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Incomplete penetrance in primary immunodeficiency: a skeleton in the closet

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Abstract

Primary immunodeficiencies (PIDs) comprise a diverse group of over 400 genetic disorders that result in clinically apparent immune dysfunction. Although classically considered mendelian disorders with complete penetrance, we now understand that absent or partial clinical disease is often noted in individuals harboring disease-causing genotypes. Despite the frequency of incomplete penetrance in PID, no conceptual framework exists from which to categorize and explain these occurrences. Here, by reviewing decades of reports on incomplete penetrance in PID we identify four recurrent themes of incomplete penetrance, namely genotype quality, (epi)genetic modification, environmental influence, and mosaicism. For each of these principles, we review what is known, underscore what remains unknown, and propose future experimental approaches to fill the gaps in our understanding. Although the content herein relates specifically to inborn errors of immunity, the concepts are generalizable across genetic disease.

Keywords

penetrance; variable expressivity; primary immunodeficiency; human genetics; mosaicism

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Conflict of Interest Statement

On behalf of all authors, the corresponding author states that there is no conflict of interest.

Introduction

Primary immunodeficiencies (PIDs) are a heterogeneous group of inborn genetic errors that result in broad or narrow susceptibility to infections, predisposition to malignancy, or disorders of immune overactivation. Since the first descriptions of inherited immunodeficiency in the mid-20th century (Wiskott, 1937; Lutz, 1946; Kostmann, 1950; Bruton, 1952; Aldrich, Steinberg and Campbell, 1954), PIDs were branded as mendelian disorders. In the subsequent decades, the number of recognized PIDs has exploded, now exceeding over 400 unique entities (Tangye *et al.*, 2020). Immense progress has been achieved in our understanding of the basic immunology and clinical pathogenesis surrounding these diseases. However, these advances have cast a shadow: although originally ascribed mendelian inheritance, these disorders often display imperfect segregation of gene mutations with disease traits.

Known as incomplete penetrance, this term can be broadly defined as any absence of clinical disease in individuals harboring a known disease-causing genotype. Precise terminology is crucial. Incomplete penetrance is synonymous with reduced penetrance. While penetrance measures the binary presence or absence of the disease trait, a genetic defect may also present with a range of disease severity or varying clinical phenotypes—a concept known as variable expressivity. For the purposes of this review, variable expressivity will be discussed under the umbrella of incomplete penetrance, as the origins can be largely overlapping. Lastly, fully-penetrant and monogenic are nonsynonymous, as either may occur without the other. Yet, both are often considered requirements for a mendelian trait.

Although incomplete penetrance is often encountered, the exact incidence is difficult to quantify. Most often, penetrance is assessed in family members of affected patients when the segregation of disease is traced from the proband. In such reports, rates of penetrance in specific PIDs range from as low as 5–10% (Yel, 2010; Kong *et al.*, 2013) to nearly 100% (Vihinen *et al.*, 1997; Candotti, 2017). Composite estimates across all PIDs indicate that ~9% families display some degree of incomplete penetrance (Stray-Pedersen *et al.*, 2017). It should be noted several inherent biases likely exist that lead to underreporting of incomplete penetrance. These include a failure to pursue or publish variants with highly reduced penetrance (reporting bias), and an inability to detect asymptomatic individuals carrying mutations in the general population (ascertainment bias).

Because this topic is often overlooked or even avoided, more is *unknown* than *known* regarding incomplete penetrance. However, the study of PID is now at a crossroads where enough cases of incomplete penetrance exist that patterns are beginning to emerge. From this vantage point, the article herein will review incomplete penetrance across PIDs and put forth 4 existing principles of incomplete penetrance that create a conceptual framework from which to categorize incomplete penetrance in PID. Within each of these, what is *known* will be reviewed and followed by what is *unknown* with future testable hypotheses that attempt to advance our current understanding. These existing principles and new ideas will lay the groundwork for future studies specifically aimed at incomplete penetrance—a focus which currently does not exist. Although the content is specific to inborn errors of immunity, the concepts can easily be generalized to genetic disease broadly.

Principle I. The quality of genetic defect affects penetrance

Known

An important distinction first needs to be defined between cellular penetrance and clinical penetrance. Cellular penetrance refers to the extent of perturbation in biological pathways or processes relevant to the mutated gene product, often measured when cells are studied in isolation with a specific assay (e.g. the signal transduction pathway of a mutated receptor). The cellular phenotype is naturally a direct function of the severity of the genetic defect. Complete protein absence, for example, results in more serious biological aberrances than hypomorphic mutations. Further, penetrance at a clinical level often, but not always, tracks with cellular penetrance. Thus, a simple model can be put forth: severity of genetic defect determines molecular dysfunction, which governs the degree of perturbation in immune cells, and therefore the tendency for clinical manifestations.

There are many cases in which this simplification holds true. Most famously, this occurs with IFNGR1-deficiency, the first described specific genetic etiology of Mendelian Susceptibility to Mycobacterial Disease, either from environmental mycobacteria (EM) or bacille Calmette-Guerin (BCG) immunization (Jouanguy *et al.*, 1996; Newport *et al.*, 1996). Autosomal recessive (AR) IFNGR1 defects with complete signaling deficiencies invariably develop BCG or EM infections by age 5 years and the clinical penetrance is complete (Bustamante *et al.*, 2014; Rosain *et al.*, 2019). On the contrary, subjects with partial IFNGR1 deficiency, which are typically autosomal dominant (AD), often remain asymptomatic for longer periods of time, have milder disease, or in some cases never develop disease (Jouanguy *et al.*, 1999; Dorman *et al.*, 2004; Bustamante *et al.*, 2014). It logically follows, and was proven experimentally, that these AD forms retain some activity when IFN- γ signaling is assayed in patient cells *in vitro*. (Jouanguy *et al.*, 1996; Dorman *et al.*, 2004).

