denovo-db version 1.6.1

http://denovo-db.gs.washington.edu/denovo-db/

August 19, 2018

1 Introduction

This is a release PDF for denovo-db version 1.6.1. This document summarizes in detail changes since denovo-db version 1.5. Please see our updated Data Usage and Release page at http://denovo-db.gs.washington.edu/den db/Usage.jsp. We invite you to email our mailing list at denovo-db@uw.edu with any comments or questions.

2 Updates to denovo-db

2.1 Small update from initial version 1.6 release

It has come to our attention that there were 98 variants included in the initial version of denovo-db 1.6 that were of low quality. We have removed these variants from the website and from the non-SSC VCF and text files. Since this is a small change we have labeled this release as version 1.6.1

2.2 Simons Simplex Collection samples

The denovo-db website has changed based on feedback we have received from the Simons Foundation. Please note that as of denovo-db v.1.6.1 the database now includes variants from the Simons Simplex Collection (SSC) with usage restrictions as follows: "The use of Simons Simplex Collection (SSC) and Simons VIP data sets is limited to projects related to advancing the field of autism and related developmental disorder research. Questions on SSC/VIP consents should be directed to collections@sfari.org." In addition, the download page now has available tab-separated text files split into SSC and non-SSC samples.

2.3 VCF files

We now provide VCF files on the download page. There is one for SSC and one for non-SSC samples. Sample data is included within the vcf in the json format.

2.4 Coding Variants Only Button

At the top of the page, we now have a button to display only coding variants and canonical splice sites in a gene. This can be very helpful to those only interested in "exomic" variants.

2.5 3D visualization

We have worked with the Karchin Lab at the Johns Hopkins University http://karchinlab.org/ to add links for each variant where data is available to visualize the variant on its 3D structure using their program muPIT http://hg19.cravat.us/MuPIT_Interactive/.

3 Description of studies

3.1 Studies by phenotype

In the following subsections we will describe the studies in denovo-db 1.6.1 in alphabetical order based on their primary phenotype.

3.1.1 Acromelic frontonasal dysostosis

Smith et al. 2014 is the only study in the database on acromelic frontonasal dysostosis. It contains data from four probands of which **three** were whole-exome sequenced.

3.1.2 Amyotrophic lateral sclerosis

There are three studies (Table 1) in denovo-db on amyotrophic lateral sclerosis (ALS). As far as we know, there are no overlaps between the three cohorts.

Table 1: Unique denominators for performing aggregate ALS analysis

Studies	Count
Steinberg2015	44
Chesi2015	47
vanDoormall2017	82
Total	173

3.1.3 Anophthalmia/Microphthalmia

There is only one study (Slavotinek2015) on anophthalmia/microphthalmia in denovo-db and it contains **25** probands.

3.1.4 Autism

There are a number of autism whole-exome, whole-genome, and targeted sequencing studies. Table 2 contains a list of all of these studies. The data come from different cohorts studied by many researchers. These include the Simons Simplex Collection (SSC), The Autism Simplex Collection (TASC), the Autism Sequencing Consortium (ASC), MSSNG, and the National Institute of Mental Health (NIMH) as well as clinical cohorts. For aggregate studies of the autism data it is important to know the sample overlaps and what to consider for analysis (Table 3).

First, we highly recommend that the targeted sequencing studies (ASD1_2, ASD3) be ignored except for individuals from the SSC (include .p1 in their name) who are present there because of their validation status. denovo-db picks variant representation in studies based on validation status so SSC variants were detected in exome but **validated** by targeted sequencing studies.

Second, the Michaelson et al. 2012 study is a set of 10 monozygotic twin pairs and for aggregate statistics only one set of the variants should be represented in analysis.

Third, although the overall denominator reported is 2,270 in de Rubeis et al. 2014 there were 825 SSC probands included so we report the difference of 1,445 in denovo-db since the SSC proband results represented in that study are present in other studies in the database.

