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Review

# Aggression in children: unravelling the interplay of genes and environment through (epi)genetics and metabolomics

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*From the womb to the adult*
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## Abstract

Aggression inflicts a huge burden on affected children, their families, and society. Estimates for the prevalence of clinical aggression in children range between 2 and 16%, and childhood aggression tends to continue into adulthood. Current psychological treatments and pharmacological interventions are not effective for all children with aggressive behaviors and there is a huge need for more personalized approaches, which requires insight into the heterogeneity and the mechanisms underlying aggression and its associated comorbidities. Here we discuss what is currently known with regard to individual differences in childhood aggression. Studies employing new opportunities in large scale genotyping, epigenetics and metabolomics technology will in future help to explain heterogeneity and highlight pathways from molecule to phenotype. The FP7-ACTION project (**A**ggression in **C**hildren: Unravelling gene-environment interplay to inform **T**reatment and **I**nterventi**ON** strategies) aims to contribute to knowledge that will help children, their families, teachers and society at large.

## Keywords

Aggression, childhood, twin studies, biomarkers.

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## Introduction

Differences among children in aggression can in part be explained by environmental risk factors, by demographic characteristics, including age and sex, and by genetic differences. Genetic risk factors may contribute independently from other risk factors, or genetic vulnerability may be modified by other influences. Such modification is often referred to as gene-environment interaction, where the interaction can be thought of as genes controlling sensitivity to environment, or as the environment controlling the expression of the genome [1]. There are different theories regarding gene-environment interaction effects, from different perspectives. The diathesis-stress model predicts that genetic vulnerability (diathesis) in the presence of environmental risk (stress) will increase the probability of behavioral problems such as aggression and also predicts that heritability of aggression will be higher for children in high-risk environments. In contrast, the bioecological model predicts that risk environments conceal genetic differences among children, and that enriched environments will amplify underlying genetic differences [2]. Future challenges are to establish which models apply to childhood aggression across different ages, genders and cultures.

Environmental exposures may be correlated with genetic variants, whereby genes alter the exposure to relevant environmental risk factors. One mechanism that creates a correlation between genetic and environmental factors is referred to as 'cultural transmission'; when parents transmit genes as well as environmental risks then the two will become correlated in their offspring. A correlation between genotype and environment will, unless explicitly modeled, become part of the heritable component when genotype and the environment shared by children from the same family are correlated.

The mechanisms that explain the variation in childhood aggression are not mutually exclusive; part of the variation may be due to additive actions of genes and environment and another part to their interaction. Here, we first turn to what is currently know about the heritability of childhood aggression, then discuss gene finding studies and some epigenetic findings and end with considering how approaches from metabolomics might help elucidate the biological mechanisms underlying childhood aggression.

Aggression and conduct disorder are among the most prevalent childhood disorders affecting approximately 6-16% of males, and 2-9% of females [3]. They can pose tremendous problems for children, their parents, their teachers, and many others involved (e.g., siblings, peers, family). In children physically aggressive behavior can be observed as early as 12 months, with a peak prevalence around 2-4 years of age and a decrease thereafter. However, a minority of children (3-7%) maintains a high level of physical aggression from childhood to adolescence and develops social adjustment problems during adulthood [4]. Left untreated, aggression is persistent, and predicts later delinquency, depression, substance abuse, difficulties in peer relations, academic functioning, occupational stability, and employment [5]. Insight into the causes of differences among children, including characterization of genetic and environmental risk and their interplay, is crucial to help children and those surrounding them.

## Genetic epidemiology of childhood aggression

A large number of genetically informative studies on aggression, conduct disorder and externalizing problems in children and adolescents shows these traits to be heritable. Heritability varies as a function of the degree and manifestation of aggression. For example, aggressive forms of antisocial behavior are more heritable than non-aggressive forms of antisocial behavior [6, 7]. Genetic influences on stability in aggression also tend to by high. A longitudinal study from the Netherlands in twins aged 3 to 12 years investigated the contribution of genetic and environmental influences on the stability of aggressive behavior [8]. The stability across age intervals ranged from 0.41 to 0.77 and genetic factors accounted for most of the stability. The longitudinal model suggested

a dynamic developmental process consisting of transmission of existing genetic effects coupled with new genetic influences. Environmental factors shared by children from the same family accounted for approximately 25% of phenotypic stability. One environmental factor, which is shared by twins and often also by siblings from the same mother, is maternal smoking during pregnancy [9].

Van Beijsterveldt et al. [8] identified some modification of genetic influences by age and sex. At younger ages (3 and 7) heritability for aggression was around 60% and about the same in boys and girls, but at ages 10 and 12 years, heritability was 67% for boys, and 50-55% in girls. In contrast, for girls shared environmental factors were more important than for boys at 10 and 12 years (29%; whereas the estimate in boys was 16 to 19%).

