Clinical Impact of Current Genetics Findings

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Atopic dermatitis (AD) is the one of the most common chronic skin diseases with prevalence rates of up to 20% in young infants and children and up to 5% in adults. The majority of patients show an onset of disease in early childhood and a spontaneous remission until adolescence, but there might be relapses, and the disease can also start in or persist into adulthood. AD presents a wide spectrum of clinical patterns and a variety of trigger factors with variable importance in the individual patient. It is frequently accompanied by elevated levels of total serum IgE antibodies and IgE-mediated responses to common allergens, and often co-occurs with other allergic disorders such as food allergy, asthma and rhinitis, giving further rise to possible subpopulations of patients [1].

Since there is no objective laboratory test or histologic finding specific for AD, diagnosis is usually made on the basis of a dermatologic examination of skin lesions considering their age-specific morphology and distribution. Further signs leading to the diagnosis of AD are the chronicity of symptoms and their association with pruritus [2]. For large epidemiologic studies, numerous diagnostic criteria have been developed in order to establish a definition for AD by using reliable discriminators resulting in increased validity and reproducibility of the diagnosis of AD. At present, the UK diagnostic criteria are most widely validated and appear to be applicable and repeatable across all ages and many ethnicities. However, as shown in a recent review, the ideal set of diagnostic criteria still has to be established [3].

The pathophysiology of AD is complex and involves a disturbance of the epidermal barrier as well as abnormal immunological and inflammatory pathways leading to a Th2-dominated immune response with a Th17 component in acute AD lesions and the progressive conversion to a Th1-dominated response in chronic AD lesions [1].

The observation that atopic diseases tend to cluster in families has led to the term atopic diathesis. The observation that a proportion of children with AD proceeds to develop allergic airway disease later in life has led to the concepts of 'atopic march', i.e. it has been suggested that AD is the cutaneous manifestation of 'the atopic phenotype' (as a common underlying trait) [4], and that there is a characteristic longitudinal progression of individuals through a predictable and sequential/overlapping series of phenotypes from AD, food allergy, through allergic rhinitis and asthma [5]. However, it is notable that a significant proportion of patients with AD is not 'atopic', having normal total serum IgE concentrations and no specific IgE responses [6, 7]. Furthermore, recent epidemiological research indicates that sensitization might simply be a shared epiphenomenon rather than a causal factor [6, 8, 9]. In addition, the longitudinal nature of the 'atopic march' is not easily reconciled with observations made in some cohort studies which suggest that the association between asthma and AD may occur much earlier, i.e. early co-occurrence of AD and early wheezing which progresses into asthma [6]. Newly discovered mechanisms such as epidermally produced thymic stromal lymphopoietin-mediated lung inflammation may provide explanations other than allergic sensitization for an early co-association of AD and asthma [10, 11]. Thus, the concepts of a common syndrome of atopic diseases and an 'allergic march' might be oversimplifications, and it appears that at least a proportion of pathophysiologic mechanisms is disease specific.

Thus, it is unclear whether AD is a single disorder with different clinical manifestations or a syndrome with unique or overlapping pathophysiologic pathways that coincide in a rather uniform clinical presentation. An unambiguous definition of patient subgroups is highly desirable in order to facilitate further epidemiologic, genetic and clinical investigations. Molecular studies could be of great nosological significance in that they might not only enhance our understanding of the atopic disease pathophysiology, but also enable a classification of AD based on the underlying genetic effects rather than on hypothetical concepts and clinical symptoms as it is the case today. A similar development already took place in other medical fields such as in neurodegenerative diseases, many of which are now defined by specific mutations in disease genes (e.g. spinocerebellar ataxias).

Evidence for the Heritability of Atopic Dermatitis

Family, twin and adoption studies have provided compelling evidence that inherited factors are of key importance in the determination of interindividual differences of susceptibility to atopic disorders, and that there is a range in phenotypic expression of this genetic predisposition [12]. Twin studies have found concordance rates for atopic dermatitis of 72–86% in monozygotic and 21–23% in dizygotic twin pairs, and segregation analyses suggested that genetic factors account for more than 70% of the variance in the susceptibility to AD [13–16]. As is the case for most traits of medical

relevance, AD does not follow a simple Mendelian monogenic inheritance, but is considered a 'complex trait' (polygenic and multifactorial). Complex traits are the result of a complicated network of numerous susceptibility loci, many of which exert additive or synergistic effects, but have only a small role when considered in isolation [17, 18]. Among other reasons, failures to identify and replicate individual genetic risk factors for complex diseases have been attributed to epistasis (gene-by-gene interactions) obscuring the effect of single loci [19, 20]. In addition, disease-predisposing genes interact with nongenetic environmental factors to determine the final phenotype.