Fourth, the Yuen2016 and Yuen2017 studies are both in the MSSNG dataset and therefore the denominator should be adjusted to Yuen2017's 1,625 total number. Also, the Yuen studies contain related affected children which should not matter for *de novo* variants except for the less common case of germline mosaicism.

In sum there are a total of 5,886 unique individuals (Table 3) with autism from exome and genome sequencing studies.

Table 2: Autism studies in denovo-db 1.6.1

Phenotype	Name	PMID	Probands	Controls	Type
autism	Iossifov	25363768	2508	1911	exome
	Krumm	25961944	2377	1786	exome
	ASD1_2	23160955	2446	0	targeted
	ASD3	25418537	3486	2493	targeted
	Turner2016	26749308	53	40	genome
	DeRubeis2014	25363760	2270	0	exome
	Michaelson2012	23260136	10	0	genome
	Lee2014	24501278	1	0	exome
	Tavassoli2014	24650168	1	0	exome
	Yuen2016	27525107	200	0	genome
	Yuen2017	28263302	1625	2	genome
	Hashimoto2015	26582266	30	0	exome
	Moreno-Ramos2015	26352270	4	0	exome
	Turner_2017	28965761	516	516	genome
	Takata_2018	29346770	262	0	exome
	Werling_2018	29700473	519	519	genome

Table 3: Unique exome/genome denominators for performing aggregate autism analysis

Cohort	Studies	Count
SSC	Iossifov, Krumm, Turner2016	2508
	ASD1_2/ASD3 (.p1 only), Turner_2017, Werling_2018	
ASC	DeRubeis2014	1445
MSSNG	Yuen2016, Yuen2017	1625
NIMH	Michaelson2012	10
Clinical	Lee2014	1
	Tavassoli2014	1
Other	Hashimoto2015	30
	Moreno-Ramos2015	4
	Takata_2018	262
Total		5886

3.1.5 Bipolar disorder

There is only one study on bipolar disorder (Kataoka2016) in denovo-db and it contains **79** probands.

3.1.6 Cantú syndrome

There is only one study (vanBon2012) on Cantú syndrome in denovo-db and it contains four probands with **one** that was exome sequenced.

3.1.7 Cerebral palsy

There is only one study (McMichael2015) on Cerebral palsy in denovo-db and it contains **98** probands.

3.1.8 Congenital diaphragmatic hernia

There is only one study (Yu2015) on congenital diaphragmatic hernia in denovo-db and it contains **39** probands.

3.1.9 Congenital heart disease

There are three studies (Lifton, Homsy2015, Sifrim2016) on congenital heart disease in denovo-db. There are overlaps between these studies. By removing all sample overlaps that we could identify, there were a total of **2,072** probands.

3.1.10 Controls

There are a few studies where there were either only controls sequenced or cases and controls. These studies are shown in Table 4. The data from these studies come from different cohorts studied by many researchers. These include the SSC, MSSNG, Genome of the Netherlands (GoNL), and others. For aggregate studies of the control data, it is important to know the overlaps and what to consider for analysis (Table 5).

We highly recommend that the targeted sequencing study (ASD3) be ignored except for individuals from the SSC (include .s1 in their name) who are present there because of their validation status.

As an additional note, Conrad2011 and Ramu2013 both study only one sample (NA12878).

In sum up there are a total of 2,278 unique control individuals (Table 5) from exome and genome sequencing studies.

Table 4: Controls in denovo-db 1.6.1

Phenotype	Name	PMID	Cases	Controls	Type
control	Iossifov	25363768	2508	1911	exome
	Krumm	25961944	2377	1786	exome
	ASD3	25418537	3486	2493	targeted
	Turner2016	26749308	53	40	genome
	Yuen2017	28263302	1625	2	genome
	GoNL	24974849	0	250	genome
	Besenbacher2014	25597990	0	10	genome
	Conrad2011	21666693	0	1	genome
	Ramu2013	23975140	0	1	genome
	Rauch2012	23020937	51	20	exome
	Gulsuner2013	23911319	105	84	genome
	Turner_2017	28965761	516	516	genome
	Werling_2018	29700473	519	519	genome

3.1.11 Developmental disorder

There is only one study on developmental disorder (DDD2017) in denovo-db and it contains **4,293** probands.

