



**LACK OF POSITIVE HERITABILITY FINDINGS IN AUTISM
PROVIDES COMPELLING EVIDENCE TO SHIFT PRIORITY
TO MORE PROMISING ENVIRONMENTAL FACTORS
RESEARCH**

Implications of Autism Genome Project Consortium Findings

Mark F. Blaxill
Vice President, Coalition for SafeMinds

April 2007

Executive Summary

For many years, the heritability hypothesis has found broad support among scientists working in autism, with some claiming that autism is as much as 90% inherited. The hypothesis states that the critical events in the causation of autism occur during *meiosis* and *fertilization* when genes from each parent recombine and are passed on to a child. Over the last decade, numerous genome scans by different groups have attempted to identify in these recombination patterns the relevant DNA sequences, or “autism genes”, that are more frequently passed on from parents to affected versus unaffected children.

The earlier genome scans conducted with smaller samples have met with little success in finding or replicating prior findings of “autism genes”. So the leading researchers in the field recently combined forces in an Autism Genome Project Consortium (AGPC). By pooling resources and genetic material from nearly 1500 families with multiple affected children, the AGPC believed they could increase the odds of locating areas of the parental genome that could be linked to their autistic offspring.

The results of the AGPC effort produced a result that is little different than the result one might expect from taking a randomized group of unaffected families. It also failed to replicate any of the most highly touted suggestive findings from earlier genome scans. The negative AGPC findings provide strong evidence that heritability claims in autism are exaggerated if not false. Provided with enormous resource support and under the most favorable study conditions, the AGPC found no evidence of heritability.

The negative results highlight the weakness of the concordance evidence cited to support the heritability hypothesis. Examination of this evidence shows that: identical twins are frequently non-concordant for autism; fraternal twins are concordant for autism more frequently than siblings and at rates closer to identical twins than previously acknowledged; sibling risk may not exceed population risk as much as previously reported; and population risk is rising at a rapid rate. These considerations argue against the foundations of the heritability hypothesis.

The AGPC paper emphasized a new area with little bearing on the heritability hypothesis. Instead of frank acknowledgement of the negative genome scan findings and even a nominal consideration of its implications, the study authors chose instead to highlight isolated findings of this new area: *de novo* genetic mutations (copy number variants or CNVs) in their study subjects. Although findings of CNV frequency in autism are worth noting, the AGPC results were tentative and inconclusive. It appears that the AGPC authors preferred to change the subject to an entirely different area of genetic research rather than to reflect upon the implications of their negative findings on heritability.

The falsification of the heritability hypothesis in autism is an important finding. It suggests that what many scientists believe about autism causation is wrong. It supports the argument advanced by many autism parents and a rising number of scientists that the role of environmental factors in autism is far more important than previously recognized. And it calls for a shift in financial resources away from the pursuit of heritability research and towards environmental factors research.

Introduction

It is time to move beyond the strict heritability hypothesis of autism causation. This theory, which has dominated the research agenda in autism for three decades, has been tested repeatedly, rigorously, with extraordinary resources and under the most favorable conditions. Despite the high hopes and aggressive claims of many (“autism is one of the most heritable complex disorders, with compelling evidence for genetic factors and little or no support for environmental influence”²), the theory has failed repeated tests. These tests consistently cannot distinguish between positive findings for evidence of heritability and the null hypothesis of no heritability. In a recent publication, authors from the Autism Genome Project Consortium (AGPC) restate their allegiance to the heritability hypothesis as follows: “We hypothesize that liability to autism is due, in large part, to oligogenic inheritance in which combinations of susceptibility alleles contribute.” Unfortunately, their allegiance is not supported by their data.

The recent study findings from the AGPC provide new evidence to falsify the strict heritability theory of autism. This evidence provides support for an immediate shift in resource priorities in autism: away from continuing investment in a failed theory and towards an urgent investigation of environmental factors. This shift does not imply an abandonment of genetic research altogether; it does, however, suggest that future genetic research should be oriented to a search for genetic vulnerability factors that combine with environmental exposures to cause autism.