Approaches for Finding Atopic Dermatitis Risk Genes

Understanding the genetic architecture of common and complex diseases is of great interest to the biomedical community. In the past few years there have been tremendous advances in molecular methods and quantitative techniques that have led to remarkable progress in complex trait genetics. However, understanding the complex networks of genes, proteins, and metabolites interacting via biochemical and physical interactions to determine the phenotype remains challenging [21].

In general, there are three types of studies that have been used to identify gene variants associated with susceptibility to AD: genomewide linkage scans followed by fine mapping of a linked region, candidate gene association studies, and genomewide association (GWA) studies [22]. Alternative approaches include the use of gene expression arrays, and the combination of gene expression analyses with genomewide genotyping for quantitative trait loci mapping [23]. In addition, animal models represent a useful complement to human-based genetic studies [24]. However, for AD so far there is no single comprehensive animal model, so that many of the disease components will have to be modeled in animals as isolated traits (and subsequently in combination) to explore pathophysiological mechanisms [25].

Hints from Genomewide Studies

Genomewide linkage studies are hypothesis-free scans comparing the transmission of genetic information with the disease within families. To this end, a relatively small set of highly polymorphic markers that cover the entire genome is investigated. While linkage studies have been very successful in mapping rare single-gene disorders, the technique has proven to be less powerful for mapping complex diseases, in which multiple low-risk genetic variants are involved. In addition, linkage regions usually extend over large distances that might contain hundreds of genes and thus require intensive follow-up fine mapping analyses [26].

To date five genomewide linkage studies have been carried out on AD. The results from these genome screens largely differ from one another, and under a threshold

of no more than 10 cM distance between linkage peaks replication can only be considered for a locus on chromosome 3p24 [27, 28]. The lack of replication of linkage peaks in independent studies might be due to genetic heterogeneity or differences in ascertainment schemes and phenotype definitions, sample sizes, marker panels and analytical methods, but more likely it reflects the limitations of linkage studies for the dissection of complex traits, especially when utilized on small samples sizes. Apart from *filaggrin* (*FLG*), which accounts for part of the significant linkage signal on 1q21 [29], the underlying disease genes for all other susceptibility loci identified by that approach remain elusive. Interestingly, regions linked to AD show only very limited overlap to those of asthma, suggesting that susceptibility to asthma and eczema is mediated through different genes rather than through a shared susceptibility to a common atopic background in family aggregated forms of these diseases. The AD loci identified thus far are, however, closely coincident with psoriasis susceptibility regions, e.g. 1q21, suggesting that these conditions share susceptibility loci in genomic regions encoding genes most relevant for the skin as target organ. These overlaps of associations may hint to shared and general effects of dermal inflammation, immunity and structure and to an important role for proteins expressed by epithelial cells in both diseases [30].

The advent of the genomewide association (GWA) approaches, which had become feasible through newly developed high-throughput single nucleotide polymorphisms (SNP) genotyping platforms and knowledge gained from the HapMap project, has revolutionized the discovery of genetic variants associated with complex diseases [31]. In the past years, hundreds of common low-risk variants (i.e. those that are present in more than 5% of the population and typically with ORs of 1.2–3.0) could be identified for more than 70 complex disorders and traits, which however explain only a modest proportion of heritability [32]. In general, GWA studies clearly represent a powerful new tool. However, the potential of GWA studies needs to be kept in perspective. GWA approaches present many logistical, technical and biostatistical challenges, and have several significant limitations. These limitations include false-positive and false-negative results and susceptibility to bias through incomplete coverage of SNPs in the genome, genetic and disease heterogeneity, the insensitivity to rare variants (such as *FLG* mutations), structural variants (such as copy-number variants), and variants in recombination hotspots, the need for the large sample sizes and follow-up investigations (to detect causal variants) and the lack of information on gene function [33]. However, GWA studies clearly have the potential to significantly advance our understanding of the genetics and pathogenetic mechanisms of complex diseases such as eczema, if the studies are performed under stringent conditions, are sufficiently powered, and are thoroughly reproduced in independent populations [34].