A similar hierarchy is noted with STAT1 defects: AR complete deficiency with absent type I-III interferon signaling leads to complete penetrance of lethal intracellular bacterial and viral infections (Dupuis *et al.*, 2003; Chapgier *et al.*, 2006; Vairo *et al.*, 2011); AR partial deficiency with reduced signaling leads to penetrant but milder intracellular bacterial disease (Chapgier *et al.*, 2009; Kong *et al.*, 2010; Kristensen *et al.*, 2011); whereas AD forms with LoF point mutations retaining some function cause predominantly mycobacterial disease but with incomplete penetrance (Dupuis *et al.*, 2001; Chapgier *et al.*, 2006; Sampaio *et al.*, 2012; Tsumura *et al.*, 2012). While this demonstrates that partial deficiencies of essential genes can potentiate incomplete penetrance, so can complete deficiencies of non-essential genes of type I-III IFN signaling, which leave some signaling still intact. This can readily be observed in the deficiencies of *STAT2*, *TYK2* and *IFNAR2*, with severe viral disease affecting 3–5/7, 8/10, and 1/2 individuals receptively (Minegishi *et al.*, 2007; Hambleton *et al.*, 2013; Duncan *et al.*, 2015; Kreins *et al.*, 2015; Moens *et al.*, 2017; Taft and Bogunovic, 2018; Sarrafzadeh *et al.*, 2019).

Beyond infectious susceptibility, allele-penetrance associations also exist in other PIDs, including mutations of *STAT3* (Jägle *et al.*, 2019) *PRF1* (Feldmann *et al.*, 2002; Molleran Lee *et al.*, 2004), and *AIRE* (Oftedal *et al.*, 2015). While the functional impact of each variation must be studied in isolation, at times, genetics alone can lead the way. For

example, a recent cohort of congenital asplenia owing to *RPSA* mutations revealed marked incomplete penetrance, but no differences in functional prediction were apparent between incompletely penetrant and fully penetrant mutations. Yet, all missense mutations with incomplete penetrance were structurally located together, as were those with complete penetrance. Likewise, an *RPSA* mRNA noncoding structural defect resulted in incomplete penetrance, whereas a noncoding variant that lead to complete transcript decay conferred complete penetrance (Bolze *et al.*, 2018). These findings suggest that milder hypomorphic variants likely retain some residual function, which in some individuals is sufficient for normal spleen development. These cases illustrate that, even when incompletely understood, the severity of the defect associates with penetrance.

Upon first approximation, autoimmune lymphoproliferative syndrome (ALPS) also fits this mold in that penetrance appears to be a function of the location of the *FAS* mutation, the most common cause of ALPS. Homozygous or compound heterozygous forms of ALPS-FAS are fully penetrant and especially severe, early in onset, and often lethal (Rieux-Laucat *et al.*, 1995; Le Deist *et al.*, 1996; Kasahara *et al.*, 1998; van der Burg *et al.*, 2000). Heterozygous mutations are less penetrant. Among these AD variants, an additional hierarchy exists: missense variants of the intracellular domain are more highly penetrant (63%−90%) as compared to those in the extracellular domain (30% – 52%). It follows that the dominant-negative mechanism of ICD mutations leads to more severe apoptosis defects that those of the ECD, which act by haploinsufficiency (Kuehn *et al.*, 2011). Clearly, a relationship exists between the nature of the variant and disease probability. However, some defective Fas-mediated apoptosis can be identified in nearly 100% of individuals across all variants. Furthermore, some ‘asymptomatic’ individuals even exhibit lymphocyte expansions or autoantibody presence without clinical autoimmunity or true lymphoproliferation (Infante *et al.*, 1998; Jackson *et al.*, 1999; Bleesing *et al.*, 2001). Defining the threshold after which these subclinical cellular defects cross into clinically-apparent disease will be key for better understanding this model.

Unknown

However, there are many instances in which there is no apparent association between the magnitude of the pathogenic variant and penetrance. In the most extreme case, this model fails to explain that complete genetic deficiencies (deletions, frameshifts, etc) can exhibit variable penetrance. This discrepancy is well captured in CTLA4 haploinsufficiency; despite large, intensively-studied cohorts, no associations between genotype and penetrance have been observed (Kuehn *et al.*, 2014; Schubert *et al.*, 2014; Schwab *et al.*, 2018). For example, in a recent analysis of 133 subjects from 54 unrelated families carrying 45 different heterozygous *CTLA4* mutations, only 90 exhibited disease features. Whether the pathogenic variant was missense, nonsense or frameshift had no apparent bearing on penetrance. Further, both unaffected and affected mutation carriers exhibit similar immunologic phenotyping and *in vitro* CTLA4 dysfunction, suggesting complete cellular penetrance (Schwab *et al.*, 2018). However, cellular penetrance is fully dependent on the phenotype in question and the sensitivity of the assay implemented. Thus, if examined more closely, the loss of surface CTLA4 expression was, in fact, less severe in unaffected carriers (Schwab *et al.*, 2018). This indicates that although the CTLA4 genotype cannot explain disease

segregation, the degree of CTLA4 cellular perturbation still correlates with disease presentation. Along these lines, related deficiencies in T-cell regulation that represent more severe phenocopies of CTLA4-haploinsufficiency (LRBA deficiency, IPEX) demonstrate nearly complete penetrance (Lopez-Herrera *et al.*, 2012; Gámez-Díaz *et al.*, 2016). Therefore, additional disease modifiers must exist that influence the degree of T-reg dysfunction. Yet, their exact identity remains unknown, as neither secondary germline hits, somatic variation or reversion, viral exposure history nor HLA restriction can solely explain disease segregation (Schwab *et al.*, 2018).