It’s important to place these new findings in proper context. The largest full genome scan ever performed, the AGPC has been years in the making and required Herculean efforts to organize and execute. Many organizations were involved, although the National Alliance for Autism Research (NAAR, now subsumed into Autism Speaks) was the primary initial sponsor in orchestrating the project. The AGPC effort, which required the cooperation of numerous diverse parties to share credit and resources, is a “consortium of consortiums”, formally an alliance between four groups: the Autism Genome Consortium (AGC), the International Molecular Genome Study for Autism Consortium (IMGSAC), the Collaborative Programs for Excellence (CPEA) and the Autism Genetics Resource Exchange (AGRE). Three of these consortia—AGC, IMGSAC and AGRE—contributed participants, resources, and materials to the AGPC from nine prior genome scanning groups.³⁻¹²

The AGPC collected and combined genetic samples and data from nearly 1500 families, each of which had at least two affected siblings. Their paper—just published

in *Nature Genetics*—listed 135 authors, including 24 “lead investigators.” The author roster includes many of the most active and prominent autism scientists and reads like a who’s who of the extended autism genetics research enterprise. The AGPC was a landmark effort; the only prior genetics project of comparable scale was the sequencing of the human genome itself. If one were going to find meaningful heritable genetic effects in autism, this approach was the right way to do it. And certainly, the discovery of some kind of positive result would have been an important contribution to the science of autism.

The AGPC study was designed to heighten the sensitivity of the analysis to genetic causation effects and therefore maximized the possibility of a favorable result. The study subjects were limited to “multiplex families” in which at least two children were diagnosed with an autistic spectrum disorder (ASD). The starting sample of nearly 1500 families provided unprecedented statistical power (prior studies were limited to a range of 28-345 families). This large sample gave the investigators the opportunity to pursue multiple analytical strategies, segment the study sample into numerous sub-groups and exercise stringent quality control measures that allowed them to eliminate families in which the data quality was less robust (the final linkage analysis used data from only 1,168 of the original 1,496 families). The flexibility afforded by the large study sample gave the investigators the freedom to pursue multiple iterations as follow ups to their initial results and not be constrained by *ex ante* hypotheses. Instead of a single full genome scan, the authors estimate that “we effectively performed the equivalent of four to five independent genome scans.”¹

In light of the importance of this project and the power of its findings, a clear look at the reported study findings and their implications are warranted. Such an analysis should distinguish between the research evidence described in the scientific journal and the public relations commentary that has accompanied its release.

A sample of positive comments in the press from prominent study authors includes the following:

- “We have known for years that autism is a strongly genetic disorder--this study helps us to significantly advance research on genetic mechanisms,” said [Dr. Fred] Volkmar, study co-author, Yale Child Study Center Director and the Irving B. Harris Professor of Child Psychiatry, Pediatrics and Psychology.¹³
- “Not only have we found which haystack the needle is in, we now know where in the haystack that needle is located,” said [Dr. Peter] Szatmari... head of child psychiatry at McMaster University. ... “This

is a major breakthrough in our efforts to better understand the disorder and improve diagnosis and treatment for patients and their families.”¹⁴

- “The evidence suggests that autism is over 90 percent caused by genes,” said Dr. Joseph Buxbaum.”¹⁵

Negative AGPC Results

The study findings themselves provide no support for these claims and no favorable outcomes for autism science; indeed, the most striking conclusion, in light of the remarkable resources and favorable conditions, was that *the AGPC results were indistinguishable from the null hypothesis of no heritability effect*. To place the findings in the clearest possible relief, we would point out three key points.

1. *The AGPC study reported only a single “suggestive linkage” result from their entire full genome scan and no significant findings.* The suggestive finding emerged on a region of the short arm of chromosome 11, or 11p12-p13. In genome scans, a linkage score is considered “significant” if the Z-score exceeds 4.1 and “suggestive” if the Z-score exceeds 3.2.¹⁶ One region on chromosome 11 crossed the suggestive linkage threshold with a score of 3.57. But because of the immense size of the human genome there is a large chance that random variations in linkage will produce false positive results, so suggestive results like this need to be treated with great skepticism. Eric Lander and Leonid Kruglyak, the geneticists who developed the statistical standards for interpreting full genome scans, have argued that there is a high probability that any genome scan will produce one suggestive linkage finding due to chance alone. To illustrate their point, Lander and Kruglyak directly tested the null hypothesis in a simulated genome scan.

