

### QUESTION 3: WHAT CAUSED THIS TO HAPPEN AND CAN IT BE PREVENTED?

IACC Strategic Plan Objectives	Planning Group Summary	Funding 2008-2013
<b>3.S.A.</b> Coordinate and implement the inclusion of approximately 20,000 subjects for genome-wide association studies, as well as a sample of 1,200 for sequencing studies to examine more than 50 candidate genes by 2011. Studies should investigate factors contributing to phenotypic variation across individuals who share an identified genetic variant and stratify subjects according to behavioral, cognitive, and clinical features.	<b>Funding:</b> The recommended budget has been partially met. <b>Progress:</b> Progress has been made on this objective through the funding of several GWAS and sequencing projects. The current number of 6,000 GWAS subjects falls short of the goal of 20,000, but the number of whole exome sequences far exceeds 1,200, and could also reach 6,000 in the next year. Whole exome sequencing has identified 7-10 candidate genes, and promises to move closer to the goal of 50 in the future. Progress is being made in CNV studies. Overall, the work is on target. <b>Remaining Gaps, Needs, and Opportunities:</b> More subtyping and genotype-phenotype work outside of syndromic forms of autism, as well as natural history studies, are needed. <b>Funding:</b> The recommended budget has been partially met. <b>Progress:</b> There has been progress on the understanding of exposures, but more work needs to be done to apply this directly to autism research. Progress has made through methodological advances embedded in epidemiological studies funded by NIEHS, but those projects are not captured by the Portfolio Analysis because they are not specific to autism. <b>Remaining Gaps, Needs, and Opportunities:</b> The primary obstacle to completion of this objective has been funding to identify and validate exposure markers. There is a need for biomarkers of exposure; exposomics should be a priority area for future research. <b>Funding:</b> The recommended budget has been nearly met, but work still needs to continue on this objective. <b>Progress:</b> The funding allocated to this area so far has primarily supported building infrastructure that can now be expanded to include more subjects, more data, and more analytical projects. <b>Remaining Gaps, Needs, and Opportunities:</b> Continued benefit will be derived from past investments as these resources are expanded and pooled.	\$38,587,633 \$813,227 \$26,903,311 \$188,455 \$3,608,312 \$10,794,995
<i>IACC Recommended Budget: \$43,700,000 over 4 years</i>		
<b>3.S.B.</b> Within the highest-priority categories of exposures for ASD, identify and standardize at least three measures for identifying markers of environmental exposure in biospecimens by 2011.		
<i>IACC Recommended Budget: \$3,500,000 over 3 years</i>		
<b>3.S.C.</b> Initiate efforts to expand existing large case-control and other studies to enhance capabilities for targeted gene-environment research by 2011.		
<i>IACC Recommended Budget: \$27,800,000 over 5 years</i>		
<b>3.S.D.</b> Enhance existing case-control studies to enroll racially and ethnically diverse populations affected by ASD by 2011.		
<i>IACC Recommended Budget: 3,300,000 over 5 years</i>		
<b>3.S.E.</b> Support at least two studies to determine if there are subpopulations that are more susceptible to environmental exposures (e.g., immune challenges related to infections, vaccinations, or underlying autoimmune problems) by 2012.		
<i>IACC Recommended Budget: \$8,000,000 over 2 years</i>		
<b>3.S.F.</b> Initiate studies on at least 10 environmental factors identified in the recommendations from the 2007 IOM report "Autism and the Environment: Challenges and Opportunities for Research" as potential causes of ASD by 2012.		
<i>IACC Recommended Budget: \$56,000,000 over 2 years (revised in 2010)</i>		

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**3.S.G.** Convene a workshop that explores the usefulness of bioinformatic approaches to identify environmental risks for ASD by 2011.

**Funding:** The workshop identified in this objective was held in 2011.

**Progress:** This objective has been completed and a report is available.

**Remaining Gaps, Needs, and Opportunities:** There is a need to develop an exposome. A forum for the sharing of new technologies and standardized assessments would also be useful in moving this field forward.

