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Trans- and inter-generational epigenetic inheritance in allergic diseases

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Abstract

It has become clear that early life (including *in utero* exposures), is a key window of vulnerability where environmental exposures can alter developmental trajectories and initiate allergic disease development. However, recent evidence suggests that there may be additional windows of vulnerability to environmental exposures in the parental generation before conception, or even in previous generations. There is evidence suggesting that information of prior exposures can be transferred across generations, and experimental animal models suggest that such transmission may be conveyed through epigenetic mechanisms. While the molecular mechanisms of inter- and trans-generation epigenetic transmission have yet to be determined, the realisation that environment before conception may alter risks of allergic diseases, has profound implications for the development of public health interventions to prevent disease. Future research in both experimental models and in multigenerational human cohorts is needed to better understand the role of inter- and trans-generational effects in asthma and allergic disease. This will provide the knowledge basis for a new approach to efficient intervention strategies aimed at reducing the major public health challenge of these conditions.

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INTRODUCTION

Asthma and allergies have increased exponentially over recent decades of industrialization and urbanization. The impact and severity of these multifactorial diseases are still rising in many low and lower-middle income countries, particularly among younger age groups (1–4), causing a substantial burden of disease from early childhood years. Despite major initiatives for prevention, no strategies have so far succeeded in substantially decreasing morbidity. Asthma and allergy now constitute major common chronic inflammatory diseases worldwide, and are recognized as a global public health concern (5).

Extensive literature has addressed a large number of factors shown to be associated with asthma and allergic disease (6, 7). The more traditional risk factors include environmental toxicants (810), indoor mould and dampness (11), outdoor air pollution (12, 13), occupation (14, 15), and dietary factors (16–18). Women's hormonal/metabolic status (19, 20), climate factors (21, 22), tuberculosis (23), parasitic worms (24), and overall loss of protective factors such as reduced exposure to infectious agents and symbiotic microorganisms (25) are also of interest. Epidemiological research has increasingly acknowledged the importance of developmental origins, with early environmental exposures, being key determinants for later onset of allergic diseases (26–28). In particular, early life biodiversity (29–31) is believed to play a role in the causality of allergies. This focus on early life development has driven a search for new approaches starting during pregnancy and early childhood to prevent allergies. However, to date, no intervention has proved effective to substantially reduce or prevent asthma and allergies.

An emerging understanding of the pathophysiological mechanisms involved in development and persistence of allergic diseases, reveals complex gene-environment interactions, with many genes have been identified in which genetic variants are associated with allergic phenotype (32–35), and interact with multiple environmental factors. However it is clear that the inherited sequence variation associated with allergic disease across the genome identified to date only explains a part of the heritability of allergic disease (36).

The epigenome refers to the information in the genome, that lies "above" the DNA sequence, controls the expression of genes by mechnisms such as DNA methylation and histone modifications. Importantly, the epigenome is in part heritable through cell division (mitosis) and is fundamental to control tissue differentiation and cellular responsiveness. The epigenome of a cell or tissue is determined by both DNA sequence and cellular or organismal environmental exposures, as well as by stochasticity. Partially stable in the course of mitosis, epigenetic information establishes a memory (or signature) of past exposures particularly in developmental transitions. Thus, the epigenome integrates influences of the genome, development and environmental exposures, and is increasingly being recognised to play a key role in the pathophysiology of disease (37).

Epigenetics has been defined by Ptashne in 2007 by three criteria: (I) a change in the activity of a gene that does not involve a mutation, (II) that is initiated by a signal, and (III) that can result in altered disease risk in the absence of the signal that initiated its change (38). Classically, four epigenetic mechanisms have been identified: (a) DNA methylation, (b) histone modification, (c) chromatin remodeling, and (d) small (21- to 26-nt) non-coding RNAs. There is ample evidence that DNA methylation (DNAm) fulfills all three criteria required to be considered as an epigenetic mechanism (39–41). Histone modifications fulfill the criteria as they have the potential to result from exogenous signals such as cigarette smoke, alter gene activity, and are maintained through mitosis (42–44). However, meiotic inheritance of histone modification has only been demonstrated in *C. elegans* (45). DNAm usually works hand in hand with histone modifications to activate or silence genes by influencing chromatin structure and it's accessibility by transcription factors (46). MicroRNAs (miRNAs) are also controlled by exogenous factors and alter gene activity by either inhibiting translation or degrading messenger RNAs (mRNA) (47, 48). For instance, in humans, miRNAs have been demonstrated to be differentially expressed in current and never smokers, and to be related to particulate matter exposure (42, 49). Currently there is little evidence that environmentally induced miRNAs expression patterns can be inherited (50). However, since miRNAs are part of the genetic code, it is possible that DNAm may affect the activity of miRNAs and thus facilitate inheritance.