So far, only one GWA screen has been carried out for AD. This GWA study incorporated more than 307,000 SNP markers and 10,000 individuals from both family and case-referent panels mainly collected from Germany [35]. A robust site of

association was identified on chromosome 11q13.5, with the strongest association observed for SNP rs7927894, which is located in an intergenic region between two annotated genes, *chromosome 11 open reading frame 30 (C11orf30)* and *leucine rich repeat containing 32 (LRRC32)* [UCSC Genome Browser, Human Genome March 2006 assembly, 259 <http://genome.ucsc.edu>]. This association has recently been confirmed in another independent population of Irish pediatric AD cases [36]. Interestingly, the same risk allele (rs7927894 allele A) also showed an association with Crohn's disease in another GWA study [37]. The causative gene or gene product defined by this SNP, however, remains to be identified and functionally characterized. Within the AD GWA study, the association of four prevalent *FLG* null mutations with eczema could again be confirmed, a potential susceptibility SNP located within the gene encoding the filaggrin-related protein hornerin from within the EDC was found, and putative, nominally significant associations of SNPs in six additional loci were observed. Clearly, follow-up studies are needed to determine out causal variants and associated phenotypes.

GWA studies have also resulted in the identification of novel susceptibility genes for asthma (*ORMDL3*, *CHI3L1*, *PDE4D*, *IL13-RAD50*) [38–41], as well as for total IgE in the gene encoding the high-affinity receptor for IgE (*FCER1A*), in the *STAT6* and in the *IL13-RAD50* locus [42]. These genes have been replicated and functional studies have supported their relevance in asthma and atopy, whereas their potential role in eczema is not clear yet.

Candidate Genes for Atopic Dermatitis

Candidate gene association studies analyze the distribution of genetic markers, usually SNPs, in unrelated individuals (case-control and case-cohort studies) or their transmission in families (family-based design) [21]. The selection of a candidate gene for study is based upon an a priori hypothesis. These arguments may either be positional, i.e. the gene is located in a region for which linkage had been observed in prior screening studies or functional, e.g. on the basis of a specific biological hypothesis or both.

More than 100 candidate genes have been investigated for association with AD so far, and assuming publication bias there are probably more genes for which associations have been sought but failed [43]. However, these hypothesis-driven studies mostly yielded inconsistent results. Only very few associations could be replicated in at least one independent study (table 1), and the specific phenotypes found to be associated varied, possibly indicating a role for the atopic state rather than eczema per se. Furthermore, the observed effects were mostly very modest, and even for replicated genes a considerable number of negative reports exist. Common reasons for the irreproducibility of results include inappropriate selection of candidate loci and markers, small sample sizes, inadequate assessment of the trait of interest and the use

Table 1. List of the genes and their chromosomal location that have been associated with AD in at least two independent

Gene	Location	Variant(s)	Phenotype(s)	Population	Number of subjects (cases:controls, cases/cohort)	Association	Reference
FLG	1q21.3	multiple variants	AD, extrinsic AD, childhood AD, adult AD, AD + asthma	European, European-American, Japanese, Chinese, Taiwanese	>6,000:>27,000 >3,000 families	yes	plus >20 reports (reviewed in [61, 79])
TLR9	3p21.3	rs5743836	AD	German	281 trios	yes	[80]
		rs5743836	AD	German	202 trios	yes	[80]
		rs5743836	adult AD	German	274:252	no	[80]
		rs187084, rs352139, rs352140	AD	German	281 trios	no	[80]
		rs187084, rs352139, rs352140	AD	German	202 trios	no	[80]
		rs187084, rs5743836	adult AD	German	136:129	no	[81]
IL13	5q31	rs20541	childhood AD	White Canadian	52:288	yes	[82]
		rs1800925	AD	Dutch	238:104	yes	[83]
		rs20541	AD	Japanese	185:102	yes	[84]
		rs20541	AD	German	187:98	yes	[85]
		rs1800925	childhood AD	White Canadian	52:288	no	[82]
		rs1800925, rs20541	AD	Chinese	94:186	no	[86]
		rs1800925, rs1881457	AD	Japanese	185:102	no	[84]
		rs1800925, rs2066960, rs1295686, rs20541, rs1295685	childhood AD	British	178/1,358	no	[87]