IACC Recommended Budget: \$35,000 over 1 year

\$46,991

\*This objective was completed in 2011

**3.S.H.** Support at least three studies of special populations or use existing databases to inform our understanding of environmental risk factors for ASD in pregnancy and the early postnatal period by 2012. Such studies could include:

- Comparisons of populations differing in geography, gender, ethnic background, exposure history (e.g., prematurity, maternal infection, nutritional deficiencies, toxins), and migration patterns; and
- Comparisons of phenotype (e.g., cytokine profiles), in children with and without a history of autistic regression, adverse events following immunization (such as fever and seizures), and mitochondrial impairment. These studies may also include comparisons of phenotype between children with regressive ASD and their siblings.

**Funding:** The recommended budget has been partially met, and the funded projects cover the objective well; there are 32 projects that are related to this objective, though more focus on use of databases than on special populations.

**Progress:** A positive element of progress for this objective is the existence of large monitoring databases and projects that capitalize on those resources, such as iCARE and MINERVA.

**Remaining Gaps, Needs, and Opportunities:** While progress is being made in this area, and it must be maintained in order to achieve this objective.

\$10,281,278

Emphasis on environmental factors that influence prenatal and early postnatal development is particularly of high priority. Epidemiological studies should pay special attention to include racially and ethnically diverse populations.

IACC Recommended Budget: \$12,000,000 over 5 years

**3.S.I.** Support at least two studies that examine potential differences in the microbiome of individuals with ASD versus comparison groups by 2012.

**Funding:** The number of projects in this area has been growing, with 6 projects in 2012.

**Progress:** The number of funded projects is large relative to the amount of funding, indicating that each of the projects is small, which suggests that these projects will not be sufficient in scope to complete this objective.

**Remaining Gaps, Needs, and Opportunities:** The high cost of required technology could be a barrier to the completion of this objective. These smaller pilot studies are potentially underpowered. The question of sample availability is important for this objective, along with raising researcher awareness of sample repositories.

\$749,263

IACC Recommended Budget: \$1,000,000 over 2 years

**3.S.J.** Support at least three studies that focus on the role of epigenetics in the etiology of ASD, including studies that include assays to measure DNA methylations and histone modifications and those exploring how exposures may act on maternal or paternal genomes via epigenetic mechanisms to alter gene expression, by 2012.

**Funding:** The recommended budget for this objective has been partially met, and the number of projects has been exceeded, with 22 projects supported in 2012.

**Progress:** This is a growing area of research. The current momentum in this area should be maintained.

**Remaining Gaps, Needs, and Opportunities:** An important technological need for this objective is the development of robust epigenetic measurements for small biological samples, such as blood spots. A possible barrier to research in this area is the availability and preservation quality of these samples. Large funded studies such as MARBLES might provide an opportunity to collect samples. If samples are made available, that may catalyze research in this area.

