC is frequent in individuals with autosomal dominant hyper-IgE syndrome or autosomal recessive autoimmune polyendocrinopathy syndrome 1 who have a variety of symptoms due to impaired IL-17A/F immunity (71). Following this finding, we found loss-of-function mutations in the IL17F, IL-17 receptor A (IL17RA), IL17RC, and actin-related gene 1 (ACT1) genes in patients with isolated CMC from 2011 to 2014 (72–74). Patients who have IL17RA and ACT1 mutations and do not react to IL-17E are also prone to staphylococcal infections. Surprisingly, we discovered STAT1 gain-of-function mutations in nearly half of the patients, preventing the formation of IL-17A/F–expressing T cells (75). Other viral and immunological symptoms were also present in these individuals. Biallelic mutations of RAR-related orphan receptor C (RORC) were found in individuals with both CMC and mycobacterial illness, which was surprising (76). RORC genes for the ROR- γ and ROR- γT isoforms and transcription factors that control Th17 development in mice. As a result, CMC was expected in these individuals, and they did not have any circulating IL-17A/F T cells. Mycobacterial illness, on the other hand, is their most severe phenotype. RORC also influenced the generation of IFN- γ by γδT cells and a recently discovered subtype of memory CD4+ T cells, Th1* cells, which are particularly common among Mycobacterium-reactive T cells, according to in-depth research (77). Human IL-17A and F are required for mucocutaneous immunity against Candida albicans, however they are generally redundant, according to the genetic dissection of CMC. The results for the equivalent inbred mice, which were sensitive to a wide range of experimental illnesses, were in contrast to these findings. MSMD and CMC research in the clinic revealed the basic mechanism of mycobacteriosis and candidiasis in various conditions, such as AIDS and immunosuppression: reduced IFN- γ and IL-17A/F immunity. These results cleared the door for immunotherapy with IFN- γ for mycobacteriosis patients and IL-17A/F or similar cytokines for candidiasis patients.

Invasive Dermatophytosis

Dermatophytosis, sometimes known as athlete's foot, is a frequent superficial infection. Invasive (or deep) dermatophytosis or dermatophytic illness is a disorder in which dermatophytes penetrate the skin, infiltrate the dermis and draining lymph nodes, and propagate throughout the body. Invasive dermatophytic disease patients can survive well into their 70s without contracting any additional illnesses. Since 1957, this syndrome has been demonstrated to be inherited as an autosomal recessive characteristic, most commonly among North African relatives (78, 79). We discovered the genetic defect that caused this unusual case of Mendelian illness. All of the individuals evaluated had biallelic mutations in the CARD9 gene, which codes for caspase recruitment domain family member 9 (80). A big kindred with invasive and peripheral candidiasis has previously been shown to have a deficiency of this intracellular component (81). Other invasive fungal infections' genetic foundation was discovered as a result of these investigations. As a result, CARD9 deficiency has been discovered to cause invasive fungal illness in children, adolescents, and adults. Dermatophytes, Candida, Phialophora, and Exophialia are just a few of the fungi that can be involved (82, 83). The central nervous system is frequently harmed. Each patient (and, in most cases, each kindred) is affected by a specific form of invasive fungal illness. Another example of perfect penetrance with varying expressivity is this condition. The molecular and cellular processes that underpin the patient's phenotyp's specificity are unclear. The genetic and cellular basis of propensity to invasive fungal illness in CARD9-deficient individuals is likewise an open subject. CARD9 might be a crucial component working downstream of these fungi's surface receptors on myeloid cells. These experiments demonstrated that in humans, an isolated, invasive fungal illness in a previously healthy child, teenager, or adult can exhibit strict Mendelian determinism.

Toward Non-Mendelian Monogenic Infections: Tuberculosis

We'll now focus on the finding of non-Mendelian monogenic illnesses. Surprisingly, our MSMD research found that not all genetic etiologies were fully penetrant for the MSMD case-definition phenotype. A good example is IL-12R1 deficiency (84, 85). Only around half of MSMD

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index cases' genetically afflicted siblings also had MSMD. MSMD patients with IL-12R1 deficiency had variable expressivity: they had bacillus Calmette–Guérin disease (in only a fraction of vaccinated patients) or environmental mycobacteriosis (typically in individuals not vaccinated with bacillus Calmette–Guérin), but not both, implying that live bacillus Calmette–Guérin vaccination protected against mycobacteriosis. These findings raise important issues concerning the processes behind inadequate penetrance and varied expressivity, which remain unanswered. We identified the first examples of monogenic TB (to our knowledge) in persons and even families with IL-12Rβ1 deficiency presenting only as severe tuberculosis in this scenario (86–91). These individuals were generally immune to the live bacillus Calmette–Guérin vaccination and mycobacteria found in the environment. They were, however, susceptible to the more virulent Mycobacterium TB due to IL-12Rβ1 lack. Perhaps not surprisingly, these were the studies we had the greatest trouble publishing: it turned out that reporting genetic etiologies of TB was far more difficult than reporting genetic etiologies of MSMD. Perhaps the community was not ready to embrace the possibility that severe TB could be monogenic, or monogenic tuberculosis was dismissed as a rare occurrence. One of the most positive pieces of data we've gotten so far in favour of a human genetic hypothesis of primary infectious illnesses is our identification of really monogenic TB cases. We believe that severe TB is regulated by significant levels of genetic variability, which can only be decoded through particular research strategies (15, 86, 92). The study of TB encouraged us to think more deeply about the idea that non-Mendelian monogenic inborn defects of immunity, single-gene lesions with imperfect penetrance, may impact the severity of initial infections. Indeed, the vast majority of infectious illnesses do not appear to be Mendelian features due to the inadequate penetrance of single-gene defects giving vulnerability to infection.

II. CONCLUSION

In the process of primary infection, we can suggest the following preliminary and testable model for the human genetic architecture of infectious disorders. Emerging or reemerging infectious pathogens that kill a substantial proportion of infected people select for human resistance alleles, which proliferate and become widespread alleles through natural selection. They can function in a monogenic or polygenic paradigm, as evidenced by the transmission of mutant resistance alleles in P. vivax and Plasmodium falciparum malaria endemic regions. When illnesses endanger a lower proportion of infected people (e.g., invasive fungal disease), genetically determined mortality is more likely to be the product of uncommon mutant alleles with variable expressivity and incomplete penetrance. The character of the uncommon genetic lesions may be influenced by the more frequent variations, which change the number of instances among afflicted people. This polygenic non-Mendelian monogenic determinism of primary infectious illnesses is reasonable and testable. The proportion of cases resulting from this type of genetic determinism is anticipated to decline with age, both in diseases where genetics plays only a minor role and in diseases where genetics plays a wholly hereditary role. The number of genetic instances in secondary infections and illnesses in the elderly is expected to be lower, and the proportion of monogenic cases much lower. This approach may also be applicable to a variety of noninfectious immunological abnormalities. Even for cancer and infection, the traditional examples of somatic and environmental illnesses, it is tempting to predict that the deaths of children, adolescents, and young adults may be monogenic in general, or at least triggered by a single, uncommon genetic event. This hypothesis of infrequent monogenic lesions underpinning heritable traits with inadequate penetrance or variable expressivity might be applicable to infections, allergies, autoimmunity, autoinflammation, and some malignancies.

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