Supplementary information S1 | **ASD related syndromes†**

Syndrome (*Gene*) OMIM Link^	**Proportion Syndrome with ASD**	**Proportion ASD with Syndrome**	**Estimated Frequency**	**Intellectual Impairment**	**M / F ^**	**Dysmorph.**	**Seizures**	**Speech Impaired**	**Motor**	**Other**
15q Duplication Syndrome[1]	High	~1%	<1/10,00	Yes	=	Yes (variable & minor)	Yes	Yes	Hypotonia Delayed	Reports of Sudden Death
16p11 Deletion Syndrome[2–4]	High	~1%	1/4,000	Yes	=	No	No	Yes	Hypotonia Delayed	Congenital Cardiovascular Abnormalities
22q11-13 Del (*SHANK3*)[5–7] http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=606232	High	~1%	Unknown	Yes	<1	Yes (mild)	Yes (Variable)	Yes (Absent or severely delayed)	Hypotonia	Normal or accelerated growth
Angelman Syndrome (mat. 15q11)[8,9] http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=105830	40%	<1%	1/10,000	Yes (severe)	=	Yes	Yes	Mutism	Ataxia Limb Tremor Hypotonia	Microcephaly Hypopigmentation Paroxysmal Laughter Feeding problems Scoliosis
Cortical Dysplasia Focal Epilepsy (*CNTNAP2*)[10] http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=610042	67%	Rare	Rare (Amish Isolate)	Yes	=	No	Yes	Yes (Regression subsequent to seizures)	Delayed Develop.	Cortical Dysplasia Neuronal Migration Abnormalities Diminished or absent deep-tendon reflexes
Fragile X (*FMR1*)[11] *http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=300624*	25% of Males 6% of Females	1–2%	1/4,000 Males	Yes	>1	Yes	No	Yes	Delayed Develop.	Macrocephaly Congenital Cardiovascular Abnormalities Macroorchidism Scoliosis

Joubert Syndrome (several loci)[12] http://www.ncbi.nlm.nih.gov/entrez/dspomim.cgi?id=213300	25%	Rare	Rare	Yes	=	Yes	No	Yes	Ataxia, Delayed Develop.	Brainstem/Cerebellar Hypoplasia Macrocephaly Coloboma
Potocki–Lupski (17p11)[13] http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=610883	~90%	Unknown	Rare	Yes (mild)	=	Yes	Abnorm EEG	Yes	Hypotonia	Congenital Cardiovascular Abnormalities Scoliosis Hypercholesterolemia
Smith Lemli Optiz (*DHCR7*)[14] *http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=270400*	50%	Rare	1/20,000	Yes	=	Yes	Yes	Yes	Hypotonia (infancy) Opisthokinesis	Frontal Hypoplasia Aberrant Neuronal Migration Microcephaly Congenital Cardiovascular Abnormalities Cryptorchidism Hypercholesterolemia
Rett Syndrome (*MECP2*)[15] http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=312750	N/A	~0.5%	1/10,000 Females	Yes (severe)	<1	No	Yes	Yes (increases over time)	Ataxia Spasticity Apraxia Dystonia Characteristic Hand Wringing	Cortical atrophy Microcephaly Prolonged QT (Cardiovascular) Scoliosis
Timothy Syndrome *ACNA1C)*[16] *http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=601005*	60–80%	Unknown	Rare	Yes	=	Yes	Yes (~20%)	Yes	Yes	Long QT Interval (Cardiovascular) Lethal Arrhythmia Other Congenital Cardiovascular Abnormalities Syndactyly

Tuberous Sclerosis (*TSC /TSC2*) [17] *http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=191100*	20%	~1%	1/6,000	Yes	=	No	Yes	Variable	No	Hamartomas & Cortical Tubers in Brain Cafe-au-lait spots Cardiac rhythm disturbances (~35%)

† Available data suggests that the syndromes listed above individually account for no more than 1–2% of ASD cases. This is compared to unclassified cytogenetic lesions visible by G-banding (~ 6–7% of cases) and unclassified *de novo* CNV visible by molecular techniques (~ 2–10% of cases). Taken together it is likely that known syndromes, observable cytogenetics lesions, and rare *de novo* mutations account for between 10–20% of cases. Rates depend on the population evaluated (e.g. higher in individuals from simplex vs. multiplex families, and dysmorphic/mental retardation vs. "idiopathic" populations). It should also be noted that none of the studies cited here indicate that assessment for ASD was performed blind to a patient's primary diagnosis.