The role of epigenetic regulation in the aetiology of asthma and allergy is becoming increasingly evident (51–56). Further, elucidating the epigenetic mechanisms involved in inflammation and the immune response to allergens will provide better understanding of the pathophysiology of allergic disease and a mechanistic understanding of how genes and environment interact to determine disease susceptibility. While the majority of studies of the epigenetics of allergic disease have focused on identifying epigenetic marks that are present before disease development (e.g. in cord blood) or in individuals with disease, this approach cannot explain the missing heritability (the problem where single genetic variations are unable to explain for much of the heritability in diseases) in allergic disease described above. However, the recognition that epigenetic information may be transmitted across generations (i.e. through meiosis) provides a mechanism whereby epigenetics could contribute to heritability of disease, and explain observations of trans-generational effects of environmental exposure on risk of allergic disease (57). This review aims to summarize the evidence for trans- and inter-generational inheritance of allergic disease, and the role of epimutations and epigenetic inheritance in allergic disease.

Transgenerational versus intergenerational inheritance

It is important to note that while early-life, including *in utero*, exposure to environmental factors has been shown to represent a key susceptibility window for allergic disease (58), however, this does not represent true transgenerational inheritance where epigenetic information is passed between generations. As discussed by Arshad at al. (57), there are a number of ways in which cross-generational effects may be transmitted and result in apparent transmission of disease risk between generations. Genetic inheritance across generations can explain familial resemblance in phenotypes, but cannot account for alterations in disease risk as a result of environmental exposures of prior generations in the

absence of continued exposure. Shared familial environment or other cultural effects can also result in similarity of disease phenotypes between generations. In addition, there is the possibility of epigenetically mediated effects to explain transmission of disease or the effect of environmental factors across generations. With regard to epigenetic effects it is important to distinguish between intergenerational and transgenerational inheritance (Figure 1). Intergenerational effects occur when maternal environmental exposures (F_0) have direct effects on the germ cells, or developing fetus (including the germ line of the fetus, leading to altered phenotype of the child (F_1) and possibly grandchild (F_2). On the paternal line environmental exposures of the father can have direct effects on the germ cells that will form child (F_1). A true transgenerational effect, where epigenetic information is transmitted across generations, can only be proven if the effect of exposure is transmitted to the F_2 (on the paternal line, or in a maternal line where exposure occurred only prior to conception), or F_3 (on the maternal line when exposure occurs during pregnancy), and possibly future generations, in the absence of further environmental exposure or germline mutations (Figure 1).

Others have suggested that transgenerational similarity in DNAm is attributable to genetic effects by methylation quantitative trait loci (methQTL) (59–61), i.e., single nucleotide polymorphisms (SNPs) that increase the susceptibility for the methylation of specific CpGs, such as those observed at the 17q21 asthma susceptibilty locus where there is strong association between SNPs and CpG sites related to gene expression, illustrating the complex relationship between sequence variation, CpG methylation and gene expression (62, 63). Another mechanism whereby genetic effects can cause transgenerational similarity in the epigenome is Metastable epialleles. These are alleles that are variably expressed in genetically identical individuals due to epigenetic modifications established during early development and are thought to be particularly vulnerable to environmental influences (64), such as the *Agouti* locus in mice (65). A genetic contribution is also supported by findings that methylation and gene expression differences were smaller in monozygotic compared to dizygotic twins (66, 67). Investigation of monozygotic twins have been considered to offer a human analog of inbred animal studies (68).

Evidence for inter- and trans-generational inheritance

A number of studies have shown that environmental exposures can lead to transgenerational inheritance of phenotypes in animal models. For example, in *Drosophila*, maternal high sugar caloric intake has been found to affect body composition and metabolism of at least two generations (69). In another study, exposures of mothers in early life (the larval period) to a transient high caloric diet was found to result in significant difference in offspring development and metabolism, and this also extended to the next generation (70). In *C. elegans,* it has been found that the manipulation of H3K4me3 chromatin modifiers can induce an epigenetic memory of longevity in subsequent generations (45) and the effect of starvation-induced developmental arrest can inherited through at least three generations (71).