These cases and others (Fieschi *et al.*, 2003; de Beaucoudrey *et al.*, 2011; Prando *et al.*, 2013), illustrate that the most severe genetic defects don't always equate with propensity for disease, and therefore demand alternate hypotheses. Of note, it has recently become evident that, in fact, severe genetic mutations may lead to more robust compensatory responses (El-Brolosy *et al.*, 2019; Ma *et al.*, 2019). Transcriptional adaptation, the process by which frameshifts/nonsense mutations activate transcription of homologous genes, may rescue these complete deficiencies. In these instances, either by experimental knockout or disease mutations, nonsense-mediated decay triggers upregulation of sequence-similar genes that are predicted to have partially overlapping function (El-Brolosy *et al.*, 2019; Ma *et al.*, 2019). This phenomenon poses an enticing and testable hypothesis to explain incomplete penetrance in asymptomatic disease carriers of nonsense mutations. The ability for this "genomic compensation" to rescue disease phenotypes represents an important focus of future studies.

Principle II: Genetic and epigenetic modifiers can impact penetrance of a mutation

Known

Despite sparse evidence historically, one of the often-cited mechanisms for incomplete penetrance is the presence of potential modifier genes and epigenetic regulation. With next generation sequencing (NGS) becoming commonplace, and epigenetic techniques introduced into the study of PID, we are now beginning to substantiate these occurrences.

Common variable immunodeficiency (CVID), represents a great platform from which to examine incomplete penetrance. Monogenic mutations causing CVID have been identified but explain only a fraction of cases—in fact, when identified, these single mutations are reclassified as specific diagnoses and are instead deemed "CVID-like' disorders. In some instances, epigenetic phenomena seem to predominate, as evidenced in a recent report of CVID-discordant monozygotic twins that show heightened DNA methylation in critical B-cell genes (*PIK3CD, BCL2L1, RPS6KB2, TCF3* and *KCNN4*) (Rodríguez-Cortez *et al.*, 2015). Likewise, a follow-up analysis on 23 CVID patients revealed defective demethylation of selected CpG sites during the transition from naïve to switched memory B cells (Del Pino-Molina *et al.*, 2019). Although further concrete evidence is largely nonexistent, such epigenetic changes are particularly enticing given the close association of CVID and aging.

In other cases, especially when CVID-like disease is inherited (~10–20%), the etiology is often hypothesized to be polygenic. Gene variants, like those of *TNFRSF13B, MSH5, BAFFR*, are enriched in cohorts of CVID patients but also exist in healthy populations, so are insufficient to solely drive disease (Bogaert *et al.*, 2016; de Valles-Ibáñez *et al.*, 2018). Instead, this predisposition from any one gene is thought to be driven by epistatic interactions with another (i.e. the manifestation of a genotype depends on the genotype of another gene), only some of which we've begun to define. Massaad et al. first demonstrated this effect in homozygous *NEIL3* mutations manifesting in one family as a uniformly fatal immune disease (recurrent infections and severe autoimmunity) but as a biologically-similar but clinically-silent immune dysfunction in an unrelated healthy individual. Genetic reanalysis uncovered a cryptic duplicated homozygous mutation in *LRBA*, defects of which are known to cause systemic autoimmunity, recurrent infections, and hypogammaglobulinemia. To further this "double-hit hypothesis," the authors generated *Neil3*-deficient mice, which like humans, showed no overt signs of autoimmunity unless challenged with a second insult. However, genetic epistasis was not directly documented (Massaad *et al.*, 2016).

Subsequently, epistasis was concretely evidenced in CVID by the discovery of a *de novo* Transcription Factor 3 (*TCF3*) mutation in a family already carrying a mutation of the CVID-associated *TNFRSF13B* gene. The proband with both mutations exhibited a severe CVID-like disorder and systemic lupus erythematosus. Family members with just the *TNFRSF13B* mutation displayed mild or absent disease and the proband's son with just *TCF3* mutation exhibited a partial clinical phenotype (Ameratunga *et al.*, 2017). The true synergy of epistasis was evidenced for disease severity (by clinical scoring) and biological phenotype (by *in vitro* studies). It thus logically follows that the function of proteins encoded by these two genes converge on immunoglobulin class switching pathways. A similar convergence of alike pathways and putative epistasis has also been noted in many other conditions, including: ALPS with concurrent mutations in *FAS* and *PRF1* (Clementi *et al.*, 2004) or *FAS* and *CASP10* (Cerutti *et al.*, 2007); Hyperimmunoglobulinaemia D and periodic fever syndrome from *MVK* and *TNFRSF1A* mutation (Hoffmann *et al.*, 2005); broad infectious susceptibility associated with *IFNAR1* and *IFNGR2* mutations (Hoyos-Bachiloglu *et al.*, 2017); X-linked immunodeficiency caused by *XIAP* mutation and a *CD40LG* polymorphism (Rigaud *et al.*, 2011); and in pediatric IBD in which known *NOD2* mutation likely interacting with variants in *GSDMB*, *ERAP2* or *SEC16A* (Christodoulou *et al.*, 2013).