\$16,536,350

IACC Recommended Budget: \$20,000,000 over 5 years

**3.S.K.** Support two studies and a workshop that facilitate the

**Funding:** While the recommended budget has been partially met and some

\$1,287,763

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<p>development of vertebrate and invertebrate model systems for the exploration of environmental risks and their interaction with gender and genetic susceptibilities for ASD by 2012.</p> <p><i>IACC Recommended Budget: \$1,535,000 over 3 years</i></p>	<p>projects have been funded in this area, it appears that there is a downward trend. It should be noted however that this objective overlaps partially with 2SB, that is focused on research on sex differences in ASD, and 4SB that focuses on development of animal models that can be used for understanding molecular and neural pathways that can be targeted by interventions. These pathways also may be influenced by environmental factors.</p>	
<p><b>3.L.A.</b> Conduct a multi-site study of the subsequent pregnancies of 1,000 women with a child with ASD to assess the impact of environmental factors in a period most relevant to the progression of ASD by 2014.</p> <p><i>IACC Recommended Budget: \$11,100,000 over 5 years</i></p>	<p><b>Progress:</b> Projects by Tychele Turner at Johns Hopkins and Donna Werling at UCLA that are using animal models to investigate sex differences in autism are coded to 2SB. The following 2010 workshop sponsored by NIEHS, <a href="#">Autism and the Environment: Advancing the Science</a>, touched on this topic, but it was not the main focus of the workshop.</p> <p><b>Remaining Gaps, Needs, and Opportunities:</b> The development of animal models for more broad ASD research is coded to question 4, and the use of such models to answer environmental exposure questions is a next step for this objective.</p> <p><b>Funding:</b> The recommended budget for this objective was met, but emphasis on this objective should continue in the future.</p>	<p><b>\$15,194,483</b></p>
<p><b>3.L.B.</b> Identify genetic risk factors in at least 50% of people with ASD by 2014.</p> <p><i>IACC Recommended Budget: \$33,900,000 over 6 years</i></p>	<p><b>Progress:</b> The Group is concerned about the lack of continued funding for EARLI. More positively, MARBLES is continuing and projects analyzing the previously collected EARLI data are also in process.</p> <p><b>Remaining Gaps, Needs, and Opportunities:</b> A barrier to this type of work is the extremely high cost of building the necessary infrastructure. With MARBLES and previously with EARLI, there has been some progress on infrastructure. It is important to maintain these cohorts where possible, to collect a wide range of samples, and to use them for multiple studies to capitalize on investments made.</p> <p><b>Funding:</b> While the recommended budget for this objective has been met, further work is needed to identify genetic risk factors in at least 50% of people.</p>	<p><b>\$169,806,458</b></p>
<p><b>3.L.C.</b> Determine the effect of at least five environmental factors on the risk for subtypes of ASD in the prenatal and early postnatal period of development by 2015.</p> <p><i>IACC Recommended Budget: \$25,100,000 over 7 years</i></p>	<p><b>Progress:</b> Currently, whole exome analysis projects that for 20% of people, a genetic risk factor can be identified, and inclusion of CNV data might push this toward 30%.</p> <p><b>Remaining Gaps, Needs, and Opportunities:</b> The initial budget recommendation for this objective was made based on the assumption that GWAS studies would provide risk factor identification, but sequencing has proven more fruitful. Since this technique is more expensive, a higher budget will be required to meet the goal of 50%.</p> <p><b>Funding:</b> The recommended budget was partially met, and several projects were funded, but it appears there is a downward trend toward maintaining projects that began. This objective partially overlaps with 3LA.</p>	<p><b>\$5,349,089</b></p>
<p><b>3.L.D.</b> Support ancillary studies within one or more large-scale, population-based surveillance and epidemiological studies, including U.S. populations, to collect data on environmental factors during preconception, and during prenatal and early postnatal development, as well as genetic data, that could be pooled (as needed) to analyze targets for potential gene/environment interactions by 2015.</p> <p><i>IACC Recommended Budget: \$44,400,000 over 5 years</i></p>	<p><b>Progress:</b> Epidemiological studies coded to other objectives (e.g. EARLI) may also represent progress in this area.</p> <p><b>Remaining Gaps, Needs, and Opportunities:</b> A barrier to the completion of this objective is the undefined nature of ASD subtypes, both phenotypically and etiologically, lack of prenatal samples, and the lack of longitudinal follow-up of at-risk subgroups. This field is still developing and needs support.</p> <p><b>Funding:</b> The recommended budget for this objective has been met, with most of the studies coded to this area relating to CADDRE.</p>	<p><b>\$63,013,714</b></p>
<p>(Core Activities)</p> <p><b>Total funding for Question 3</b></p>	<p><b>\$17,656,815</b></p>	<p><b>\$380,818,136</b></p>