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GENETIC AND PRENATAL RISK FACTORS FOR AUTISM: IMPLICATIONS FOR RISK-ENRICHED DEVELOPMENTAL SURVEILLANCE

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Abstract Background: Autism spectrum disorder (ASD) has a heterogeneous developmental etiology involving common polygenic liability, rare inherited and de novo variants, and prenatal or perinatal contexts. Group-level associations are often misinterpreted as individual causes, creating risks of deterministic prediction and parental blame.

Objective: To critically synthesize genetic and prenatal ASD risk evidence and clarify how it may inform risk-enriched developmental surveillance without replacing clinical assessment.

Methods: A structured narrative search of PubMed/MEDLINE and authoritative guidance identified English-language publications from 1 January 2014 through 4 September 2026, supplemented by landmark earlier evidence. Priority was given to population heritability studies, genome-wide and exome-sequencing cohorts, systematic reviews, meta-analyses, umbrella reviews, and clinical guidelines. Evidence was evaluated for replication, design, confounding, biological plausibility, specificity, and clinical actionability. No new quantitative synthesis was conducted.

Results: Genetic contribution is substantial but distributed across common polygenic variation, copy-number variants, and rare damaging variants affecting diverse neurodevelopmental processes. Penetrance and expressivity vary, and identified variants are often pleiotropic. Replicated prenatal or perinatal associations include advanced parental age, maternal metabolic and infectious conditions, selected medication exposures, prematurity, and neonatal complications. Most effect sizes are modest, exposures are correlated, and residual confounding, familial factors, indication bias, and selection limit causal interpretation. No individual risk factor is necessary or sufficient for ASD. The most defensible clinical application is intensified, repeated developmental surveillance in defined high-likelihood groups, combined with indicated etiological evaluation and needs-based referral.

Conclusions: Etiological evidence supports a probabilistic liability model rather than deterministic screening. Genetic and prenatal information should guide counseling, medical evaluation, prevention of established maternal-child health risks, and surveillance intensity; it should not independently label a child. Diverse prospective cohorts and genetically informed causal designs are needed.

Keywords: autism spectrum disorder; genetics; prenatal exposure; heritability; environmental risk; causal inference; developmental surveillance

Highlights

• ASD liability reflects common and rare genetic variation interacting with developmental context.

• Heritability is a population statistic and does not provide an individual diagnosis or fixed prognosis.

• Prenatal associations require cautious causal interpretation because confounding and indication bias are common.

• Risk factors can justify closer surveillance but cannot replace observation, standardized screening, or assessment.

1. Introduction

ASD encompasses diverse developmental profiles involving social communication, behavior, sensory processing, cognition, language, and adaptive function [1,3]. Etiological research has identified a strong genetic contribution and numerous prenatal or perinatal correlates. Translating this evidence into clinical practice is difficult because population associations are easily converted into overconfident individual predictions. A factor may increase average probability while remaining neither necessary nor sufficient for ASD.

Early recognition can improve access to assessment and individualized support, yet etiological uncertainty should not delay care [5,6]. Conversely, risk status should not be treated as diagnosis before developmental features are present. The clinically relevant question is how genetic and prenatal information can improve surveillance and counseling while preserving uncertainty, avoiding blame, and preventing unnecessary medicalization.

1.1 Objective and conceptual contribution

This review integrates genetic architecture, prenatal and perinatal epidemiology, causal-inference limitations, and clinical surveillance. It proposes an actionability framework that separates evidence of association, evidence of causation, etiological diagnostic yield, and usefulness for developmental monitoring.

2. Methods

2.1 Search strategy and eligibility

PubMed/MEDLINE was searched using combinations of “autism spectrum disorder,” “heritability,” “polygenic,” “copy-number variant,” “de novo,” “exome sequencing,” “prenatal,” “maternal infection,” “maternal diabetes,” “obesity,” “medication exposure,” “prematurity,” “parental age,” “risk factor,” “umbrella review,” and “causal inference.” English-language evidence from 1 January 2014 through 4 September 2026 was considered, with seminal earlier meta-analyses and current clinical guidance added. Priority sources were large population and genomic cohorts, systematic reviews, meta-analyses, umbrella reviews, and guidelines. Small exploratory studies were used only for context.

2.2 Evidence interpretation

Evidence was grouped into common genetic liability, rare and structural variation, family recurrence, prenatal exposures, and perinatal conditions. Appraisal emphasized replication, sample size, phenotype and exposure measurement, temporality, dose-response, negative controls, sibling comparison, control of familial and socioeconomic factors, and specificity of outcome. This was not a registered systematic review; screening was not duplicated and formal study-level risk-of-bias scores were not generated.