“To illustrate the random fluctuations expected in a whole genome scan, we generated simulated genotypes assuming independent assortment throughout the genome—that is that there are no trait causing loci. All positive scores in such data necessarily represent random fluctuations, not true linkage...[In the simulation, a] single region on chromosome 14 reached the status of suggestive linkage, as expected, while no region showed significant linkage. If these results had occurred in a real dataset, an investigator would likely call attention to the possibility of linked genes on chromosome 14...The example thus illustrates that

*false positives can cluster in candidate regions and otherwise mimic true loci.”*¹⁶

The suggestive region on chromosome 11p12 has come up as a region of interest in only one prior autism genome scan⁸, and was falsified in the rest. In other words, the AGPC findings are little different from the results one would expect from a random number generator. Substitute chromosome 11 for chromosome 14 in the above quotation and you would have a description that is virtually identical to the AGPC results.

2. *The AGPC finding falsified all suggestive study results from previous regions of interest.* Prior genome scans have been similarly inconclusive. Like this study’s reporting of 11p, they have reported a number of suggestive findings. The first major genome scan performed by the IMGSA^{3,4} yielded a number of suggestive findings, most notably for regions on chromosomes 2q, 7q and 17q. None of these findings have received consistent support. For example, a Stanford group¹⁷ found suggestive linkage on chromosome 1p, but nothing on 2q, 7q or 17q; one AGRE scan⁸ found some suggestive evidence of heritability on chromosome 17q, but not on 7q or 2q; a scan from a group at the Seaver Autism Center¹⁰ in New York City found suggestive evidence for heritability on chromosome 2q, but not on chromosome 7q and 17q; and other collaborations such as PARIS⁵, CLSA⁶, CAT⁹ reported a diffuse set of results in new regions on chromosomes 6q, 13q and Xq, respectively, but with no consistent support for the earlier regions of interest. The strongest finding to date has come from two recent AGRE samples^{18,19}, in which an initial report of linkage on chromosome 17q was replicated in a sample that excluded male subjects. Notably, the authors stated that “taken together, these samples provide a replication of linkage to this chromosome region that is, to our knowledge, *the first such replication in autism* [emphasis added].”¹⁹

But the AGPC scan found no evidence of even suggestive linkage for any of these three regions on 2q, 7q and 17q. In the world’s most powerful scan to date, multiple analyses of sub-groups, including analyses that eliminated males, could not yield even a hint of support for the solitary replication finding on 17q, and not even suggestive findings for chromosomes 2q and 7q. In effect, the AGPC results demonstrated that the findings of previous scans reported as “promising” differed little from a random number generator.

3. *Based on only two cases out of 3,000, the AGPC authors promoted the importance of a new heritability gene candidate on chromosome 11, based on an unusual mutation found in the Neurexin 1 (NRXN 1) gene of two sisters.* The authors' case for the importance of the NRXN 1 finding in a single family is a puzzling claim and is supported neither by the AGPC evidence nor any cited studies. Chromosomal abnormalities have been a common subject of analysis in the autism genetic literature, with typical reports of abnormality rates falling in a range from 0-15% and averaging about 5%.^{2,20} But these reports vary wildly in their methods, their intent and their time of publication; most notably, they report no standard for what to expect in terms of chromosomal abnormality in an unaffected individual. Such standards are a critical and until recently unexplored topic in human genetics (see below). The NRXN 1 finding relied almost entirely on a new technique for identifying such abnormalities known as copy number variant (CNV) analysis. Further tests on the NRXN 1 mutations and transmission patterns from parent to child in the broader sample were inconclusive and provided no evidence for heritability in any functional variant of NRXN 1. Despite this negative result, the authors chose to place great emphasis on the potential significance of this isolated finding, both in their paper and in subsequent media accounts. In light of the absence of evidence for the heritability of any functional variant of NRXN 1, the authors appear to be offering an implicit transition to a new theory of genetic causation in autism—i.e., that autism is caused by an unusual excess of chromosomal damage that may not be a result of inheritance but rather of *de novo* mutation—but they do this only indirectly and provide no elaboration for how such a theory might work. Although this shift in hypotheses from heritability to *de novo* mutation is of historical importance, the authors fail to note it. They also fail to note that such *de novo* DNA alterations may be caused by environmental exposures.