Evidence for transgenerational effects of environmental exposures have also been found in vertebrate models. For example, exposure of zebrafish embryos to the environmental toxin benzo[a]pyrene has been found leading to neurobehavioral and physiological deficits in the

F_2 generation (72). In mammals, it has been demonstrated that early life traumatic stress in the paternal line resulted in altered microRNA (miRNA) expression, and behavioural and metabolic responses in the progeny (73).

Exploring potential trans- and intergenerational epigenetic inheritance in multi-generational human studies is difficult due to the long life-cycle of humans, lack of data accuracy (often using participant recall of their own and previous generations' exposures and outcomes), difficulty in controlling for confounding factors, and ethical issues (74). None-the-less, observational studies have suggested that transgenerational effects may exist that cannot easily be attributed to cultural and/or genetic inheritance (75). For example, a study of the Överkalix population in northern Sweden suggested paternal transgenerational effects in humans. In these studies, longevity and specific causes of death were linked to detailed historical records of harvests and food supply experienced by previous generations in early life (76, 77). Studies of the Dutch famine of 194445 have also revealed that offspring born during the famine were smaller compared to those born the year before the famine, and that they had increased risk of metabolic and cardiovascular disease in adulthood. Although differences in DNA methylation have been found in adult female offspring exposed to the famine in utero, and that these offspring effects persist for two generations, it is not established that these differences are present in germ cells and are truly reflecting an epigenetic transgenerational inheritance (78).

Molecular mechanisms of inter- and trans-generational inheritance

The germ cells undergo extensive epigenetic reprogramming, from their earliest presence in the embryo until the mature reproductive cells, and the best described reprogramming phases occur in early embryonic development and in the pre-puberty period (79). The germ cells are believed to be more susceptible to environmental influences during these reprogramming phases. However the precise molecular mechanisms underlying transgenerational inheritance still remain unclear. It is hypothesized that transmission of information occurs through epigenetic variation in sperm, oocytes, or both sets of gametes. There are several mechanisms, such as DNAm, histone modification, or changes in non-coding RNA (ncRNA) that could play an important role in transmitting epigenetic information from one generation to the next (79–81). Due to it's stability in stored DNA samples and comparative ease of measurement, DNA methylation has been the most studied epigenetic mechanism in human studies of inter- and 225 transgenerational effects. However, DNAm undergoes two rounds of erasure, in the formation of gametes and shortly after fertilisation, and it is unclear whether, or how, memory of CpG site methylation is maintained through meiosis. None-the-less, it has been found that the sperm epigenome may be altered by chemical compounds, such as the endocrine disruptor vinclozolin, and result in transgenerational inheritance via DNAm of induced adult-onset disease to the F_3 generation (82). In Agouti mice, methyl donor supplementation during pregnancy altered the trajectory of obesity across generations due to altered expression of the agouti gene resulting from changes in DNAm in the offspring (83). Histone modification is another potential route for transgenerational inheritance. *C. elegans*, though they do not exhibit DNAm like mammals, can impart heritable epigenetic changes, generated from histone modification, to subsequent generations (45). Another possible mechanism for conveying epigenetic information

between generations is ncRNAs, such as microRNA (miRNA), small interfering RNA (siRNA), and piwi-interacting RNA (piRNA), which can potentially act as mediators of environmentally induced transgenerational inheritance. These ncRNAs show enhancer-like function and can control chromatin structure. Gapp et al. demonstrated that traumatic stress in early life altered mouse miRNA expression, and behavioural and metabolic responses in the progeny. The phenotype of the progeny could be recapitulated by injection of sperm miRNAs into fertilised oocytes (73).

Epigenetic transmission across generations in allergic disease

Evidence for transmission across generations in allergic disease in animal models

Several intergenerational murine models provide evidence that preconception allergen sensitization impacts on the development of antigen-specific (T and B cell) immune responses in offspring, predisposing to development of asthma and atopy (84–86). Mechanisms involved in regulation of allergic response have been associated with epigenetic changes of the *IL-4* gene promoter (86) as well as altered DNAm in dendritic cells (87).