3. Genetic architecture

3.1 Heritability and family aggregation

Population and family studies demonstrate substantial genetic contribution to ASD liability [7]. Heritability quantifies variance attributable to genetic differences under specific population conditions; it does not mean that an equivalent percentage of one person’s autism was “caused by genes.” Estimates can change with ascertainment, diagnostic definition, and environment. Familial recurrence enriches likelihood and supports repeated surveillance of younger siblings, but outcomes within families remain variable [26,29].

3.2 Common polygenic variation

Genome-wide association studies show that many common variants of individually small effect contribute to liability [8]. Polygenic scores summarize part of this distributed signal but currently explain insufficient variance for stand-alone population screening. Their transportability is reduced when discovery data do not represent the ancestry of the target population. A score may also correlate with related neurodevelopmental traits, emphasizing pleiotropy rather than ASD specificity.

3.3 Rare variants and de novo mutation

Large exome-sequencing studies implicate rare protein-truncating and damaging missense variants in genes involved in neuronal development, synaptic biology, and transcriptional regulation [9]. Copy-number variants and defined genetic syndromes can also contribute. Diagnostic yield is higher when ASD co-occurs with intellectual disability, congenital anomalies, epilepsy, dysmorphic features, or a suggestive family history. Even pathogenic variants may show incomplete penetrance and variable expressivity; the same variant can be associated with different developmental outcomes.

3.4 Clinical genetic evaluation

Genetic evaluation can identify an etiological diagnosis, guide recurrence counseling, and occasionally prompt syndrome-specific medical surveillance. It should be accompanied by pre- and post-test counseling addressing possible positive, negative, uncertain, and incidental findings. Genetic testing is etiological assessment—not a replacement for behavioral diagnosis or developmental needs assessment. Broad population prediction using polygenic scores is not ready for routine care.

Genetic evidence	Inference	Potential clinical value	Limitation
Family aggregation	Meaningful inherited liability at group level	Earlier repeated surveillance and counseling	No deterministic prediction
Common variants	Polygenic contribution across many loci	Research stratification	Limited individual prediction; ancestry bias
Rare/de novo variants	High-impact contribution in a minority	Etiological diagnosis and medical surveillance	Variable penetrance and expressivity
Copy-number variants/syndromes	Defined mechanisms in selected cases	Testing when clinically indicated	Often non-specific to ASD phenotype

4. Prenatal and perinatal risk evidence

4.1 Parental age and reproductive factors

Meta-analyses have associated advanced maternal and paternal age with ASD [11–13]. Potential mechanisms include de novo mutation, epigenetic processes, obstetric complications, and social or familial selection. Maternal and paternal age are correlated with each other and with healthcare and socioeconomic factors. Age therefore provides modest risk enrichment at the population level but has poor specificity and should not be used for individual labeling.

4.2 Maternal metabolic conditions

Maternal diabetes and obesity have been repeatedly associated with elevated ASD probability [11–14]. Inflammation, oxidative stress, placental function, and altered fetal metabolic signaling

are plausible pathways. However, obesity and diabetes correlate with medication use, diet, socioeconomic circumstances, obstetric intervention, and genetic liability. The appropriate clinical response is evidence-based prevention and management for broad maternal and infant health benefits—not promises that controlling one factor will prevent ASD.

4.3 Infection, fever, and immune activation

Maternal infection or fever during pregnancy has been associated with neurodevelopmental outcomes in some studies [11–14]. Exposure definitions, gestational timing, pathogen, severity, treatment, and healthcare use vary substantially. Mechanistic models involving maternal immune activation are biologically plausible, but observational human data cannot identify a single pathway. Vaccination and appropriate treatment of infection should follow established maternal-health guidance; ASD etiology should not be inferred from an isolated illness.

4.4 Medication exposures and confounding by indication

Selected prenatal medication exposures, most notably valproate, have important neurodevelopmental implications. For many other medicines, observed associations may reflect the underlying maternal condition, genetic liability, disease severity, or correlated behaviors rather than a direct drug effect. Sibling comparisons, paternal negative controls, comparison with exposure outside pregnancy, and dose-timing analyses can reduce but not eliminate confounding. Medication should never be stopped solely because of a generalized ASD-risk statement; individualized benefit-risk decisions require the treating clinician.

4.5 Prematurity and neonatal complications

Preterm birth, low birth weight, hypoxic or inflammatory complications, and neonatal intensive-care exposures are associated with higher rates of multiple neurodevelopmental outcomes, including ASD [11–14]. These indicators are not ASD-specific and may lie on shared causal pathways or reflect severity of early illness. They support structured developmental follow-up rather than etiological certainty.