Overstated Heritability Arguments

Beyond its specific findings, the commentary in the AGPC paper reiterated common misstatements about the high degree of heritability in autism. This consistent overstatement of the arguments supporting a high degree of “genetic loading” in autism provides what should now be seen as a false foundation for a failed theory. Indeed, upon close examination, the commonly cited evidence that makes up this theoretical foundation is incorrect in almost all of its particulars.

More specifically, the evidence base for high genetic loading can be described as a series of simple mathematical relationships (each of which we describe sequentially below):

*Monozygotic twin (MZ) concordance rates ≈ 100%
>> dizygotic twin (DZ) concordance rates ≈ sibling
concordance rates >> population prevalence.*

Each link in this sequence is proving to be weaker than the assertion commonly offered. Let us take each common assertion in turn.

- *Monozygotic (identical) twin concordance rates are nearly 100%.* The AGPC authors claim that “twin studies show a concordance of 60-92% for monozygotic twins.” This claim rests on a selective citation of the evidence. Three twin studies²¹⁻²³—published in 1985, 1989 and 1995 and covering twin populations born well before the sharp autism increases of the 1990s—form the core evidence base for the claim of high MZ twin concordance. Based on a sample of 50 identical twin pairs, these three studies report 43 pairs in which both twins meet criteria for autism, for an average 86% concordance rate and a range of 60-90% MZ twin concordance. There are, however, several other studies that report lower rates. The first autism twin study, from 1977, reported MZ concordance of only 36%.²⁴ Another more recent study reported MZ twin concordance of 44%.²⁵ A recent unpublished study may have had rates as low as 59%.²⁷ Recognizing that MZ twins also share highly similar pre- and post-natal environments, the observance of high concordance need not be surprising and reports of concordance rates below 50-60% should neither be ignored nor minimized.
- *The ratio of monozygotic to dizygotic (identical to fraternal) twin concordance rates is very high.* The AGPC authors assert that concordance rates of 60-92% in MZ twins contrast with rates of 0-10% in DZ twins. The primary source of this evidence comes from just two concordance studies^{22,23} with small samples of twin pairs (21 and 27 twin pairs respectively) all of whom were born before the recent sharp increases in autism rates. Yet these two studies are used to suggest that the MZ/DZ concordance rate ratio is effectively infinite. This selective sampling ignores two other twin concordance studies, one of which²⁴ found relatively low MZ twin concordance alongside a 0% DZ concordance rate, another of which²¹ found a 23% DZ twin concordance rate alongside a 96% MZ twin concordance rate. Taken together, the twin pairs in all four of these studies show an MZ twin concordance of 77% and a DZ twin concordance of

11% (including evidence of additional twin pair reports cited in one study²¹), giving a concordance rate ratio of 7. This ratio is high, supporting a strong role for genetic factors in early autism cases, but not nearly as high as the AGPC authors imply. More recent autism twin studies suggest that the MZ/DZ concordance ratio is even lower than these early studies: one study reports a MZ/DZ concordance rate ratio of less than 2 in a population sample²⁶; another unpublished study of California twins estimated an MZ/DZ concordance ratio somewhere in the range of 1.6 to 6.3 (based on an MZ concordance rate ranges between 58-88% and a DZ concordance rate range of 14-36%). The analysts of the California twins noted that “These data suggest that heritability estimates from previous studies may have overestimated the role of genetics and underestimated the role of environmental factors in the etiology of autism.”²⁷ We concur; the overall findings from all of the twin studies suggest that MZ and DZ twin concordance rates are far more similar than advocates for the strong heritability hypothesis report.