3.1.12 Early onset Alzheimer's disease

There is only one study (Rovelet-Lecrux2015) on early onset Alzheimer's disease in denovo-db and it contains **12** probands.

Table 5: Unique exome/genome denominators for performing aggregate control analysis

Cohort	Studies	Count
SSC	Iossifov, Krumm, Turner2016	1911
	ASD3 (.s1 only), Turner_2017, Werling_2018	
MSSNG	Yuen2017	2
Other	GoNL	250
	Besenbacher2014	10
	Conrad2011/Ramu2013	1
	Rauch2012	20
	Gulsuner2013	84
Total		2278

3.1.13 Early onset Parkinson's disease

There is only one study (KunRodrigues2015) on early onset Parkinson's disease in denovo-db and it contains **21** probands.

3.1.14 Epilepsy

There are five studies on epilepsy with a total of **532** probands. The studies are shown in Table 6.

Table 6: Unique denominators for performing aggregate epilepsy analysis

Studies	Count
epi4k2013	264
Veeramah2012	1
Barcia2012	3
Veeramah2013	10
Helbig2016	254
Total	532

3.1.15 Intellectual disability

There are four studies on intellectual disability with a total of **1,010** probands. The studies are shown in Table 7.

Table 7: Unique denominators for performing aggregate intellectual disability analysis

Studies	Count
deLigt2012	100
Rauch	51
Halvardson2016	39
Lelieveld2016	820
Total	1010

3.1.16 Mixed

There is only one study (Jonsson2017) with mixed phenotypes in denovo-db and it contains **1548** probands.

3.1.17 Neural tube defects

There is only one study (Lemay2015) on neural tube defects in denovo-db and it contains **43** probands.

3.1.18 Schizophrenia

There are five studies on schizophrenia with a total of **800** probands. The studies are shown in Table 8.

Table 8: Unique denominators for performing aggregate schizophrenia analysis

Studies	Count
Gulsuner2013	105
McCarthy2014	57
Fromer2014	623
Smedemark-Margulies2016	1
Kranz2015	14
Total	800

3.1.19 Sporadic infantile spasm syndrome

There is only one study (Dimassi2015) on sporadic infantile spasm syndrome in denovo-db and it contains **10** probands.

3.1.20 Tourette disorder

There are two studies (Table 9) in denovo-db on Tourette disorder. As far as we know, there are no overlaps between the two cohorts.

Table 9: Unique denominators for performing aggregate Tourette disorder analysis

Studies	Count
Eriguchi2017	10
Willsey2017	511
Total	521

3.2 Studies considered for denovo-db but not included in version 1.6.1

3.2.1 Jin et al. 2017, PMID: 28991257

We had hoped to add the Jin et al. 2017 study to the database, which studied the exomes of 2,645 parent-offspring trios with congenital heart disease. Unfortunately, we were not able to disentangle the sample overlaps between this paper and the other congenital heart disorder papers in the database so did not include it.

4 Appendix

In the appendix we describe the location of the data in the original papers.

4.0.1 ASD1_2, PMID:23160955

The data from this paper comes from Tables S11 and S14.

4.0.2 ASD3, PMID:25418537

The data from this paper comes from Supplementary Data 1 and 2.

4.0.3 Barcia2012, PMID:23086397

The data from this paper comes from Supplementary Table 2 and the number of trios exome sequenced (n = 3) is described in the main text.

4.0.4 Besenbacher2014, PMID:25597990

The data from this paper comes from Supplementary Data 3. The count of n = 10 trios is from the abstract.

4.0.5 Chesi2015, PMID:23708140

The data from this study comes from Table 1 and the trio count of n = 47 is from the abstract.

4.0.6 Conrad2011, PMID:21666693

The data from this study comes from Table S1 and only the sites that were marked as germline *de novo* in sample NA12878 were retained for denovo-db. Since the coordinates were on hg18, we lifted them over to hg19.