Interestingly in most of these cases, one of the two hits were previously reported as a causative variant in isolation. This poses an apparent paradox, because true epistasis requires a synergistic interaction of >2 genetic loci resulting in unmasking or increased severity of disease. Thus, one might suppose that these isolated cases (e.g. *TCF3* (Boisson *et al.*, 2013) and *LRBA* alone (Lopez-Herrera *et al.*, 2012; Revel-Vilk *et al.*, 2015; Gámez-Díaz *et al.*, 2016)) were either milder disease forms or that these "isolated" cases actually contained an unknown modifier gene. For example, in a family of 4 with homozygous LoF LRBA mutations, the one unaffected sibling showed an intermediate apoptotic defect, suggesting that other genetic differences likely exist that regulate penetrance (Revel-Vilk *et al.*, 2015).

Alternatively, rather than epistatic interactions triggering a single disease etiology, these combinatorial genetic defects may instead produce blended phenotypes, so called because of the overlapping clinical disease that results from the co-occurrence of two independent monogenic defects. Blended phenotypes are remarkably frequent across clinical genetics (~5% of rare disease diagnoses) (Yang *et al.*, 2014; Driggers *et al.*, 2016; Posey *et al.*, 2016), and have recently been identified in unique immunodeficiencies caused by separate and distinct genetic defects (Chinn *et al.*, 2017; Rae *et al.*, 2017). Whether by blended phenotypes or epistasis, digenic inheritance is becoming a well-recognized determinant of expressivity and penetrance.

Unknown

The examples above point to combinatorial genetic hits, each of which are seemingly rare. However, what remains unknown is the role of common variation in the incomplete penetrance of rare disease. In regard to epistasis, it is plausible that the modifier gene could be a common variant that only plays a pathogenic role in combination with a rare mutation. This is likely to be the case in monogenic forms of autoimmunity (e.g. APS1, IPEX, CTLA4), in which relatively common autoimmunity-associated *HLA* alleles likely modify risk for specific autoantigens (Oftedal *et al.*, 2015). More substantively, it has been suggested that X-linked variable immunodeficiency segregates with relatively common variations in *CD40LG* (Rigaud *et al.*, 2011) and susceptibility to familial Mediterranean fever is modified by the interactions of *MEFV* mutations with polymorphisms in *SAA1* (Migita *et al.*, 2013). Although not a PID, non-syndromic midline craniosynostosis caused by rare SMAD6 mutations with common BMP2 variations remains the most well-substantiated example of this inheritance pattern and demonstrates that future studies in PID will require careful study of exceptionally large cohorts (Timberlake *et al.*, 2016). With such large-scale studies, investigation of other nuanced phenomena becomes possible as well. In particular, mutational burden, in which the aggregate effect of many minor deleterious variants regulates disease risk, may prove relevant for PID, as it has for other types of rare disease (Cady *et al.*, 2015; Girard *et al.*, 2015; Guo *et al.*, 2018).

These examples also suggest that the exact division between rare and common or monogenic and polygenic are unknown. For example, rare mutations leading to complete TYK2 deficiency result in monogenic susceptibility to TB and MSMD with relatively high penetrance (~80%) (Kreins *et al.*, 2015; Boisson-Dupuis *et al.*, 2018). Conversely, it was recently demonstrated that a common *TYK2* variant (4.2% allele frequency in Europeans) predisposes to tuberculosis (OR 89.3) and MSMD (OR 23.5) at the homozygous state in endemic regions. The estimated penetrance was ~80% and 0.05% for TB and MSMD respectively (Boisson-Dupuis 2019, (Kerner *et al.*, 2019). Although not considered a PID, these studies suggest that susceptibility to common infections can be caused by relatively frequent AR disorders in a proportion of patients. As more patients and healthy individuals are sequenced, with computational advances in tandem, many more such disorders on the borders of rare / common and monogenic / polygenic will likely be identified.

As we expand these NGS approaches to cover the whole genome, it is likely that we also uncover significant frequencies of noncoding variants with strong effects on characterized

pathogenic mutations in the coding space. To date, less than 29 PIDs are associated with pathogenic variants in the noncoding genome—further, the bulk of these variants are located immediately proximal to exons (Telenti, 2019). In addition, the existence of compound heterozygosity in which a coding mutation and a noncoding cis regulatory variant cooperate to cause PIDs was recently documented (Thaventhiran *et al.*, 2018). Whether these cases represent rare oddities or the tip of an iceberg remains unknown. With further exploration by whole genome sequencing, we are likely to not only identify causative variants in the regulatory regions, but also noncoding modifier alleles in *cis* and *trans* that change the expression of already pathologic mutations and regulate penetrance.

Akin to noncoding variation, copy number variations (CNVs) affecting critical immune genes could potentiate or curb the effects of deleterious alleles by gene dosage effects. Several global and site-specific CNVs have already been linked to PIDs (Green *et al.*, 2011; Orange *et al.*, 2011; Keller *et al.*, 2014; Al-Mousa *et al.*, 2016; Bradshaw *et al.*, 2018). However, the impact of CNV on penetrance remains unexplored and will require tailored studies technically equipped to capture large structural variation.

Lastly, we postulate that protective variants—coding and noncoding—also exist that are capable of rescuing aberrant biology in *cis* and in *trans*. It is easy to conceive that common variants in proteins that interact with the mutated proteins may have significantly more or less functional capability and can therefore rescue the deficient function of the defective gene product. However, given the complexity of interactions, these discoveries will likely prove especially evasive.

Principle III. Defined environmental exposures can shape manifestations of immune defects.