A number of studies have demonstrated adverse effects of maternal smoking and nicotine exposure on offspring pulmonary function. *In utero* smoking has been demonstrated to affect lung growth and maturation (88), causing alveolarization defects and decreased expression of retinoic acid signalling pathway elements (89), as well as induced airway remodelling and lung structure changes in mice offspring (90). Prenatal nicotine exposure has been shown to decrease forced expiratory flow rates mediated through α7 nicotinic acetylcholine receptors (nAChRs) (91), and to affect global lung methylation levels and down-regulate PPARy expression in the progeny (92).

Maternal particle exposure has also been linked to adverse effects on offspring's lung health. Murine models have found associations between diesel exhaust particles (DEP), and increased asthma susceptibility in F_1 pups, with distinct methylation changes located to promoter regions of genes related to lung development, interleukin (IL)-4 and interferon (IFN)-y signaling (93–95), as well as an activation of aryl hydrocarbon receptor (AhR) and oxidative stress-regulated genes (96). Maternal exposure to specific phthalates (mono-n-butyl phthalate, a metabolite of butyl benzyl phthalate (BBP)), has been shown to increase the risk for persistent airway inflammation in offspring and to induce aberrant DNAm in genes involved in Th2 differentiation (97).

Murine models have demonstrated that maternal exposure to microbial components and supplementation of probiotic bacteria can modulate the immune response in the offspring by suppressing allergic sensitization and airway inflammation in the F_1 generation (98–100). It has also been shown that maternal glucocorticoid-induced stress during pregnancy can increase airway inflammation and susceptibility to allergy in the offspring (101).

Multigenerational murine models are emerging, and effects of phthalate exposures through enhanced eosinophilic airway inflammation have been reported to persist in the F_2 generation (97). It has been shown that exposure to fungi of the F_0 generation was associated with decreased immunoglobulin E and airway eosinophilia as well as altered methylation in

genes regulating T helper cells in third-generation (F_2) mice (102). In a recent study by Gregory et al., elevated asthma risk following intrauterine exposure to particulate air pollution was identified up to the F_3 generation (93). This model suggests a transgenerational effect on asthma susceptibility from exposure to environmental particles. The transgenerational murine model developed by Rehan et al. shows that nicotine exposure of pregnant rats is associated with increased airway resistance in F_3 offspring when challenged with metacholine (103).

Evidence for transmission across generations in allergic disease in humans

The long life-cycle of humans makes investigating epigenetic transmission across generations in human a challenge. However, recently several studies with various solutions as to obtaining multi-generation data have been published (Table 1). In different cohorts, higher asthma risk in persons whose *maternal* grandmother smoked has been found, even if the mother did not smoke (104–109). In the North European RHINE study, higher asthma risk was found in persons whose *paternal* grandmother smoked (110). Further, this study found that father's smoking before age 15 years was associated with particularly high asthma risk in future offspring. This finding was replicated in an analysis of two generations in the RHINESSA cohort, using advanced statistical modelling and also accounting for unmeasured confounders. Ongoing analyses of RHINESSA give supportive evidence for a role of father's early puberty exposure in offspring health; showing lower lung function in offspring whose father smoked before age 15 (111), differential DNAm related to father's smoking (112), and higher asthma risk in offspring of fathers that became overweight before voice break (113). In an analysis of the ECRHS (European Community Respiratory Health Survey) cohort, in which asthmatic/allergic disease status was measured in the parent generation at three time points over twenty years and offspring allergies reported by the parents at the third study wave, the authors found stronger associations of offspring allergies with parental asthmatic and allergic disease activity as measured before conception as compared to parental status after birth (114). This indicates that disease activity might induce changes that are transmissible to the next generation, rather than a role of shared environment, this has been termed "induced epigenetic transmission" (57). Finally, a study of helminths and allergies in two generations in Norway found that fathers' Toxocara exposure was associated with daughters' allergies, and mother's Toxocara with sons' allergies (24). While parental exposure was not measured preconception, the sex-specific pattern might indicate a role for epigenetic transmission given parent of origin effects are seen for both genetic variation and epigenetic variation (115, 116), and risk of asthma in offspring from parental asthma has also been shown to be related to the sex of the affected parent (117).