Table 1. Continued

Gene	Location	Variant(s)	Phenotype(s)	Population	Number of subjects (cases:controls, cases/cohort)	Association	Reference
SPINK5 (LEKTI)	5q32	rs2287774	asthma	Chinese	669:711	yes	[88]
		rs2303067	childhood AD	British	148 families	yes	[89]
		rs2303067	childhood AD	British	73 families	yes	[89]
		rs2303067, rs2303063, rs2303061, rs2303062, rs2303066, rs2303068	AD	Japanese	124:110	yes	[90]
		rs2303067, rs2303063, rs2303064, rs17860502, rs2303070	AD + asthma	Japanese	41 families	yes	[91]
		rs2303067	AD	German	486 trios	yes	[92]
		rs2303067	AD	German	773:3992	no	[92]
		rs2303067	childhood AD	Irish/UK	418:552	no	[92]
		rs2303067	childhood AD	UK	1583/7746	no	[92]
		rs2303067	childhood AD	German	220/1161	no	[93]
		rs2303067, rs2303063, rs3756688	AD + asthma	Dutch	78:200	no	[94]
		rs2303067, rs2303063, rs3756688	AD + asthma	Dutch	175 trios	no	[94]
		rs2303067	AD	French	99:102	no	[95]
		rs2303063, rs2303064	childhood AD	British	148 families	no	[89]
		rs2303063, rs2303064	childhood AD	British	73 families	no	[89]
		rs2303063, rs2303065	AD	Japanese	124:110	no	[90]
		rs2303067, rs2303064, rs2303063, rs2303070	asthma	Chinese	669:711	no	[88]

Table 1. Continued

Gene	Location	Variant(s)	Phenotype(s)	Population	Number of subjects (cases:controls, cases/cohort)	Association	Reference
		rs2303067, rs2303063, rs2303064, rs17860502	AD	German	308 trios	no	[96]
CMA1 (chymase)	14q11	rs1800875	adult AD	Japanese	100:100	yes	[97]
		rs1800875	childhood AD	Japanese	145/851	yes	[98]
		rs1800875	intrinsic AD	Japanese	47:100	yes	[99]
		rs1800875	adult AD	German	242/1875	yes	[100]
		rs1800875	AD	Japanese	100:101	no	[101]
IL4RA	16p12–11	rs2057768), rs2107356, rs8060798, rs8060938, rs12927172	AD	Japanese	101:75	yes	[102]
		rs1805011	adult AD	Japanese	27:29	yes	[103]
		rs1801275	infantile flexural AD	British	245/1051	yes	[104]
		rs1805010, rs1805012	adult AD	Japanese	27/29	no	[103]
		rs1805010, rs1805011, rs1801275	extrinsic AD	Japanese	302:122	no	[105]
		rs12927543	AD	Japanese	101:75	no	[102]
		rs1805011, rs2234898, rs1805012, rs1801275, rs1805015	AD	Chinese	94/186	no	[86]
NOD1 (CARD4)	7p15-p14	rs2736726, rs2075817, haplotype	adult AD	German	457/1417	yes	[106]
		rs2975632, rs2075822, rs2907749, rs2907748	AD	German	189 trios	yes	[106]
		haplotype	AD	German	392:297	yes	[107]

Table 1. Continued

Gene	Location	Variant(s)	Phenotype(s)	Population	Number of subjects (cases:controls, cases/cohort)	Association	Reference
RANTES (CCL5)	17q11.2-q12	rs2107538	childhood AD	German	188:98	yes	[108]
		rs2107538	AD	Japanese	62:14	yes	[109]
		rs2107538, rs2280788	extrinsic AD	Japanese	389:177	yes	[110]
		rs2107538, rs2280788	childhood extrinsic AD	Hungarian	128:303	no	[111]

of inappropriate controls, flaws in study design and inappropriate statistical modeling, failure to replicate, and genetic and environmental heterogeneity [20].

Based on reported data, only *FLG*, which is presented and discussed in more detail below, appears to represent a strong and consistent AD risk gene across all collections in all populations and in multiple large independent studies.