Known

Differences in environment are frequently offered as explanations for phenotypic discrepancies. Their net effect, now labeled the “exposome,” encompasses many factors relevant to the immune system including infections, resident microbes, diet/metabolism, and radiation. In fact, many of these insults are sufficient to trigger a secondary immunodeficiency in previously healthy individuals (Chinen and Shearer, 2010). Despite these robust effects, which are burgeoning disciplines in the broader field of immunology, only few well-substantiated examples for environmental modifiers in PIDs exist to date.

These factors are most readily appreciable in the case of susceptibility to infection, as exposure to infectious agents can vary greatly. In the simplest case, individuals harboring mutations that confer susceptibility to specific pathogens do not present if never exposed to that microbe. This is most readily appreciated in individuals with mutations linked to BCG-disease that did not receive BCG vaccine (Zhang *et al.*, 2015).

Yet, variable microbial exposures not only influence primary infections but also subsequently shape adaptive responses. At least for invasive pneumococcal disease from IRAK4- and MyD88-deficiencies, age and the immunity built with it are known to be major determinants of disease. Penetrance is highest by age 10, but IPD recurrence and mortality

subsequently falls with age—presumably from acquired anti-pneumococcal immunity (Picard *et al.*, 2010). This example raises the possibility that environmental exposures, which are thought to incite clinical presentations, can also protect. The best demonstration of this phenomenon exists in the incomplete penetrance seen in deficiency of TIRAP, a critical adapter in TLR-based sensing. Despite this complete innate immune defect, only 1/8 TIRAP-deficient homozygotes exhibited staphylococcal disease. In the other 7, acquired anti-LTA (staphylococcal lipoteichoic acid (LTA) Abs) rescued TLR-dependent susceptibility to staphylococcus (Israel *et al.*, 2017). This remains one of the most clearly substantiated demonstrations of environmental factors that explain disease segregation.

Infection may also trigger immune dysregulation beyond acute infection, as we now understand that pathogens are often the inciting event to autoimmune and autoinflammatory disorders. This notion is well captured in familial haemophagocytic lymphohistiocytosis (HLH), a previously fatal disease characterized by excessive macrophage and lymphocyte activity. When identified early in life, individuals with disease-causing mutations exhibit the hallmark cellular dysfunction prior to the development of clinical disease (Feldmann *et al.*, 2002). Further, upper respiratory or gastrointestinal infections tend to be present around the onset of HLH (Sung *et al.*, 2001). This sequence suggests that a known, and likely nonspecific infectious trigger is required for presentation. Such factors may account for variable disease presentation when mutation-carrying individuals are compared at a single point in time.

Other forms of environmental influence can also modulate penetrance in PID. LIG4-mutated individuals, who suffer lymphocyte deficiencies and nonimmune features due to DNA repair defects, are often clinically unremarkable until treated with chemotherapy and radiotherapy. Therefore, asymptomatic carriers of LIG4 mutations, may have yet to receive sufficient double-strand break insults to cross the threshold of disease (Felgentreff *et al.*, 2016). As these events are difficult to pinpoint in human patients, animal models have begun to interrogate these matters experimentally. In addition to the above example in *Neil3*-deficient mice (Massaad *et al.*, 2016), families with Schimke immune-osseus dysplasia (SIOD) display reduced penetrance that is insufficiently explained by their biallelic mutations in *SMARCAL1*, a conserved chromatin regulator (Bökenkamp *et al.*, 2005; Dekel *et al.*, 2008; Elizonod *et al.*, 2009). Drosophila and murine models for SMARCAL1 deficiency, which recapitulate the chromatin and transcriptional aberrances of SIOD, suggest that an additional environmental (heat-shock or pharmacologic) or genetic insult to transcription is required for disease manifestation (Baradaran-Heravi *et al.*, 2012).

Unknown

Immunization both provides answers and poses mysteries to the role of environmental exposures in variable penetrance. BCG vaccination for instance, represent an extremely well-controlled “experiment” of penetrance in which all individuals receive an identical pathogen at a similar age. Yet, we still observe incomplete penetrance for MSMD, as in IL12RB1 deficiency (~70% penetrance), suggesting that simple environmental differences cannot fully explain penetrance (Bustamante *et al.*, 2014). Likewise, some PID-specific pathogens are nearly ubiquitous, as in herpes simplex encephalitis (HSE), a sporadic disease

with known monogenic etiologies (Abel *et al.*, 2010; Bradley *et al.*, 2014). Despite nearly complete cellular defects in TLR3-dependent IFN immunity, 4/6 TRIF-deficient, 2/3 UNC-93B-deficient, 3/8 TLR3-deficient, 3/4 IRF3-mutant, and 2/3 TBK1-hypomorphic reported individuals have developed HSE (Casrouge *et al.*, 2006; Zhang *et al.*, 2007; Guo *et al.*, 2011; Sancho-Shimizu *et al.*, 2011; Herman *et al.*, 2012; Lim *et al.*, 2014; Andersen *et al.*, 2015; Mørk *et al.*, 2015).

In these cases, incomplete penetrance may instead be a function of other factors, including age at exposure. In support of this, HSE patients are most often young and recurrence is rare (Abel *et al.*, 2010). In cases with repeated HSE in childhood, patients have survived to adulthood and no longer develop HSE episodes (Whitley and Kimberlin, 2005; Zhang *et al.*, 2007; Lim *et al.*, 2014). This suggests that prior exposures may effectively immunize and regulate disease penetrance. We speculate that asymptomatic mutation carriers may have previously received non-infectious or exceedingly low-quantity exposures to HSV1 that are insufficient for productive infection but capable of inducing adaptive immune responses that potently neutralize future challenges that are truly infectious. A similar effect may occur with IL12RB1 deficiency, as patients that acquire BCG disease tend to be mutually exclusive with patients with environmental mycobacteriosis, suggesting that one may immunize against the other (Fieschi *et al.*, 2003; de Beaucoudrey *et al.*, 2011). The same mechanisms could apply to other infectious susceptibilities, both broad and narrow, but of course will require experimental evidence.