While maternal diet is increasingly recognised as a risk factor for offspring asthma and atopy (118), there is no current evidence to suggest that inter- or transgenerational effects occur in allergic disease. However maternal dietary factors such as Vitamin D and Fatty Acids that have been associated with asthma risk have also been shown to be associated with DNA Methylation changes at birth in offspring (119, 120). Further research is needed to understand whether these methylation changes lie on the casual pathway between maternal diet and offspring allergic phenotype.

Methodology for studying epigenetic transmission across generations in allergic disease

Several approaches have been undertaken to explore transgenerational epigenetic inheritance in multi-generational human studies, including recruiting the offspring of birth cohort participants who are now reaching reproductive age, recruiting offspring / grandoffspring of adult cohorts, and use of offspring recall and/or registry data to determine phenotype and/or exposures in parental generations. As mentioned before, all these approaches come with advantages and disadvantages, with compromises between prospective data collection and ease / length of cohort recruitment required. However there are a number of multigenerational cohorts available that are already beginning to allow the assessment of inter- and transgenerational effects in allergic disease (57). While most studies have used regression models to assess the effects of prior exposure on outcome, other approaches such as logistic regression analyses with generalized estimating equations and multilevel mediation models within a hierarchical framework (104) are being ustilised to account for familial clustering.

Several statistical approaches have been used to evaluate epigenetic inheritance of methylation in multigenerational cohorts. Correlation is one of the most used methods (121, 122). Strong positive correlation between parent-offspring pairs indicate a higher level of similarity of DNAm between generations. Some studies choose weighted correlation instead of Pearson correlation to minimize the variance of the correlation estimate (123). However, observed similarity of DNAm could also be due to the fact that parent-offspring share the same environmental factors. To distinguish environmental factors from inheritance, narrow sense heritability is defined as $h^2 = \frac{var(A)}{var(P)}$, where $Var(A)$ is the variance due to the average effects of inheritance and $Var(P)$ is the total variance. Two major approaches, path analysis model (PAM) and variance of component model (VOM), are generally used to estimate heritability (124). The component of variance can be obtained by ANOVA or fitting linear mixed models (123, 125). The linear mixed model is more flexible in adjusting for covariates, accounting different types of study designs, and explicity addressing environmental variation (123, 126). In addition to studying epigenetic inheritance at level of individual CpGs, transgenerational inheritance can also be evaluated for groups of CpGs that share similar pattern of DNAm transmission (127). This approach, which incorporates unsupervised cluster into beta regression, was recently developed by Han et al. (127), and was able to identify sets of CpGs that have same/different inheritance patterns between mother-offspring and father-offspring.

Conclusions

In conclusion, there is inceasing evidence from both invertebrate and vertebrate expirmental models that transmission of epigenetic information across generations occurs. Furthermore, experimental animal models also suggest this can lead to altered lung and immune development in response to environmental exposures in previous generations. In humans, studies based on historical data suggest a role for transgenerational inheritance in general, and analyses of human multi-generation data suggest intergenerational environmental effects in asthma and allergies. Unmeasured confounding is a matter of concern in non-experimental studies in which the exposure is not randomized (128). The only human study

addressing unmeasured confounding in this context found that this error was very small (104), still human studies will need to be informed and complemented by careful studies in experimental models where duration of exposures can be tightly controlled to determine precise windows of vulnerability and randomised to avoid confounding.

Careful study design will be needed to show that the changes to the epigenome induced by environmental effects actually are passed across generations in humans, and the underlying epigenetic mechanisms determined. Multi-generational cohort studies based on national and international collaboration should be established to prospectively and with a clear time order address the question on whether inter- and transgenerational inheritance are contributing to the risk of allergic diseases, and maximium use should be made of registry data, which can provide retrospective validated information for some generations, shortening the time frame necessary to study effects over multiple decades.

Another important area for future research is the issue of tissue specificity of DNA methylation. In epigenetic studies, unlike studies of DNA sequence variation, the cellular source of DNA samples is an essential consideration in study design given the extent of tissue specific methylation (129). The majority of studies of the epigenetics of allergic disease have utilized peripheral blood leukocytes due to ease of sampling and availability of stored samples from historical cohorts, though both nasal brushings (130, 131) and saliva (132) have also been used. Recently a comparison of blood, buccal, nasal and bronchial epithelial tissue methylation profiles has demonstrated that nasal epithelium represents the best proxy for bronchial epithelial cells (133). However, with respect to inter- and transgenerational effects, it is likely that the effects on the epigenome of exposures to the developing embryo, or transmitted through meiosis, may manifest in multiple tissues, though remains to be established.