- *Dizygotic (fraternal) twin concordance rates are the same as singleton sibling concordance rates.* The heritability hypothesis predicts no difference in concordance rates between fraternal twins and siblings, since their genetic relationship is the same. A difference in rates would suggest a role for environmental factors in autism causation. Three recent twin studies²⁷⁻²⁹ have in fact suggested that twinning itself is a risk factor for autism, since twins pairs have been found at an unusually high rate in efforts to recruit populations of affected sibling pairs. One of these studies²⁸ suggested that the rate of DZ twin concordance was over four times the expected rate for DZ twins in the overall population and another calculated a 60% higher twinning rate in autism.²⁷ In light of arguments suggesting that twin studies in general confuse the relative impact of genes and environment³⁰, the conclusions drawn from twin studies appear far greater than the twin evidence supports.
- *Sibling concordance rates are far higher than population prevalence rates.* Autism risk in non-twin siblings is commonly estimated to be 4-5%.^{2,30} Compared to historic autism prevalence rate estimates of 4-5 per 10,000, the sibling risk would constitute a risk level 100 times higher than population risk, suggesting a very strong role for familial autism risk. In light of more recent autism prevalence rates of about 1% in some geographies³²⁻³⁴, and little comparable evidence of sibling risk in these more recent cohorts, the relative role of

familial autism risk, though likely still important, needs to be recalculated based on the newer overall risk rates. Given the huge reliance on the sibling and twin recurrence rates for justification of continued genetics funding, it is remarkable that newer studies on this subject have not been done.

- *There is no upward trend in autism rates; any increase in reported rates is due to better diagnosing.* In light of historic autism estimates of 4-5 per 10,000 and recent estimates of full syndrome autism of 40-50 per 10,000, the evidence for an increasing trend over time is overwhelming.³⁵ It almost goes without saying, but bears repeating, that a change in prevalence to this degree requires an environmental trigger of some type and cannot be explained by inheritance alone, or even by random mutation-causing or epigenetically-altering mechanisms.

Need to Justify Genetic Research Funding

In contrast to the tendency of the authors to overstate the foundations of the heritability hypothesis in the published paper and associated press commentary, one notable aspect of the AGPC article was the failure to note properly the weakness of the findings. The negative linkage scores are given one sentence in the *Results* section. The Lander and Kruglyak standards are mentioned in small print in the notes to a single graph. A single sentence in the *Discussion* section, “None of our linkage results can be interpreted as ‘statistically significant’ because we have performed numerous analyses of the data,” is ignored in the remaining portions and in the overall tone of the article. The vast majority of the reporting and discussion is devoted to the CNV findings, which themselves are noted in passing as being inconsistent across families and even within sibling pairs.

CNV is emerging as a promising technique to examine *de novo* genetic variations in the human genome. This approach is quite consistent with a model of environmental causation and may indeed offer greater promise than heritability research in addressing the contribution of genetic abnormalities to the pathogenesis of autism. But variation in the human genome is by no means unexpected and, as there is very little in the way of a track record for CNV research in human disease, much of this work remains exploratory. A recent study by Sebat and colleagues, many of whom are AGPC authors, found a rate of *de novo* mutation of 10% in a small sample of simplex autism families, as compared to a 1% rate in controls and 2.6% in multiplex families.³⁶ This is an interesting, if modest, finding, yet the claims of the authors are extravagant. “As technology for

discovering spontaneous germline mutation in children improves, the proportion of autism cases with detectable events is bound to rise.” In their enthusiasm, the authors neglect to comment on several limitations of their findings, such as the weak effect in boys, the possibility for uncontrolled variation in geographic and environmental effects and the absence of any larger standard for copy number variation beyond the 196 controls.

The AGPC CNV results are even more tentative and the related linkage findings are barely suggestive of anything useful. Taken together with the Sebat et al study, this newfound enthusiasm for CNV research without even noting the collapse of the heritability hypothesis raises the possibility that the AGPC findings are being used in an instrumental fashion to justify a new phase of speculative genetics research. In light of this promotional emphasis, it is worth noting that a significant portion of the AGPC investigators are part of a commercial enterprise. At a minimum, the universities and hospitals hosting all of the AGPC groups are dependent on continuing funding to support their genetic research activities. In addition, roughly 20% of AGPC authors have been listed as inventors on a gene patent, many of which involved genes involved in autism. Notably, a full 50% of the AGPC *lead investigators* have filed gene patents.³⁷ The list of commercially involved authors includes Drs. Buxbaum, Sutcliffe, Rodier, Betancur, Schellenberg, Wijsman, Scherer, Pericak-Vance, Haines, Geschwind, Cantor, Devlin, Monaco, Gilliam, Gilberg, Leboyer, Tanzi and Sheffield.

