Supplementary Information for

Identification of NCAN as a candidate gene for developmental dyslexia

Authors

Elisabet Einarsdottir, Myriam Peyrard-Janvid, Fahimeh Darki, Jetro J. Tuulari, Harri Merisaari, Linnea Karlsson, Noora M. Scheinin, Jani Saunavaara, Riitta Parkkola, Katri Kantojärvi, Antti-Jussi Ämmälä, Nancy Yiu-Lin Yu, Hans Matsson, Jaana Nopola-Hemmi, Hasse Karlsson, Tiina Paunio, Torkel Klingberg, Eira Leinonen, Juha Kere

Supplementary methods

Supplementary table 1 – List of FANTOM5 human tissues used in

correlation analysis. The brain-tissues and non-tissues together make up the "all tissues" set.

Supplementary table 2 - Spearman correlation (R) between the expression of known DD susceptibility genes and *NCAN*, as assessed from the FANTOM5 dataset. Values range from -1 (negative correlation) to 1 (positive correlation). The correlations in all tissues (A), brain tissues (B) and non-brain tissues (C) are shown. Correlations over 0.5 are highlighted in yellow, strong positive correlations (>0.8) are highlighted in orange.

Supplementary table 3 - Regions of white matter significantly associated with genetic variation in several known DD susceptibility genes and *NCAN* (Brainchild dataset).

Supplementary table 4 – Regions of white matter significantly associated with genetic variation in several known DD susceptibility genes and *NCAN* (Brainchild dataset) using a p 0.01 threshold.

Supplementary table 5 - Regions of grey matter and their association with genetic variation in *NCAN* (FinnBrain dataset).

Supplementary table 6 - MNI coordinates for the associations of *NCAN* variants to infant grey matter volumes. (FinnBrain dataset).

Supplementary figure 1 - All NPL graphs per chromosome

Non-parametric linkage (NPL) scores for each autosomal chromosome (1-22). The x-axis indicates the position along the chromosome in cM; the y-axis indicates NPL score (LOD). The K&C lin (linear) and exp (exponential) models of weighing are shown (black and blue lines, respectively).

Supplementary dataset 1 - All NPL values per chromosome

Non-parametric linkage scores (LOD) and the associated p-value for the linear and the exponential models of weighing, for each of the chromosomes 1-22. This data is presented graphically in Supplementary figure 1.

Supplementary dataset 2 - All stop/non-synonymous and rare genetic variants within the ten linkage regions of interest, as determined by exome sequencing of individual 3935.

Supplementary dataset 3- All stop/non-synonymous and rare genetic variants within the ten linkage regions of interest, as determined by exome sequence data obtained from individual 3821.

Supplementary Methods for

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Genotyping and linkage analysis:

Genotyping

Two µg of genomic DNA was used by the SNP&SEQ Technology Platform in Uppsala, Sweden for genotyping on Illumina HumanCoreExome12v1-0 genotyping arrays. This array contains assays for 243 345 variants. The genotyping was performed using the Illumina Infinium assay and the results were analyzed using the software GenomeStudio 2011.1 from Illumina (San Diego, US). Genotyping was performed based on cluster files generated from a set of 800 samples genotyped in other projects. Genome build 37 was used as reference. One CEPH control sample with known genotypes (from HapMap) was included in the genotyping. All data storage and the majority of subsequent analyses were performed through the BC|GENE system from BCPlatforms (www.bcplatforms.com, Espoo, Finland).

Quality control

Quality control of the data included removing all individuals with <99% call rate from the analysis, all markers with <95% call rate and any marker with any number of CEPH/HapMap inconsistencies. Subsequently, markers with a minor allele frequency of <5% in the dataset were removed from the analysis. Pedcheck ¹ was run to identify inconsistencies in inheritance, identifying low quality genotypes as well as highlighting possible sample mix-ups or incorrectly defined family relationships. All markers showing any inheritance error in any sample were removed from the analysis. Unlikely genotypes were identified using the -- error option in Merlin v1.1.2 (www.csg.sph.umich.edu/abecasis/Merlin) ². Any such unlikely genotypes were also removed.

Linkage analysis

We pruned the genotype dataset to avoid inflation of linkage. PLINK v.1.07 ³, (www.pngu.mgh.harvard.edu/~purcell/plink) was used to allow no markers within a 50-marker sliding window to have an r² of more than 0.2. This reduced set of 28 085 markers was used for subsequent linkage analysis. The information content of the linkage analysis, using the pruned-in set of variants, was on average >95% (as assessed by the --information function of Merlin). The Rutgers genetic map v.3 (www.compgen.rutgers.edu/download_maps.shtml) ⁴ was used for the linkage analyses and any marker not found on this map was excluded from subsequent linkage analyses. The output of the analysis is presented as K&C LOD scores ⁵, hereafter called NPL, and accompanying p-values.

Library preparation, alignment and variant calling for next generation Exome sequencing:

One hundred ng of genomic DNA from one affected individual was used for exome sequencing at the Uppsala Genome Center (Science for Life Laboratory, Uppsala University, Uppsala, Sweden). An AmpliSeq library was prepared and run on an Ion Proton (Life Technologies, Carlsbad, CA, US) instrument, according to standard protocols. The sequencing was performed on P1 chips, producing 200 bp reads.