Turning to modification of heritability by environmental exposures, for externalizing problems in children, a weak association was found between attending formal child care and higher externalizing problems, especially when parental socio-economic status was low. Heritability was lower for formal child care and in lower socio-economic conditions. In 7 year-olds, the difference in heritability between the formal child care group of low socio-economic status and the home care group of high socio-economic status was 30%. These findings supported a bioecological model in which heritability is lower in circumstances associated with more problem behavior [2]. Molenaar et al. [10] tested for genotype-by-environment interaction on aggression in children using newer methods that do not require measuring the environment. Parental ratings of problem behavior from 14,755 twin pairs (5.3 years) indicated that environmental influences increased in children who were genetically more predisposed to aggression. First results such as these offer promise for a more comprehensive model of the etiology for childhood aggression.

## Heritability estimates for childhood aggression from SNP data

Estimates for heritability may be obtained from twin or adoption data, but also from unrelated children, if SNP data are available [11]. Genome-wide single nucleotide polymorphisms (SNPs) can be used to create a measure of genetic similarity between all possible pairs of (unrelated) children and this measure can then be used to predict phenotype similarity between children. With such a prediction model, the SNP-based heritability for oppositional defiant disorder (ODD) in children was estimated at 28% [12]. For externalizing behavioral problems, estimates were 12% when based on maternal assessment and 44% when based on teacher ratings. For aggression, the SNP-based heritability was between 10% and 54% [13]. Heritability estimates based on SNP data are typically lower than those based on twin data, because twin-based heritability estimates tend to include all genetic effects.

## Biomarkers from genetic association studies

At the molecular level, association studies of candidate genes have focused on polymorphisms in genes involved in neurotransmission and hormonal regulation. Genes involved in serotonin and dopamine regulation have received the most attention, and polymorphisms in genes involved in serotonin and dopamine metabolism were indeed found to be significantly associated with aggression in humans and in animals such as monoamine oxidase A (*MAOA*), dopamine receptor 2 (*DRD2*) and the serotonin transporter (*5-HTT* or *SLC6A4*) genes [4, 14]. Zhangh-James and Faraone [15] examined all aggression phenotypes in the OMIM (Online Mendelian Inheritance in Man) Catalog and identified 95 disorders with aggressive symptoms in at least one individual with a well-defined genetic variant. In total, 86 causal genes were retrieved, with the most significantly enriched canonical pathways, previously implicated in aggression, providing strong evidence to support a causal role of serotonin and dopamine signaling pathways in the pathogenesis of aggression.

The first genome-wide association study of childhood aggression [14] identified one region on chromosome 2p12 at near genome-wide significance (top SNP rs11126630). In gene-based analyses, the *AVPR1A* (arginine vasopressin receptor 1A) gene was significantly associated with aggression. It is possible that functional variation in the arginine vasopressin receptor is responsible for higher levels of aggressive behavior, as was shown in rodents [16]. Variation in *AVPR1A* is also of interest in human social behavior [17].

## Biomarkers from epigenetics studies

Epigenetic mechanisms including DNA methylation regulate gene expression throughout

development and may mediate genetic and environmental effects on complex traits such as aggression. In their review of the developmental origins in humans of physical aggression and early-life adversity, Provençal et al. [4] identified epigenetic alterations in genes regulating cytokines, the HPA axis and 5-HT as being of particular interest.

There are currently no epigenome-wide association studies (EWAS) of childhood aggression, but van Dongen et al. [18] carried out an EWAS in 2,029 adults to localize regions in the genome where DNA methylation level is associated with aggressive behavior. DNA methylation was measured in whole blood by the Illumina HM450k array and the association between aggressive behavior and DNA methylation level was tested at 411,169 autosomal sites. Gene ontology analysis, in which categories of genes rather than single methylation sites are tested, highlighted that genes involved in developmental and central nervous system processes were enriched among higher ranking genes from the EWAS. Higher ranking methylation sites also showed enrichment for DNase I Hypersensitive sites and promoter regions. The two top sites were near the *TRPS1* gene on chromosome 8 and near *PARD6G-AS1* on chromosome 18. Interestingly, the region on chromosome 8 harbors a suggestive SNP association for major depressive disorder and is also linked to a whole range of other complex traits based on genome-wide association studies (UCSC genome browser). In the same study, analyses of DNA methylation levels in 20 pairs of monozygotic twins highly *discordant* for aggression revealed top sites near *RAB39* (chromosome 11), *SIGLEC10* (chromosome 19) and *PREP* (chromosome 6). The latter gene codes for prolylendopeptidase; a proteinase that cleaves small neuropeptides and peptide hormones, such as angiotensin, thyrotropin releasing hormone, gonadotropin releasing hormone, neurotensin, vasopressin and oxytocin.