Filaggrin

Among the loci linked to AD is the susceptibility region for psoriasis and ichthyosis vulgaris (IV), a common monogenic disorder of keratinization, on chromosome 1q21 [44], which contains the epithelial differentiation complex (EDC) [45]. The EDC is a dense cluster of genes, all of which are involved in the terminal differentiation of the keratinocytes [46]. The EDC gene *filaggrin*, which displays a complex highly repetitive sequence, encodes a key protein in the formation of the outermost keratin layer of the skin [47]. The large precursor of filaggrin, profilaggrin, is expressed in the keratohyalin granules of the stratum granulosum, and during formation of the cornified cell envelope it is dephosphorylated and proteolytically cleaved into the N-terminal S-100 protein and 10–12 individual filaggrin peptides [48, 49]. After cleavage, the amino-terminal domain of filaggrin enters the nucleus, where it has been suggested to have a role in regulating terminal differentiation, whereas the liberated filaggrin peptides participate in the aggregation of keratin filaments into bundles thereby promoting the flattened shape of corneocytes. Thereafter, they are released from the filaments and progressively degraded into hygroscopic amino acids and derivatives of amino acids which are believed to function as ‘natural moisturizers’ of the skin, which contribute to skin hydration, maintenance of skin pH and antimicrobial defense [50, 51]. Thus, filaggrin and its breakdown products have profound effects on skin barrier function.

Fig. 1. Diagram of the human profilaggrin gene and domain structure. Exon 1 encodes untranslated sequence only, exon 2 contains the start codon, and the large (12,753 bp) exon 3 encodes most of the N-terminal domain and 10–12 filaggrin monomers. The position of reported loss-of-function mutations is indicated by arrows. Figure adapted from O'Regan et al. [112].

A genetically determined filaggrin deficiency was first considered to be involved in ichthyosis vulgaris, a common disease leading to an excessive scaling of the skin, and in eczema [52]. However, many confounders such as inconsistencies in the reported inheritance pattern, erroneously reported linkage, and a repetitive gene sequence limiting amplification delayed confirmation of this association until in 2006 two loss-of-function *FLG* mutations (R501X and 2282del4) could be identified that exhibited a semidominant pattern of inheritance with incomplete penetrance [52].

In the meantime more than 30 *FLG* mutations have been reported [53], seven of them common at least in one population studied [54, 55]. Interestingly, many variants appear to be population specific, with most variants identified in populations of European ancestry, while other *FLG* gene mutations appear to be restricted to Asian populations [54, 56] (fig. 1). All these variants lead to frameshifts, premature stop codons, or nonsense mutations and prevent the production of free filaggrin in the epidermis. Carriers of one *FLG* mutation show marked reduction of *FLG* expression as measured by immunohistochemistry, whereas processed filaggrin is completely absent in homozygotes and compound heterozygotes [52, 54].

The well-known clinical association between IV and AD and the previously observed decrease of filaggrin expression in AD [57, 58] suggested that *FLG* loss-of-function mutations might also be of relevance for AD. Subsequently, Palmer

et al. showed that both the R501X and 2282del4 alleles are strong predisposing factors for AD [59]; following this initial report an impressive series of independent replication studies (for reviews, see [55, 60, 61]) has provided unequivocal evidence that *FLG* null alleles are major risk factors for AD. These studies also indicate that *FLG* null alleles predispose particularly to an early-onset, severe and persistent course of AD with allergic sensitizations (for reviews, see [55, 62]). Remarkably, *FLG* null alleles are rather common with carrier frequencies of ~8% in the general population and around 20% in AD cases [61, 63, 64]. In two large population-based studies [65, 66] it was demonstrated that, assuming causality, filaggrin mutations account for up to 15% of the total causality of all AD in these populations. Thus, *FLG* mutations are the strongest and best replicated genetic risk for AD to date.

FLG null alleles show an incomplete penetrance of 38.5% for the manifestation of clinically relevant AD. Recently, a strong association of *FLG* mutations with dry skin as an intermediate trait could be shown [67, 68]. Thus, it seems plausible that *FLG* mutations primarily cause a 'dry or defective skin barrier' which, when driven by additional genetic and environmental factors, results in AD in a large proportion of carriers.

So far, studies on *FLG* mutations were primarily performed in AD cohorts while their role in atopic diseases independently from AD has not been fully determined. Several studies showed that *FLG*-deficient AD is characterized by an increased risk for allergic sensitization, elevated IgE levels, and concomitant asthma and/or allergic rhinitis (for reviews, see [55, 62]). However, filaggrin is not expressed in the human bronchial mucosa [69], and so far only associations with asthma in the presence of AD and with asthma severity, but not with asthma per se, have been observed [59, 70, 71]. Thus, it has been suggested that asthma in individuals with AD could be secondary to sensitization through a primarily defective epidermal barrier [72, 73]. This hypothesis is supported by a recent population-based study on adults which demonstrated associations of *FLG* mutations with 'dry skin' independent from the presence of AD, whereas associations with elevated IgE levels were only observed in atopic individuals [74]. More recent functional studies indicated that filaggrin mutations are associated with decreased levels of natural moisturizing substances, increased transepidermal water loss and increased skin pH, whereas they do not seem to contribute to the altered ceramide profile observed in AD [75, 76]. However, more research is needed to elucidate the phenotypic characteristics caused by *FLG* mutations. Furthermore, the hypothesis of a 'dry or defective barrier' in *FLG*-mutation carriers remains to be proven [62].