Yet, perhaps the most important interactions with microbial species occur with those bacteria, fungi and viruses that naturally colonize our tissues. The microbiome represents our first and most abundant exposure to microbial organisms. It is therefore unsurprising that in the last decade the microbiome has proven to be a major determinant of immune function and disease (Belkaid, 2015; Gilbert *et al.*, 2018). Despite these strong associations, the relevance of the microbiome in PIDs, the most extreme immune pathologies, is yet unknown. Recent studies demonstrating altered bacterial microbiota in CVID, which correlate with immune activation (Jørgensen *et al.*, 2016; Fiedorová *et al.*, 2019) have begun to scratch the surface, but the direction of causality remains unclear. We hypothesize that specific microbiota regulates the penetrance of PIDs by shaping the relative tolerance and reactivity of the innate or adaptive immune system. The divergence of the microbiome with respect to geography and diet may underlie PID phenotypes that vary across populations with similar monogenic lesions. However future studies that include microbial sequencing in PID cohorts will be required moving forward.

Lastly, it should also be noted that the environment of modern times differs markedly from that which our ancestral immune systems evolved. Just a century ago, when mortality from infectious causes was 200-fold more frequent, up to one-third of children died before the age of five (Roser, Ritchie and Dadonaite, 2019). It is likely that a study on the genetics of infectious disease a century ago, with the tools of today, would have identified far more common alleles as causative. Yet in modern times, these genetic susceptibilities are likely masked by sanitation, vaccination and antibiotic usage. Close examination for these potential alleles in isolated systems may be informative and contribute to our understanding of incomplete penetrance. On the other side of the coin though, our recent use of

immunosuppressants in the clinic may draw out new and old genetic susceptibilities with surprising frequency and pathogen specificity.

Principle IV. Mosaicism of disease-causing alleles reduces clinical penetrance.

Known

The above discussions assume that all cells in affected individuals carry the same mutation, but we now understand that cells differ genetically with surprising frequency within a single individual. Genetic mosaicism originates from post-zygotic (*de novo*) mutations that arise during the embryonic or postnatal period. At first believed to be a rare occurrence in PIDs, somatic mutation is now understood to be rather common. In fact, a recent systematic analysis across PIDs using targeted deep sequencing in 128 families estimated mosaicism to be 23.4% (Mensa-Vilaró *et al.*, 2019).

Disease occurrence, onset or severity are often less intense in cases of mosaicism, as a direct consequence of gene dosage. Reduced penetrance in mosaic PID was first documented in an extraordinary case followed through the 1980s and 1990s of delayed-onset ADA-deficiency, which is typically a severe form of SCID. *ADA* mosaicism was directly observed in peripheral blood cells, and overtime, ADA-normal populations overtook as clinical disease resolved (Uberti *et al.*, 1983; Arredondo-Vega *et al.*, 1990; Hirschhorn *et al.*, 1994). After this discovery, several other documentations of mosaicism followed (Puck *et al.*, 1995; O'Marcaigh *et al.*, 1997), with many presenting as mild or atypical disease phenotypes, including mutations in *NLRP3* (de Koning *et al.*, 2015; Rowczenio *et al.*, 2017), *STAT3* (Hsu *et al.*, 2013; Walker *et al.*, 2016), *FAS* (Holzelova, Vonarbourg, M.-C. Stolzenberg, *et al.*, 2004; Dowdell *et al.*, 2010), *CYBB* (Wolach *et al.*, 2005), and *TNFAIP3* (Kadowaki *et al.*, 2018). Curiously, these appear to be predominantly disorders of immune hyperactivation rather than deficiency.

As these cases accumulate, the evidence for mosaicism as a mechanism for reduced penetrance has strengthened. In a recent systematic analysis of 10 families where one member carried a post-zygotic mutation for a PID gene, 80% of mosaic individuals were asymptomatic. The remaining mosaic individuals exhibited only partial clinical disease, whereas their progeny with germline mutation status demonstrated complete disease (Mensa-Vilaró *et al.*, 2019). Likewise, examination of variant read frequencies in a family with PIK3CD mutations revealed that affected siblings harbor more mutant cells than their mildly-affected father, with allele fractions of 37%−54% and 15%, respectively (Stray-Pedersen *et al.*, 2017). However, when mutant cells predominate in the relevant cell compartment, differences between germline and somatic cases fade. For example, ALPS patients harboring FAS mutations in ~100% of their double-negative T-cells (the pathologic cell-type of ALPS) demonstrate complete disease despite undetectable levels of mutation in whole blood. (Holzelova, Vonarbourg, M. C. Stolzenberg, *et al.*, 2004; Dowdell *et al.*, 2010).

Somatic mutations may also create "second hits" that allow an otherwise clinically-silent disease to manifest. For example, ALPS patients have been documented to carry both an

inherited heterozygous *FAS* mutation and a somatic event in the second *FAS* allele, including missense mutations, nonsense mutations or loss of heterozygosity (Magerus-Chatinet *et al.*, 2011; Neven *et al.*, 2011; Hauck *et al.*, 2013). Alternatively, the second hit may be at a different locus, as in a recent report of a somatic *FAS* mutation complexed with an existing *CASP10* mutation (Martínez-Feito *et al.*, 2016). In all cases, relatives who never developed a second mutation post-zygotically remained asymptomatic or partially affected, substantiating the importance of 'second hit' mosaicism on incomplete penetrance.