These findings suggest that DNA methylation in peripheral tissues such as blood is likely to be associated with aggressive behavior and may lead to new biomarker discovery.

## Biomarkers and metabolomics

Metabolomics may have a significant impact on understanding the complex biological processes involved in childhood aggression. By identifying biomarkers of aggression based on metabolomics in urine, it should be possible to unravel processes and pathways leading to physical and other forms of childhood aggression. If metabolomic markers in urine can be used as biomarkers in clinical practice, they may improve subtyping of aggression and aid preventative and therapeutic strategies. Urine is an easily accessible tissue in children and metabolomics in urine has great potential to identify new translational biomarkers for childhood aggression. The metabolome can be affected by genotype and by environmental factors and represents a critical component that includes an individual's reaction to environmental changes. Understanding the metabolic phenotype can provide essential insights in an individual's current physiological status that could ultimately be used for predicting his or her outcome. Such 'biomarker in urine' approaches for children would improve translation to clinical practice, as stable individual biomarkers of clinical utility that are relatively easy to use are currently hardly available. Hagenbeek et al. [19] have reviewed the current knowledge on biochemical biomarkers for aggression. They identify candidate biomarkers shared across the aggression subclasses identified by different systems, and putative biomarkers unique to a particular subtype of a particular system and argue that a better understanding of aggression and its subtypes will benefit from a more holistic approach to the study of aggression biochemistry as provided by metabolomics.

## Conclusions

Childhood aggression does not occur in isolation. In addition to a need to understand the heritability differences between subclasses of aggression, their interaction with environment, and to discover subclass-specific biomarkers, we also need to understand the comorbidity of pediatric aggression with other disorders. **Tab. 1** summarizes for girls and boys, ages 3 and 7, the correlations of aggression with overactive behavior and attention problems, with rule breaking, with anxious/depression, and with thought, sleep and social problems. The correlations speak to high comorbidity of childhood aggression with other disorders, and aggression thus is a phenotype that needs to be studied for multiple reasons. For example, Bartels et al. [20] looked at the comorbidity of aggression and rule breaking behavior and found that 80% of the shared variance could be explained by genetic pleiotropy, i.e. co-

**Table 1.** Correlations between aggression and other childhood emotional and behavioral problems. Behavior of the children was rated by mothers and fathers at ages 3 and 7 years in twins from the Netherlands Twin Register. Correlations are presented separately for boys and girls. Behavioral problems were assessed by the Child Behavior Check List.

| AGE 3 | BOYS | | GIRLS | | AGE 7 | BOYS | | GIRLS | |
|---|---|---|---|---|---|---|---|---|---|
| | MOM | DAD | MOM | DAD | | MOM | DAD | MOM | DAD |
| **Oppositional** | .644 | .635 | .625 | .622 | **Rule breaking** | .678 | .661 | .660 | .622 |
| **Withdrawn** | .401 | .383 | .356 | .383 | **Withdrawn** | .426 | .437 | .453 | .479 |
| **Anxious** | .266 | .280 | .250 | .276 | **Anxious/dep** | .508 | .508 | .522 | .524 |
| **Overactive** | .537 | .519 | .502 | .492 | **Attention** | .599 | .613 | .584 | .588 |
| **Somatic** | .162 | .158 | .181 | .179 | **Somatic** | .247 | .263 | .297 | .285 |
| **Sleep** | .302 | .295 | .303 | .304 | **Social** | .517 | .499 | .507 | .495 |
| | | | | | **Thought** | .370 | .348 | .365 | .324 |

The number of observations for maternal ratings is 17,246-17,559 at age 3 and 11,106-11,094 for age 7; the number of paternal ratings is 11,646-11,971 at age 3 and 7,869-7,986 for age 7.

occurrence of these traits is mainly caused by a common set of genes.

To gain a better understanding of the variation in childhood aggression, and to address the needs of patients, the ACTION consortium (**A**ggression in **C**hildren: Unravelling gene-environment interplay to inform **T**reatment and **I**nterventi**ON** strategies) was established. Twelve partners from the Scandinavian countries (Finland and Sweden), the UK, the Netherlands, and Italy together with scientists from the USA and Australia aim to collaborate to solve questions and problems indicated by clinicians, social workers and others working with children with aggression. First, the ACTION research program will provide an inventory of such questions and problems. After discovery of putative biomarkers in population samples, these findings will be validated in clinical cohorts and the results of the ACTION consortium will provide the basis for an overarching model that integrates the multilevel empirical findings into a comprehensive framework of aggression and its risk indicators. Based on this framework, ACTION aims to develop profiles of risk assessment together with guidelines to improve decision-making on the development and implementation of preventative and treatment strategies, addressing the critical needs and problems identified by those working with aggressive children.

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## Declaration of interest

The Authors declare that there is no conflict of interest.

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