Based on a post-hoc analysis of a subset of children from the German MAS birth cohort it was also claimed that the combination of *FLG* mutations and early sensitization to food allergens represents a remarkably strong predictor for later asthma [77]. Indeed, an easy-to-measure biomarker to identify individuals at risk for asthma before disease manifestation would be highly desirable and an obvious

prerequisite for effective primary prevention measures. However, results from the study that was based on only a small number of infants ($n = 10$) with AD, *FLG*-null alleles and sensitization to food allergens who made the transition to asthma later in childhood need to be interpreted with caution. In addition, no stepwise regression method was applied and the same data was used to both develop and evaluate the predictor. Thus, independent replication and application of such a predictor to an a priori data set are needed to validate the prediction value for asthma.

Clinical Impact of Genetic Findings

Without doubt, the identification of risk genes for AD is of great importance to increase our knowledge of its pathophysiologic mechanisms. Genetics will help to critically review our current concepts of diagnosis and treatment of AD and help to develop more effective approaches.

Despite much effort and progress over the past 2 decades, our understanding of the complex genetic susceptibility to AD remains in the early stages, as it is the case for other complex diseases. Major barriers to progress are the high phenotype variability of AD, its incomplete penetrance and its modification through environmental influences. Based on reported data, only *FLG* appears to clearly convey a strong and consistent AD risk across populations and in multiple large independent studies. Most other candidate genes for AD show inconsistent replication patterns. Data on the recently identified AD susceptibility gene from chromosome 11 identified by a GWA study [35] has not yet been replicated sufficiently to judge its relevance and robustness.

There is a need for further large-scale and whole genome studies both to clarify the roles of currently suggested candidate genes and to identify additional novel susceptibility loci. For AD, gathering data through genomewide approaches is still at an early stage and, in general, the ability to interpret genomic data accurately, evaluate their clinical utility, and use them to develop new prevention or treatment measures will require much effort in the future.

GWA studies for complex diseases so far mostly identified variants with small effects explaining only a small proportion of disease susceptibility. Nevertheless, such variants might well help to identify new and specific disease pathways and help to develop treatments that act on those pathways in individual patients.

The best example for this to date is the association of filaggrin with AD. Filaggrin deficiency seems to cause a frequent subtype of AD which develops on the basis of a mutation in the *FLG* gene ('single-gene subtypes') and not because of the predisposing effects of multiple genes and interacting environmental factors. This subtype of AD might require different treatments and potentially different preventive strategies. Since most of the *FLG* mutations identified thus far cause premature

stop codons, novel treatment approaches based on molecular modulation of transcription activity recently identified to work in numerous genes could also be applied to filaggrin deficiency to enhance the gene's expression [78]. Further investigations on the precise characteristics and factors influencing penetrance of the FLG-related AD type will help to distinguish it from other forms of AD. If a special FLG-related subtype of AD can be defined early, a precise molecular diagnosis made in a patient might help to influence the course of the disease specifically and also enable a more reliable prediction of disease risk and appropriate treatment for the patient's offspring and relatives. With ongoing research and novel genetic techniques such as whole genome sequencing, further subphenotypes of AD may be identified by genetics and the AD syndrome will be replaced by defined molecular diagnoses.

However, much remains to be done before genetic findings can finally be translated into an improved classification and the development of new and more targeted interventions. True causal variants need to be identified, functionally characterized and considered in interaction with each other and with environmental influences. Other sources of genetic variation such as copy number variation and epigenetic changes must be explored, and more holistic approaches integrating phenotypic variables and information from genomic, transcriptional, proteomic, metabolomic (and other) sources will be needed. Traditional phenotype definitions will have to be revisited based on familial components, heritable endophenotypes, and genetic markers. Although much has already been discovered, much remains to be learned about how the genome influences AD risk and pathobiology. The awaited era of genomics in personalized medicine is not yet here, but a glimpse into the potential future of molecular medicine can already be gained.

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