More recently, Dr. Scherer—a member of the scientific advisory board of CombiMatrix, a lead investigator of the AGPC and the Director of the Center for Applied Genomics at the University of Toronto—announced a commercial partnership with CombiMatrix to develop genetic screening techniques.³⁸ This partnership appears to be reliant on the AGPC data and would therefore have a clear commercial interest in a positive result. Certainly, there is nothing wrong with public private partnership, but it is important to recognize that academic researchers involved in patent development and commercial activities may hold economic interests that rise above their career interests in funding their own research. Of particular note in this era of journal policing of conflicts of interest by authors, the “Competing Interests Statement” at the end of the paper by *Nature Genetics* says, “The authors declare that they have no competing financial interests.”

Conclusion

In summary, the AGPC findings provide the strongest support to date for the case to shift autism research resources away from deterministic heritability research

and towards environmental investigations, including investigation of gene-environment interactions. Despite their weak evidence and unsupported claims, the study authors have not adequately faced the implications of three decades of failure in the gene transmission hypothesis of autism causation. Instead, they continue to promote new and speculative genetic research projects. These authors are influenced by their institutional and commercial interests and their advocacy should be considered in that light. It is time to move on to more productive activities and focus research on the areas that can more rapidly help individuals with autism and prevent future cases through removal of environmental triggers.

References

1. The Autism Genome Project Consortium. Mapping autism risk loci using genetic linkage and chromosomal rearrangements. *Nature Genetics* 2007;39:319 – 328.
2. Veenstra-Vanderweele J, Christian SL, Cook EH Jr. Autism as a paradigmatic complex genetic disorder. *Annu Rev Genomics Hum Genet.* 2004;5:379-405.
3. International Molecular Genetic Study of Autism Consortium. A full genome screen for autism with evidence for linkage to a region on chromosome 7q. *Hum Mol Genet.* 1998;7(3):571-8.
4. International Molecular Genetic Study of Autism Consortium (IMGSAC). A genomewide screen for autism: strong evidence for linkage to chromosomes 2q, 7q, and 16p. *Am J Hum Genet.* 2001;69(3):570-81.
5. Philippe A, Martinez M, Guilloud-Bataille M, Gillberg C, Rastam M, Sponheim E, Coleman M, Zappella M, Aschauer H, Van Maldergem L, Penet C, Feingold J, Brice A, Leboyer M. Genome-wide scan for autism susceptibility genes. Paris Autism Research International Sibpair Study. *Hum Mol Genet.* 1999;8(5):805-12.
6. Barrett S, Beck JC, Bernier R, Bisson E, Braun TA, Casavant TL, Childress D, Folstein SE, Garcia M, Gardiner MB, Gilman S, Haines JL, Hopkins K, Landa R, Meyer NH, Mullane JA, Nishimura DY, Palmer P, Piven J, Purdy J, Santangelo SL, Searby C, Sheffield V, Singleton J, Slager S, et al. An autosomal genomic screen for autism. Collaborative linkage study of autism. *Am J Med Genet.* 1999;88(6):609-15.
7. Liu J, Nyholt DR, Magnussen P, Parano E, Pavone P, Geschwind D, Lord C, Iversen P, Hoh J, Ott J, Gilliam TC; Autism Genetic Resource Exchange Consortium. A genomewide screen for autism