4.0.7 DDD_2017, PMID:28135719

The data from this paper comes from Supplementary Table 1 and the count of families (n = 4,293) comes from the abstract. We also noticed that some individuals have very high numbers of variants (up to 36 in the exome). This may be a consideration for aggregate statistical analysis.

4.0.8 deLigt2012, PMID:23033978

The data from this paper comes from Table S3 and the number of trios (n = 100) comes from the abstract.

4.0.9 DeRubeis2014, PMID:25363760

The data from this paper comes from Supplementary Table 3. The proband count for trios (n = 2,270) comes from the main text and the removal of the 825 SSC trios for denominator counts is based on Supplementary Table 1. This results in 1,445 individuals.

4.0.10 Dimassi2015, PMID:26138355

The data from this paper comes from Table 1 and the count of n = 10 is from the abstract.

4.0.11 epi4k2013, PMID:23934111

The data from this paper comes from Supplementary Table 2 with sample names from Supplementary Table 1. The count of n = 264 comes from the abstract.

4.0.12 Eriguchi2017, PMID:28608572

The data from this paper comes from Table 3 and the number of n = 10 comes from the abstract.

4.0.13 Fromer2014, PMID:24463507

The data from this paper comes from Supplementary Table 1. The number of n = 623 trios comes from that supplementary table legend.

4.0.14 GoNL, PMID:24974849

The data from this paper was downloaded from the website that was in the URLs section of the paper: http://www.nlgenome.nl/ The file at this website was named GoNL_DNMs.txt The number of n = 250 trios comes from the abstract.

4.0.15 Gulsuner2013, PMID:23911319

The data from this paper comes from Table S3. The number n = 105 comes from the results section. The number n = 84 comes from the main text.

4.0.16 Halvardson2016, PMID:27334371

The data from this paper comes from Supplementary Table 2. The number of n = 39 trios comes from the abstract.

4.0.17 Hashimoto2015, PMID:26582266

The data from this paper comes from Table 1. The number of n = 30 trios comes from the abstract.

4.0.18 Helbig2016, PMID:26795593

The data from this paper comes from Tables S3 and S7. The number n = 254 comes from the "Exome sequencing strategy" section of the paper.

4.0.19 Homsy2015, PMID:26785492

The data from this paper comes from Supplementary Database S2. The number n = 1,213 trios comes from the main text.

4.0.20 Iossifov, PMID:25363768

The data from this paper comes from Supplementary Table 2. The numbers 2,508 and 1,911 come from the main text.

4.0.21 Jonsson2017, PMID:28959963

The data from this paper comes from Supplementary Table 4 and the number of n = 1548 comes from the abstract. After emailing the authors it is best to label this set as mixed phenotypes since some are "controls" and some are not. Please note the original de novo variant file was on build 38 and we used liftover to get the coordinates on hg19.

4.0.22 Kataoka2016, PMID:27217147

The data from this paper comes from Table S2. The number n = 79 comes from the abstract.

4.0.23 Kranz2015, PMID:26091878

The data from this paper comes from Table 1. The number n = 14 comes from the abstract.

4.0.24 Krumm, PMID:25961944

The data from this paper comes from Supplementary Table 1. The number n = 2,377 comes from the abstract and the number 1,786 comes from the methods section.

4.0.25 Kun-Rodrigues, PMID:26362251

The data from this paper comes from Table 1. The number n = 21 comes from the abstract.

4.0.26 Lee2014, PMID:24501278

The data from this paper comes from Table 1. We only retained one of the monozygotic twin pairs for the database.

4.0.27 Lelieveld2016, PMID:27479843

The data from this paper comes from corrected Supplementary Table 2. The number n = 820 comes from the main text.

4.0.28 Lemay2015, PMID:25805808

The data from this paper comes from Table 1. The number n = 43 comes from the abstract.

4.0.29 Lifton, PMID:23665959

The data from this paper comes from Table S4. The number n = 362 comes from the abstract.

4.0.30 McCarthy2014, PMID:24776741

The data from this paper comes from Supplementary Table 3. The number n = 57 comes from the abstract.