Yet, somatic mutation can also rescue disease rather than cause it. Several cases have been documented in which somatic reversions underlie mild or absent clinical disease that appears as variable expressivity or incomplete penetrance. For instance, reversion in DOCK-8 deficiency, which occurs in roughly half of affected patients, associates with longer survival and less severe allergic disease, albeit similar infectious susceptibility (Jing *et al.*, 2014). Several other examples exist of reversions underlying incompletely penetrant clinical disease, including in ADA (Ariga, Oda, *et al.*, 2001), XLA (Stephan *et al.*, 1996; Speckmann *et al.*, 2008), WASP (Ariga, Kondoh, *et al.*, 2001; Boztug *et al.*, 2007), leukocyte adhesion deficiency (Tone *et al.*, 2007), X-linked immunodeficiency with ectodermal dysplasia due to mutations in *NEMO* Nishikomori 2004, Omenn syndrome with *CARD11* deficiency (Fuchs 2015), and IKBKG-associated immunodeficiency (Stray-Pedersen *et al.*, 2017). Interestingly, these reversions may even be second-site mutations of the mutated gene that create altered non-WT, but still functional, gene products (Boztug *et al.*, 2008).

Although most mosaic PIDs appear stable with time (Rowczenio *et al.*, 2017; Mensa-Vilaró *et al.*, 2019), somatic reversions that bestow a fitness advantage allow reverted cells to selectively expand and reestablish healthy immune cell populations. For instance, reversions of mutations in JAK3, an essential mediator of lymphocyte development, can repair immune cell proliferation and differentiation. In one family with JAK3 hypomorphic mutations, the asymptomatic sibling showed CD4+ T-Cell reversion, whereas a brother without this reversion suffered recurrent respiratory tract infections (Ban *et al.*, 2014). In an extreme case, McDermott and colleagues reported a WHIM patient cured by a process known as chromothripsis, or "chromosome shattering," in which chromosomes undergo massive deletion and rearrangement. Fortuitously, this event deleted the mutated CXCR4 allele in a single hematopoietic stem cell, which then took over the bone marrow and reconstituted immune function (McDermott *et al.*, 2015). However, if the selective pressure is removed, as in the case of enzyme replacement therapy in ADA-deficiency with reversions or allogeneic stem cell therapy, the WT cells seemingly lose their selective advantage and proportionally decline (Ariga, Kondoh, *et al.*, 2001).

Unknown

Despite strong associations between mosaicism and mild disease, there are cases in which mosaic mutations lead to severe disease (Niemela *et al.*, 2011; Takagi *et al.*, 2011; Shiota *et al.*, 2015; Walker *et al.*, 2016; Ma *et al.*, 2017; Gruber *et al.*, 2019). Of note, some of these cases are the first and only reports of patients with such mutations, suggesting that these defects may be embryonically/perinatally lethal at germline status. Although these instances may be the exception that proves the rule of mosaicism in incomplete penetrance, it fails to

explain many others (Del Bel *et al.*, 2017; Gruber *et al.*, 2019; Mensa-Vilaró *et al.*, 2019). Evolving technologies and expanded cohorts will be central to answering the remaining questions. As Sanger sequencing previously failed to detect many low-frequency somatic variants, standard WES and WGS also suffer inherent limits of detection. This is not simply a function of total mosaic fractions, but also of the tissue being assayed. Many somatic mutations have been documented to be only detectable in specific immune cell types (Dowdell *et al.*, 2010; de Koning *et al.*, 2015; Walker *et al.*, 2016), and it is likely that many more such cell-type specific mutations exist, including extra-haematopoietically.

Yet beyond the genotype, it has recently become clear that mosaicism can also exist at the transcript level across genetically identical cells (Reinius and Sandberg, 2015). Similar to X-inactivated genes, autosomal genes can be expressed from a single allele in a random fashion across cells from one individual. This restriction to one allele can occur dynamically, as in transcriptional bursting (Deng *et al.*, 2014; Reinius *et al.*, 2016), or remain fixed over time in what is designated as monoallelic expression (MAE) (Gimelbrant *et al.*, 2007; Jeffries *et al.*, 2012; Borel *et al.*, 2015; Reinius and Sandberg, 2015). Remarkably, up to 10% of the autosomal genome exhibits this phenomenon (Gimelbrant *et al.*, 2007). For these genes, allelic bias is established in lineage differentiation by a unique chromatin signature and persists with subsequent cell division (Nag *et al.*, 2013; Gendrel *et al.*, 2014).

Although we increasingly understand the nature of this epigenetic phenomenon, we have yet to grasp the functional consequences, especially in light of genetic disease. Heterozygous mutations occurring in MAE genes will create a mixture of both WT- and mutant-expressing cells with divergent phenotypes in affected individuals. We hypothesize that, by creating this mosaic “transcriptotype”, MAE can modulate the functional impact of disease-causing mutations. Because the proportions of cells expressing one allele or another vary at random (Gimelbrant *et al.*, 2007; Jeffries *et al.*, 2012; Borel *et al.*, 2015), MAE may help explain phenotypic variation in genetic disease. For AR disease, this phenomenon will present in affected carriers, whereas in AD disease, mosaicism will reduce penetrance of disease phenotypes in patients.