Factor group	Evidence interpretation	Confounding concern	Appropriate action
Advanced parental age	Replicated modest association	Reproductive and socioeconomic selection	Counsel probabilistically; routine surveillance
Maternal diabetes/obesity	Consistent group-level elevation	Shared genetics, treatment, healthcare factors	Optimize maternal health; monitor development
Infection/fever	Timing- and definition-dependent association	Severity and healthcare-use bias	Prevent/treat infection per guidelines
Medication exposure	Drug-specific evidence varies	Strong confounding by indication	Individual specialist benefit-risk review
Prematurity/neonatal illness	Non-specific neurodevelopmental risk	Severity and survival/selection effects	Enhanced developmental follow-up

5. Association is not causation

Causal interpretation requires more than statistical significance. Confounding occurs when a third factor influences both exposure and outcome; selection bias occurs when inclusion depends on related variables; measurement error may differ by healthcare access; and multiple testing can produce unstable findings. Reverse causation is less likely for prenatal exposures but familial liability may influence parental health, treatment, reproductive timing, and recognition of child development. Small relative risks can also have limited predictive value when exposure is common or non-specific.

Triangulation strengthens inference by combining designs with different biases: prospective cohorts, sibling comparisons, negative controls, natural experiments, Mendelian randomization where assumptions are credible, and mechanistic studies. Consistency alone is insufficient if studies share the same confounding structure. Clinical statements should therefore specify whether evidence supports association, probable causal contribution, or established preventable harm.

6. Gene–environment interplay and developmental heterogeneity

Genetic and environmental categories are not independent. Genetic variation can influence exposure probability, placental response, metabolism, immune regulation, and sensitivity to developmental perturbation. Environmental conditions can alter gene expression without changing DNA sequence. These interactions are difficult to estimate because large samples, precise timing, repeated measures, and replication are required. Current evidence supports an interacting liability model, but it does not support personalized prediction from a small panel of genes and exposures.

7. Translation to risk-enriched surveillance

Stage	Clinical action	What risk information contributes	Safeguard
Preconception/prenatal care	Optimize established maternal health risks	Broad health counseling, not ASD prediction	Avoid blame and unsupported prevention claims
Newborn/infant follow-up	Identify defined genetic or neonatal high-risk groups	Sets frequency of developmental monitoring	Risk status is not diagnosis
Repeated surveillance	Elicit concerns, assess milestones and trajectory	Lowers threshold for standardized screening/referral	Normal early visit does not close monitoring
Etiological evaluation	Offer clinically indicated genetic/medical assessment	May identify syndrome and associated health needs	Counsel variable penetrance and uncertain results
Diagnostic and needs assessment	Integrate history, observation, development, and differential diagnosis	Provides context only	Support is based on needs, not causal certainty

Risk-enriched surveillance allocates closer follow-up to groups with higher average likelihood while preserving universal developmental surveillance. Examples include younger siblings of

autistic children, infants with defined genetic syndromes, and children born very preterm or with significant neonatal complications. Repeated observation is preferable to a one-time etiological score because developmental trajectories diverge. Referral should be triggered by concern or developmental evidence, not delayed until genetic testing is complete.

8. Counseling, ethics, and equity

Etiological counseling should use absolute as well as relative risk when available, explain uncertainty, and state that most associations do not identify a single cause in an individual child. Language that implies maternal fault is scientifically inaccurate and harmful. Autistic people and families should participate in setting research priorities and defining useful outcomes. The goal of early recognition is access to support and understanding, not prevention of neurodiversity through unvalidated prediction.

Genomic evidence is disproportionately derived from populations of European ancestry, and prenatal cohorts differ in healthcare access and exposure measurement. Prediction models may therefore amplify existing inequities. Diverse recruitment, community partnership, local validation, affordable counseling, and protection against genetic discrimination and unauthorized data use are central to responsible translation.

9. Research priorities

Future studies should expand ancestry and geographic diversity; integrate genomic, placental, exposure, and longitudinal developmental data; measure exposure timing and dose precisely; use negative controls and family-based designs; preregister analyses; replicate interaction findings; and report absolute risks. Surveillance trials should test whether risk enrichment improves time to evaluation, family experience, and developmental support without increasing stigma, false reassurance, or unnecessary investigation.

10. Limitations

This structured narrative review was not registered and did not use duplicate study selection, formal study-level risk-of-bias instruments, or new meta-analysis. English-language restriction may omit relevant regional studies. The breadth of genetic and prenatal research required selective emphasis, and rapidly evolving genomic evidence may alter future estimates. The proposed surveillance framework therefore requires adaptation and prospective evaluation in local health systems.

11. Conclusion

ASD etiology is best represented as heterogeneous developmental liability arising from common and rare genetic variation interacting with prenatal, perinatal, and postnatal contexts. Heritability does not determine an individual outcome, and prenatal associations rarely identify a single cause. Clinically, risk information can justify closer, repeated surveillance and indicated etiological evaluation, but it cannot replace developmental observation or comprehensive assessment. Careful causal language, equitable evidence, and needs-based support are essential for responsible translation.

Declarations

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