- susceptibility loci. *Am J Hum Genet.* 2001;69(2):327-40.
8. Yonan AL, Alarcon M, Cheng R, Magnusson PK, Spence SJ, Palmer AA, Grunn A, Juo SH, Terwilliger JD, Liu J, Cantor RM, Geschwind DH, Gilliam TC. A genomewide screen of 345 families for autism-susceptibility loci. *Am J Hum Genet.* 2003;73(4):886-97.
 9. Shao Y, Wolpert CM, Raiford KL, Menold MM, Donnelly SL, Ravan SA, Bass MP, McClain C, von Wendt L, Vance JM, Abramson RH, Wright HH, Ashley-Koch A, Gilbert JR, DeLong RG, Cuccaro ML, Pericak-Vance MA. Genomic screen and follow-up analysis for autistic disorder. *Am J Med Genet.* 2002;114(1):99-105.
 10. Buxbaum JD, Silverman JM, Smith CJ, Kilifarski M, Reichert J, Hollander E, Lawlor BA, Fitzgerald M, Greenberg DA, Davis KL. Evidence for a susceptibility gene for autism on chromosome 2 and for genetic heterogeneity. *Am J Hum Genet.* 2001;68(6):1514-20.
 11. McCauley JL, Li C, Jiang L, Olson LM, Crockett G, Gainer K, Folstein SE, Haines JL, Sutcliffe JS. Genome-wide and Ordered-Subset linkage analyses provide support for autism loci on 17q and 19p with evidence of phenotypic and interlocus genetic correlates. *BMC Med Genet.* 2005;6:1.
 12. Schellenberg GD, Dawson G, Sung YJ, Estes A, Munson J, Rosenthal E, Rothstein J, Flodman P, Smith M, Coon H, Leong L, Yu CE, Stodgell C, Rodier PM, Spence MA, Minshew N, McMahon WM, Wijsman EM. Evidence for multiple loci from a genome scan of autism kindreds. *Mol Psychiatry.* 2006;11(11):1049-60, 979.
 13. "Autism Gene Identified By Yale And Global Consortium", *Medical New Today.* February 24, 2007.
 14. "Canadian-led research identifies new genetic regions linked to autism", *The Canadian Press.* February 18, 2007
 15. "ABC Reports New Autism Study Finds Genetics, Not Toxins, to Blame for Rise in Cases." By Ken Shepherd, *Business & Media Institute.* February 19, 2007.
 16. Lander E, Kruglyak L. Genetic dissection of complex traits: guidelines for interpreting and reporting linkage results. *Nat Genet.* 1995;11(3):241-7.
 17. Risch N, Spiker D, Lotspeich L, Nouri N, Hinds D, Hallmayer J, Kalaydjieva L, McCague P, Dimiceli S, Pitts T, Nguyen L, Yang J, Harper C, Thorpe D, Vermeer S, Young H, Hebert J, Lin A, Ferguson J, Chiotti C, Wiese-Slater S, Rogers T, Salmon B, Nicholas P, Petersen PB, Pingree C, McMahon W, Wong DL, Cavalli-Sforza LL, Kraemer HC, Myers RM. A genomic screen of autism: evidence for a multilocus etiology. *Am J Hum Genet.* 1999;65(2):493-507
 18. Stone JL, Merriman B, Cantor RM, Yonan AL, Gilliam TC, Geschwind DH, Nelson SF. Evidence for sex-specific risk alleles in autism spectrum disorder. *Am J Hum Genet.* 2004;75(6):1117-23.
 19. Cantor RM, Kono N, Duvall JA, Alvarez-Retuerto A, Stone JL, Alarcon M, Nelson SF, Geschwind DH. Replication of autism linkage: fine-mapping peak at 17q21. *Am J Hum Genet.* 2005;76(6):1050-6.
 20. Xu, J., Zwaigenbaum, L., Szatmari, P. & Scherer, S.W. Molecular cytogenetics of autism. *Curr Genomics.* 2004;5:347-364.
 21. Ritvo ER, Freeman BJ, Mason-Brothers A, Mo A, Ritvo AM. Concordance for the syndrome of autism in 40 pairs of afflicted twins. *Am J Psychiatry.* 1985;142(1):74-7.
 22. Steffenburg S, Gillberg C, Hellgren L, Andersson L, Gillberg IC, Jakobsson G, Bohman M. A twin study of autism in Denmark, Finland, Iceland, Norway and Sweden. *J Child Psychol Psychiatry.* 1989;30(3):405-16.
 23. Bailey A, Le Couteur A, Gottesman I, Bolton P, Simonoff E, Yuzda E, Rutter M. Autism as a strongly genetic disorder: evidence from a British twin study. *Psychol Med.* 1995;25(1):63-77.
 24. Folstein S, Rutter M. Infantile autism: a genetic study of 21 twin pairs. *J Child Psychol Psychiatry.* 1977;18(4):297-321.
 25. Kates WR, Burnette CP, Eliez S, Strunge LA, Kaplan D, Landa R, Reiss AL, Pearlson GD. Neuroanatomic variation in monozygotic twin pairs discordant for the narrow phenotype for autism. *Am J Psychiatry.* 2004;161(3):539-46.
 26. Constantino JN, Todd RD. Autistic traits in the general population: a twin study. *Arch Gen Psychiatry.* 2003;60(5):524-30.
 27. Croen LA, Grether JK, Hallmayer J. A population-based study of autism among twins in California. *IMFAR, Orlando, FL, November 2002:*69.
 28. Greenberg DA, Hodge SE, Sowinski J, Nicoll D. Excess of twins among affected sibling pairs with autism: implications for the etiology of autism. *Am J Hum Genet.* 2001;69(5):1062-7.
 29. Betancur C, Leboyer M, Gillberg C. Increased rate of twins among affected sibling pairs with autism. *Am J Hum Genet.* 2002;70(5):1381-3.
 30. Joseph J. Twin studies in psychiatry and psychology: science or pseudoscience? *Psychiatr Q.* 2002;73(1):71-82.
 31. Jorde LB, Hasstedt SJ, Ritvo ER, Mason-Brothers A, Freeman BJ, Pingree C, McMahon WM, Petersen B, Jenson WR, Mo A. Complex segregation analysis of autism. *Am J Hum Genet.* 1991;49(5):932-8.