While this hypothesis remains unsubstantiated, supporting evidence has begun to accumulate. Computational predictions suggest an enrichment of MAE in genes for which gain-of-function variants with AD inheritance are linked to neuropsychiatric disease (Savova *et al.*, 2017). Experimentally, disease-related genes have been demonstrated to undergo MAE (Adegbola *et al.*, 2015) and, recently, the first gene mutation with allelic bias was documented (Gruber *et al.*, 2019). Clearly, future studies aimed at testing MAE in PID genes are warranted, which will require careful and intensive experimentation to compare expression across single cells. As most single cell technologies currently lack sufficient depth and breadth of transcript coverage for meaningful study, and clonal systems are biased, significant technological advance will be required. Nevertheless, if certain PID genes undergo MAE, our classical notion of heterozygosity would need to be redefined.

Conclusions

Failing to understand penetrance in PID has hindered our advance in human genetics. By amassing the cases of variable penetrance in PID, this review aimed to illuminate where connections lie, and gaps persist. It is clear that four major influences continually reduce penetrance (partial genetic defects, (epi)genetic modifiers, environmental influences and mosaicism), while others remain unexplored (genomic compensation, protective variants, sub-infectious inoculations, monoallelic expression) (Figure 1). Although discussed separately, these driving principles likely work in tandem and interact. It should be noted that the biggest breakthroughs in these domains have come not only from reports of large cohorts, but also intense study of single patients. Thus, furthering our understanding of penetrance will require studies of comprehensive depth and breadth.

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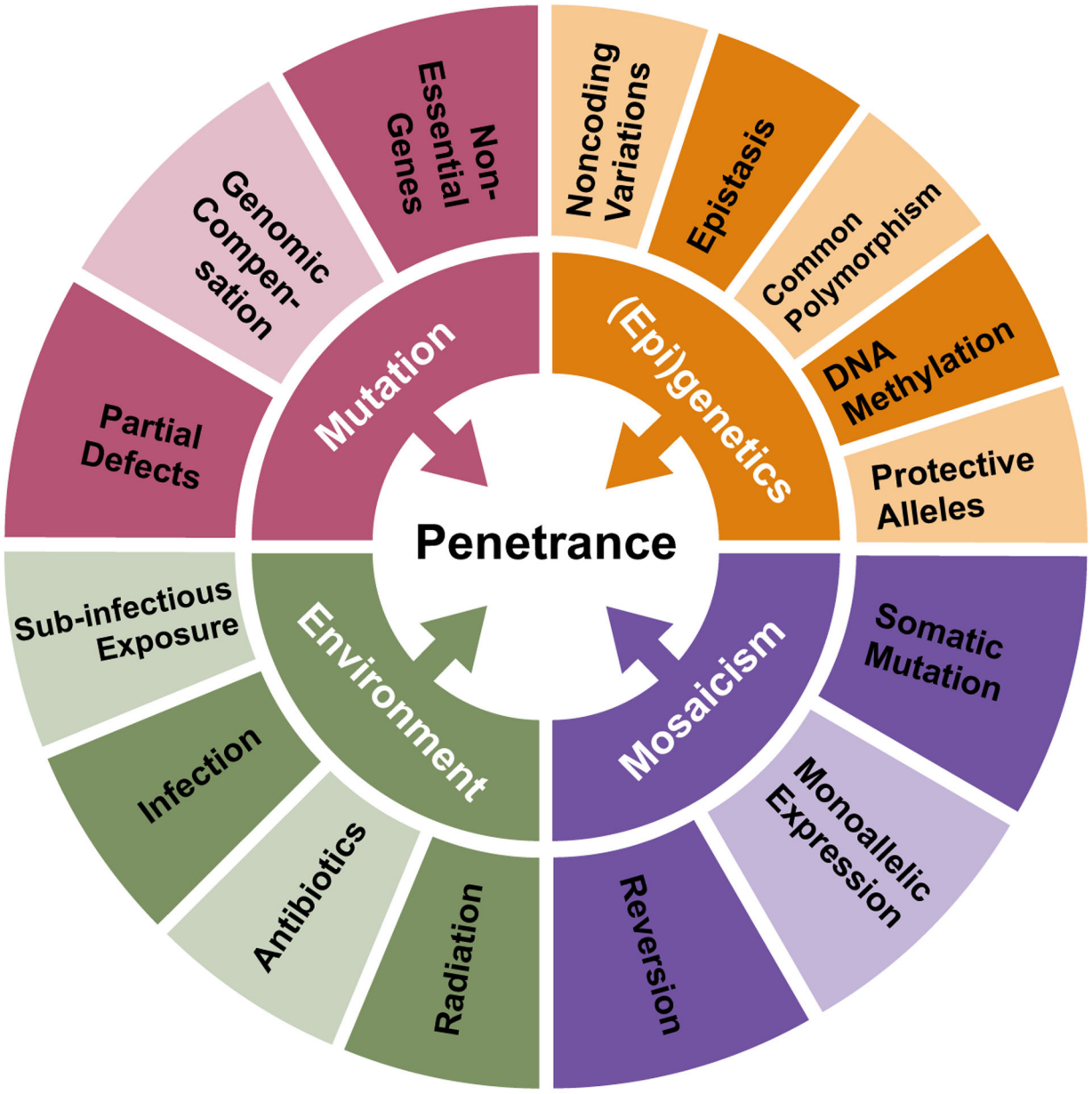

Figure 1. Four principles of incomplete penetrance in primary immunodeficiency.

Inner circle represents the four broad principles of incomplete penetrance, with the outer circle denoting specific processes that are established (dark) or hypothesized (light) to contribute.