^ For M / F, '=' denotes syndromes in which ratio of affected males to females is equal to 1. '>1' and '<1' correspond to disorders with a male and female bias respectively. Subtle sex biases may become evidence in these disorders as larger cohorts are studied.

References:

1. Cook, E. H., Jr. *et al.* Autism or atypical autism in maternally but not paternally derived proximal 15q duplication. *Am J Hum Genet.* **60**, 928-934 (1997).
2. Weiss, L. A. *et al.* Association between Microdeletion and Microduplication at 16p11.2 and Autism. *N Engl J Med.* (2008).
3. Kumar, R. A. *et al.* Recurrent 16p11.2 microdeletions in autism. *Hum Mol Genet.* (2007).
4. Marshall, C. R. *et al.* Structural variation of chromosomes in autism spectrum disorder. *Am J Hum Genet.* **82**, 477-488 (2008).
5. Manning, M. A. *et al.* Terminal 22q deletion syndrome: a newly recognized cause of speech and language disability in the autism spectrum. *Pediatrics.* **114**, 451-457 (2004).
6. Durand, C. M. *et al.* Mutations in the gene encoding the synaptic scaffolding protein SHANK3 are associated with autism spectrum disorders. *Nat Genet.* **39**, 25-27 (2007).
7. Moessner, R. *et al.* Contribution of SHANK3 mutations to autism spectrum disorder. *Am J Hum Genet.* **81**, 1289-1297 (2007).
8. Matsuura, T. *et al.* De novo truncating mutations in E6-AP ubiquitin-protein ligase gene (UBE3A) in Angelman syndrome. *Nat Genet.* **15**, 74-77. (1997).
9. Peters, S. U., Beaudet, A. L., Madduri, N. & Bacino, C. A. Autism in Angelman syndrome: implications for autism research. *Clin Genet.* **66**, 530-536 (2004).
10. Strauss, K. A. *et al.* Recessive symptomatic focal epilepsy and mutant contactin-associated protein-like 2. *N Engl J Med.* **354**, 1370-1377 (2006).
11. Hatton, D. D. *et al.* Autistic behavior in children with fragile X syndrome: prevalence, stability, and the impact of FMRP. *Am J Med Genet A.* **140**, 1804-1813 (2006).
12. Ozonoff, S., Williams, B. J., Gale, S. & Miller, J. N. Autism and autistic behavior in Joubert syndrome. *J Child Neurol.* **14**, 636-641 (1999).
13. Potocki, L. *et al.* Characterization of Potocki-Lupski syndrome (dup(17)(p11.2p11.2)) and delineation of a dosage-sensitive critical interval that can convey an autism phenotype. *Am J Hum Genet.* **80**, 633-649 (2007).
14. Tierney, E. *et al.* Behavior phenotype in the RSH/Smith-Lemli-Opitz syndrome. *Am J Med Genet.* **98**, 191-200 (2001).
15. Amir, R. E. *et al.* Rett syndrome is caused by mutations in X-linked MECP2, encoding methyl-CpG-binding protein 2. *Nat Genet.* **23**, 185-188 (1999).
16. Splawski, I. *et al.* Ca(V)1.2 calcium channel dysfunction causes a multisystem disorder including arrhythmia and autism. *Cell.* **119**, 19-31 (2004).
17. Baker, P., Piven, J. & Sato, Y. Autism and tuberous sclerosis complex: prevalence and clinical features. *J Autism Dev Disord.* **28**, 279-285 (1998).