32. Autism and Developmental Disabilities Monitoring Network Surveillance Year 2002 Principal Investigators; Centers for Disease Control and Prevention. Prevalence of autism spectrum disorders--autism and developmental disabilities monitoring network, 14 sites, United States, 2002. *MMWR Surveill Summ.* 2007;56(1):12-28.
33. Tebruegge M, Nandini V, Ritchie J. Does routine child health surveillance contribute to the early detection of children with pervasive developmental disorders? An epidemiological study in Kent, U.K. *BMC Pediatr.* 2004;4:4.
34. Reading R. Prevalence of disorders of the autism spectrum in a population cohort of children in South Thames: the Special Needs and Autism Project (SNAP). *Child Care Health Dev.* 2006;32(6):752-3.
35. Blaxill MF. What's going on? The question of time trends in autism. *Public Health Rep.* 2004;119(6):536-51.
36. Sebat J, Lakshmi B, Malhotra D, Troge J, Lese-Martin C, Walsh T, Yamrom B, Yamrom B, Yoon S, Krasnitz A, Kendall J, Leotta A, Pai D, Zhang R, Lee YH, Hicks J, Spence SJ, Lee AT, Puura K, Lehtimaki T, Ledbetter D, Gregersen PK, Bregman J, Sutcliffe JS, Jobanputra V, Chung W, Warburton D, King MC, Skuse D, Geschwind DH, Gilliam TC, Ye K, Wigler M. Strong Association of De Novo Copy Number Mutations with Autism. *Science.* 2007 Mar 15; [Epub ahead of print]
37. Sample patents and applications for AGPC author/inventors include: Buxbaum WO2005055807; Sutcliffe, US20070037194; Betancur, Leboyer, Gillberg and Bourgeron US20050118588; Rodier and Stodgell US6228582; Schellenberg and Wisjman US5449604; Scherer WO2000005405; Pericak-Vance, Haines and Gilbert US20040014109; Geschwind US20060051790; Cantor US7037651; Gilliam and Tanzi US5578493; Devlin US6468789; Poustka US6824972; Monaco US5239060; Sheffield US7008782; Hollander US20060105939; Ledbetter US6143504; Yu and Schellenberg US6583112.
38. "CombiMatrix Molecular Diagnostics to Utilize Autism Probe Content from a Partnership with The Centre for Applied Genomics." *Genetic Engineering and Biotechnology News*, March 7, 2007.