

Declaration of Modena 2000:

Genetics of Autism

The International Association of Child and Adolescent Psychiatry and Allied Professions (IACAPAP) convened an international working group on the Genetics of Autism in Modena, Italy, on March 16-18, 2000. The Working Group reviewed the current state of knowledge concerning the contributions of genetic factors to the pathogenesis of autism and discussed future directions and implications of research. Based on these discussions, important conclusions already can be reached.

IACAPAP is the international organization of national societies of child and adolescent mental health founded more than sixty years ago to promote child mental health through improving the delivery of services, promotion of research, and the education and facilitation of the professions involved in these fields. As a non-governmental organization (NGO) in the framework of the United Nations, IACAPAP includes more than 65 nations as members. A major goal of IACAPAP is advancing knowledge concerning developmental psychopathology and the implications of research for clinical understandings, services, and treatment of individual children. To these ends, IACAPAP convened an international Working Group in Venice, Italy, in 1998, to review the major areas of advance and future prospects for research on the field of autism. This Working Group led to an IACAPAP Declaration on Autism and Developmental Disorders. As a continuation of this process, IACAPAP convened a Working Group in Modena, Italy, in March, 2000, to review the field of genetics of autism and bring together leaders in the field to discuss avenues for facilitating future progress.

Child and adolescent psychiatrists first recognized autism almost sixty years ago. Since then, individuals with autism have been diagnosed throughout the world, in every ethnic and social group. Clinicians and researchers have learned an enormous amount about the social, cognitive and language problems in autism, the natural history, and the range of outcomes. Autism is the most severe form of early onset, developmental disorder. Individuals with autism suffer from severe disturbances in the formation and maintenance of social relations, in language and communication, and in flexible functioning and adaptation. Many individuals with autism are intellectually disabled. Individuals with the most extreme forms of autism may be mute, socially detached, burdened with stereotypic behaviors, profoundly intellectually disabled and in need of fulltime supervision. Those with milder forms may have serious problems in the areas of mutual social relations, communication, and flexibility, but they have intellectual abilities within the normal range and able to function in the mainstream of society.

For several decades, autism has attracted major commitments from clinical services and research programs because of its early onset, major impairments of functioning, burdens on individuals and their families, remarkable symptomatology that affects core areas of development, and life-long nature. Also, the scientific and policy advances that relate to autism have influenced the understanding and care of individuals with other severe psychiatric and developmental disorders. Thus, future advances in research on autism, including the genetics of this disorder, are likely to have important benefits for the broader field of research in developmental psychopathology.

Research and clinical experience concerning autism have supported the concept of autism as a developmental disorder that reflects disturbances in underlying neurobiological development and functioning. Many lines of evidence – including research findings on brain function, the presence of autistic syndromes among individuals with known genetic disorders, and the impact of profound environmental factors – support the view that autism reflects the final outcome of a range of biological and environmental processes that impact early brain maturation. Among the factors that have been associated with autism, it now appears that abnormalities in genetic endowment play the central role. This viewpoint of autism as a developmental disability is influencing social and governmental policies about the need for comprehensive programs of education, clinical care and associated services.

We are now in a new era of research on autism. Using standard diagnostic concepts (including the definitions within the international classification schemes: International Classification of Disorders, ICD 10th edition, and the Diagnostic and Statistical Manual, DSM IV) and diagnostic methods, researchers and clinicians throughout the world can communicate clearly and collaborate scientifically. Advanced scientific methods and concepts are being focused on individuals with autism, including developmental and language research methods, neuroimaging, neurochemistry, cognitive and behavioral sciences and a range of genetic methodologies.

Recent studies on autism have used many of the contemporary approaches to genetic research on complex human conditions. These approaches include studies of populations, families, twins, and individuals with specific genetic and behavioral findings. In the future, it will be important to maintain a broad range of research methodologies and to allow

investigators to pursue findings with different methodologies. Research findings on the genetics of autism have led to the recognition that inborn, genetic factors play the prominent role in the cause of the disorder. Careful investigations of identical (monozygotic) and fraternal (dizygotic) twins and of families with more than one affected individual have revealed that genetic factors appear to play a central role for the majority of cases. Mathematical models suggest that a number of genes are probably involved in the transmission of this vulnerability, but the precise number is not known nor have specific genes yet been discovered. Sophisticated genetic studies from different research groups and consortia have highlighted several areas of the human genome that are highly promising for containing genes associated with autism.