If it is firmly established that inter- and transgenerational effects are of importance in asthma and allergic disease, the potential practical consequences for public health policies are considerable. What are the time windows in which health promotion would be most efficient? A perspective on asthma and allergies might provide the knowledge basis for a new approach to efficient intervention strategies aimed at reducing the major public health challenge of asthma and allergies.

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Abbreviations:

ncRNA	(non-coding RNA)
miRNA	(microRNA)
siRNA	(small interfering RNA)
piRNA	(piwi-interacting RNA)
DNAm	(DNA methylation)
RHINESSA	(Respiratory Health In Northern Europe, Spain and Australia generation study)
ECRHS	(European Community Respiratory Health Survey)

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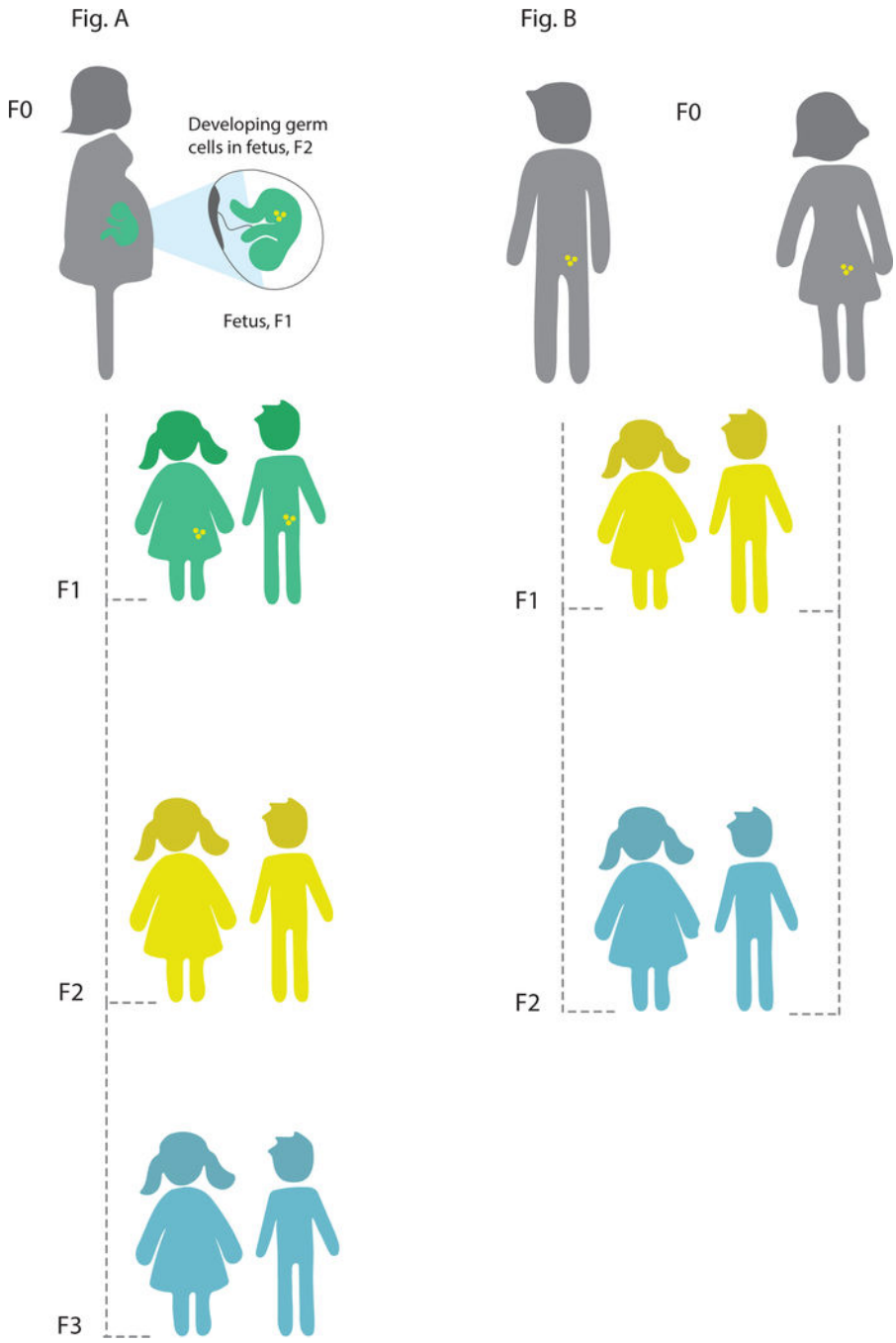