4.0.31 McMichael2015, PMID:25666757

The data from this paper comes from Supplementary Table C and the number of n = 98 comes from the abstract.

4.0.32 Michaelson2012, PMID:23260136

The data from this paper comes from Table S1 and was lifted over to hg19. The number of 10 monozygotic twin pairs comes from Figure S1. Since variants from the Michaelson paper come from a set of 10 monozygotic twin pairs, only one set of each pair should be considered if doing large aggregate *de novo* statistics.

4.0.33 Moreno-Ramos2015, PMID:26352270

The data from this study comes from Table 1.

4.0.34 Ramu2013, PMID:23975140

The data from this study comes from Supplementary Table 9. The number n = 1 comes from the main text.

4.0.35 Rauch2012, PMID:23020937

The data from this study comes from Supplementary Tables S2, S3, S6, S7, and S8. The number n = 51 and n = 20 comes from the supplement under the "Study patients" section.

4.0.36 Rovelet-Lecrux_2015, PMID:26194182

The data from this paper comes from Table 2. The number n = 12 is from the abstract.

4.0.37 Sifrim2016, PMID:27479907

The data from this paper comes from Supplementary Tables 21, 22, and 23. The Sifrim et al. 2016 study on congenital heart disorders had overlap with other studies in denovo-db. In particular, it overlapped with the DDD 2017 and Lifton studies. We removed all samples from the Sifrim paper with a DDD in the name or a CG in the name that corresponded to these two studies. Supplementary Table 2 in Sifrim paper has the information for trios and based on that table there are 859 total trios in the Sifrim 2016 set (minus DDD and Lifton).

4.0.38 Slavotinek2015, PMID:25457163

The data from this paper were derived directly from the main text.

4.0.39 Smedemark-Margulies2016, PMID:27626066

The data from this paper comes from the main text under the "Genomic Analyses" section.

4.0.40 Smith2014, PMID:25105228

The data from this paper comes from the main text.

4.0.41 Steinberg2015, PMID:25773295

The data from this paper comes from Table 3.

4.0.42 Takata_2018, PMID:29346770

The data from this paper comes from Table S1 and the number of n = 262 comes from the Experimental Procedures "Study Subjects" section.

4.0.43 Tavassoli2014, PMID:24650168

The data from this paper comes from the main text.

4.0.44 Turner2016, PMID:26749308

The data from this paper comes from Table S9. The number n = 53 comes from the abstract and the number n = 40 comes from the main text.

4.0.45 Turner_2017, PMID:28965761

The data comes from SFARI base deposition at https://base.sfari.org/ (SFARI_SSC_WGS_1, SFARI_SSC_WGS_1a). Data provided through the Simons Foundation (please see Usage page) and the number n = 516 comes from the abstract.

4.0.46 VanBon, PMID:22608503

The data from this paper comes from Table S3.

4.0.47 vanDoormall2017, PMID:28714244

The data from this paper comes from Table 1 and the number n = 82 comes from the abstract.

4.0.48 Veeramah2012, PMID:22365152

The data from this paper comes from the main text.

4.0.49 Veeramah2013, PMID:23647072

The data from this paper comes from Table 2.

4.0.50 Werling_2018, PMID:29700473

The data from this paper for DNMs comes from Supplementary Table 5 and for validations from Supplementary Table 3. The number n = 519 comes from the abstract.

4.0.51 Willsey2017, PMID:28472652

The data from this paper comes from Supplementary Table 5 and the validations from Table S2. The number n = 511 comes from the Summary section.

4.0.52 Yu2015, PMID:26034137

The data from this paper comes from Table 1.

4.0.53 Yuen2016, PMID:27525107

The data from this paper comes from Supplementary Tables S4 and S5. The number n = 200 comes from the abstract.

4.0.54 Yuen2017, PMID:28263302

The data from this paper comes from Supplementary Tables S3, S4, and S5. The total number n = 1,627 comes from the main text. Note, there are two unaffected individuals with *de novo* variants based on Table S1.

5 References

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