There are indications that the full clinical expression of the disorder reflects complex interactions between the genetic vulnerability and other biological and environmental factors. These factors that make a child vulnerable are not yet known. Genetic research also has supported the earlier clinical concept of a "developmental or autistic spectrum" that there is a broad range of expression of the underlying biological diathesis or vulnerability. In some individuals, the full-blown autistic syndrome appears; in other relatives, including some parents and siblings of individuals with autism, aspects of the disorder become manifest. Individuals with difficulties on this autistic spectrum suffer from problems in forming and maintaining social relationships. They may be awkward in their social communication and may have problems in the expression and understanding of emotions. Some individuals also may have circumscribed areas of unusual interest or ability. It is not known what leads to the full syndrome of autism or to the milder variants of the "extended" or "broader" phenotype of the autistic disorder.

The Working Group recognizes that research on the genetic factors involved with autism will require many years of sustained, multidisciplinary and multi-site research. This research requires the collaboration of experts in various disciplines, including basic developmental biological and behavioral scientists and clinical researchers. There are essential reasons for the formation and support of international research consortia that can share methods, pool data for analyses, follow-up important findings, and disseminate authentic knowledge without excessive delay. At present, most research on the genetics of autism has concentrated on populations in the United States and Europe. It is important that future research consortia include research groups and clinical populations from throughout the world. Also, there must be a spirit of collaboration between parents and individuals with autism and those who are trusted with research and treatment. Today, professionals and families are joining together to promote research and improve services, and parents are recognized as their child's most effective and essential advocates.

When genes for autism are discovered, there will be a long process to define the pathways between genetic factors and full clinical expression and the development of individuals. This process will require the collaboration among many different types of investigators and clinicians. The new field of genetics of autism raises both new hopes and new concerns. The discovery of genetic factors will eventually hopefully lead to new approaches to diagnosis and intervention, and perhaps even prevention and cure. At the same time, genetic issues raise a range of ethical and policy issues.

While it is still early and no genes are yet known, it is important for researchers, clinicians, families and others concerned about issues in social policy and ethics to begin the process of discussion and clarification of the issues raised by new understanding of genetics in autism. The Working Group affirms recent policy statements by heads of government and others that the fundamental knowledge about the human genome - just as other phenomena of nature - belongs to society as a whole. Thus, genes should not be controlled by patents. At the same time, there should be various ways of promoting and utilizing the new knowledge to benefit individuals and mankind. In addition, it is important for everyone engaged in research to disseminate accurate and current information to both the scientific and lay media in a timely fashion.

It is important to note that the discovery of genetic factors will lead to new issues for parents and families, including concerns about transmission and counseling in relation to recurrence. These clinical and policy issues will require close collaboration among families, their advocates, clinicians and other specialists in the various medical, policy, and ethical fields. In this context, those concerned about autism can learn from experience with other developmental and medical conditions in which genetic factors plays a major role.

In considering the future prospects for research on the genetics of autism, the Working Group affirms the importance of open exchange of knowledge among different researchers. The advancement of knowledge about autism will require sustained engagement by many different research groups and the capacity for sharing information and comparing findings. This is particularly relevant in relation to studies that require large numbers of families and individuals for their timely and successful completion. Also, families who volunteer to participate in research and who provide information and biological specimens have a right to

expect that investigators will facilitate the most rapid possible advancement of knowledge.

There are important policy and ethical issues in relation to the importance of sharing knowledge about autism and similar disorders while promoting as rapid an advancement of knowledge as possible. In affirming the importance of such collaboration, the Working Group is aware of the need to preserve the freedom of individual scientists and groups to pursue areas of scientific priority and the legitimate concerns about protecting intellectual/scientific priority. The scientific community must continue to develop frameworks that will allow for the balancing among different needs for assuring optimal collaboration and optimal individuality in the pursuit and reporting of research findings. In this context, the Working Group encourages researchers and consortia working on the genetics of autism to establish continuing channels for discussion and joining together for pursuit of promising findings.

The rigorous application of developmental behavioral and neuroscience to the study of autism has led to increased understanding of the clinical disorder and of individuals who suffer from it. In the future, the field of human genetics offers great promise for unraveling the underlying, biological vulnerabilities; explaining the basis of individual differences in severity and course; clarifying the complex interactions between constitutional and environmental influences; and providing new approaches to prevention, early intervention and treatment. International collaborations among research programs and consortia from throughout the world are essential to fully exploiting the potentials for genetic and other types of research. The new science of human genetics offers great hope for individuals with autism and their families, as well as applications in relation to other major neuropsychiatric and developmental disorders. At the same time, the nature and implications of genetic research raise important administrative, social policy and ethical concerns that require thoughtful, sensitive and continuing discussion among families, basic and applied researchers, clinicians, government, the faith community, and others concerned about children and adolescents and the promotion of human welfare. The knowledge gained in relation to autism will have important influences on the understanding and care of children and adolescents with other serious neuropsychiatric and developmental disorders.

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