Figure 1:

Principles of inter- and transgenerational epigenetic inheritance. (A) If a pregnant woman (F0) is exposed to an environmental stressor, her son/daughter (F1, green) and his/her germ cells that will form F2 (yellow) are also directly exposed and this may result in intergenerational effects. The third generation (F3, blue) is the 1st generation that could represent transgenerational epigenetic inheritance. (B) If a man or a woman (F0) and their

germ cells to F1 (yellow) is directly exposed to an enironmental stressor, the F2 offspring (blue) is the 1st generation that could represent transgenerational epigenetic inheritance.

Table 1:

Evidence for inter- and trasngeneration inhertiance of allergic disease in humans

Reference	Key findings/Study cohort	Exposure across generations
Accordini S et al. **A three-generation study on the association of tobacco smoking with asthma**. International journal of epidemiology. 2018.	Increased asthma risk in F2 generation due to grandmaternal smoking (F0) and paternal smoking (F1) prior to conception The European Community of Respiratory Health Study (ECRHS)	Intergenerational: F0-F1-F2
Li YF et al. **Maternal and grandmaternal smoking patterns are associated with early childhood asthma**. Chest. 2005;127(4):1232–41	Increased asthma risk in F2 generation due to maternal (F1) and grandmaternal (F0) smoking during pregnancy The Children's Health Study in southern California (CHS)	Intergenerational: F0-F1-F2
Miller LL et al. **Do grandmaternal smoking patterns influence the etiology of childhood asthma?** Chest. 2014;145(6):1213–8.	Increased asthma risk in F2 generation (female offspring) due to paternal grandmother (F0) smoking during pregnancy The Avon Longitudinal Study of Parents and children (ALSPAC)	Intergenerational: F0-F2
Magnus MC et al. **Grandmother's smoking when pregnant with the mother and asthma in the grandchild: the Norwegian Mother and Child Cohort Study**. Thorax. 2015;70(3):237–43.	Increased asthma risk in F2 generation due to grandmaternal (F0) smoking during pregnancy, independent of the mother's smoking status The Norwegian Mother and Child Cohort Study (MoBa)	Intergenerational: F0-F2
Braback L et al. **Childhood asthma and smoking exposures before conception - a three-generational cohort study**. Pediatr Allergy Immunol. 2018.	Increased asthma risk in F2 generation due to paternal grandmother smoking (F0) The Respiratory Health In Northern Europe study (RHINE)	Intergenerational: F0-F2
Lodge CJ et al. **Grandmaternal smoking increases asthma risk in grandchildren: A nationwide Swedish cohort**. Clin Exp Allergy. 2018;48(2):167–74.	Increased asthma risk in F2 generation due to paternal grandmother smoking (F0) The Respiratory Health In Northern Europe study (RHINESSA)	Intergenerational: F0-F2
Svanes C et al. **Father's environment before conception and asthma risk in his children: a multi-generation analysis of the Respiratory Health In Northern Europe study**. International journal of epidemiology. 2017;46((1):235–45.	Increased asthma risk in F1 generation due to paternal smoking (F0) prior to conception (RHINE study)	Intergenerational: F0-F1
Accordini S et al. **Three-generation effects of tobacco smoking on lung function within the paternal line**. European Respiratory Journal. 2017;50((suppl 61)):PA1178.	Lower lung function in F1 generation due to paternal smoking (F0) prior to conception (RHINESSA study)	Intergenerational: F0-F1
Bertelsen RJ et al. **Clinical markers of asthma and IgE assessed in parents before conception predict asthma and hayfever in the offspring**. Clin Exp Allergy. 2017;47(5):627–38.	Stronger associations of offspring (F1) allergies with parental (F0) asthmatic and allergic disease activity measured prior to conception as compared to parenta status after birth (ECRHS study)	Intergenerational: F0-F1