Sequences were aligned to the hg19 genome assembly using the Ion Proton pipeline and single nucleotide variants (SNVs) were called using the Torrent Suite Software (Life Technologies). The total number of mapped reads was 52 784 338; 89.94% of these were on target. 91.94% of the bases were on target. The average coverage of the exons in 3935 was 135x. Target base coverage at 1x: 98.86%. Target base coverage at 20x: 93.45%. Exome variants were annotated using ANNOVAR 17, accessed through wANNOVAR at www.wannovar.usc.edu.

Whole-genome sequencing:

A TruSeq DNA library (350 bp insert PCR-free DNA) was prepared, followed by

sequencing on an Illumina HiSeqX machine in High Output mode, with PE 2x100bp fragments and average genomic sequencing depth of 30x.

The WSG sample was analysed simultaneously with four other, idependent samples, run through the SciLife in-house Piper pipeline (BWA+GATK 3.5), available on Github

(https://github.com/NationalGenomicsInfrastructure/piper). The total number of sequence reads was 1 187 654 947, of which 99.71% were successfully aligned to the human hg19 genome reference. The median insert size was 372bp, and the average autosomal coverage was 38x. 83.41% of the reference had 30x or higher coverage. Variant calling was performed using the current GATK bestpractice guidelines ⁶ (with VQSR run on each single sample) and the list of variants was annotated using ANNOVAR.

Sanger sequencing

Sanger sequencing was used to validate the existence of the *NCAN* rs146011974 variant and assess its co-segregation with DD in the pedigree. Ten ng of DNA was amplified by PCR and sequenced by Eurofins Genomics (www.eurofinsgenomics.eu) according to standard protocols. Primers were designed using Primer3 (<u>www.bioinfo.ut.ee/primer3</u>), sequences are available upon request.

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Supplementary table 1 - FANTOM5 tissues

Brain-tissues amygdala_,_adult,_donor10196 amygdala,_adult,_donor10252 brain,_adult,_donor1 brain,_adult,_pool1 caudate_nucleus_,_adult,_donor10196 caudate_nucleus,_adult,_donor10252 cerebellum,_adult,_donor10252 cerebellum,_adult,_pool1 cerebral_meninges,_adult corpus callosum, adult, pool1 dura_mater,_adult,_donor1 frontal_lobe,_adult,_pool1 globus_pallidus_,_adult,_donor10196 globus_pallidus,_adult,_donor10252 hippocampus_,_adult,_donor10196 hippocampus,_adult,_donor10252 insula,_adult,_pool1 locus_coeruleus_,_adult,_donor10196 locus_coeruleus,_adult,_donor10252 medial_frontal_gyrus_,_adult,_donor10196 medial_temporal_gyrus_,_adult,_donor10196 medial_temporal_gyrus,_adult,_donor10252 medulla_oblongata_,_adult,_donor10196 medulla_oblongata,_adult,_donor10252 medulla_oblongata,_adult,_pool1 middle_temporal_gyrus,_donor10252 nucleus_accumbens,_adult,_pool1 occipital_cortex,_adult,_donor10252 occipital_lobe,_adult,_donor1 occipital_lobe,_fetal,_donor1 occipital pole, adult, pool1 paracentral_gyrus,_adult,_pool1 parietal_lobe_,_adult,_donor10196 parietal_lobe,_adult,_donor10252 parietal_lobe,_adult,_pool1 parietal_lobe,_fetal,_donor1 pineal_gland_,_adult,_donor10196 pineal_gland,_adult,_donor10252 pituitary_gland_,_adult,_donor10196 pituitary_gland,_adult,_donor10252 pons,_adult,_pool1 postcentral_gyrus,_adult,_pool1 putamen,_adult,_donor10196 substantia_nigra,_adult,_donor10252 temporal_lobe,_adult,_pool1 temporal_lobe,_fetal,_donor1 temporal lobe, fetal, donor1 rep2 thalamus_,_adult,_donor10196 thalamus,_adult,_donor10252

Non-brain tissues adipose_tissue,_adult,_pool1 aorta,_adult,_pool1 appendix,_adult bladder,_adult,_pool1 bone_marrow,_adult breast,_adult,_donor1 cerebrospinal_fluid,_donor2 cervix,_adult,_pool1 colon,_adult,_donor1 colon, adult, pool1 colon, fetal, donor1 cruciate_ligament,_donor2 diaphragm,_fetal,_donor1 diencephalon,_adult ductus deferens, adult duodenum, fetal, donor1 rep2 epididymis,_adult esophagus,_adult,_pool1 eye,_fetal,_donor1 Fingernail_, including_nail_plate, _eponychium_and_hyponychium, _donor2 gall bladder, adult heart_,_mitral_valve,_adult heart_,_pulmonic_valve,_adult heart_,_tricuspid_valve,_adult heart,_adult,_diseased_post,infarction,_donor1 heart,_adult,_diseased,_donor1 heart,_adult,_pool1 heart,_fetal,_pool1 kidney,_adult,_pool1 kidney,_fetal,_pool1 left atrium. adult. donor1 left ventricle, adult, donor1 liver,_adult,_pool1 lung,_adult,_pool1 lung,_fetal,_donor1 lung,_right_lower_lobe,_adult,_donor1 lymph node, adult, donor1 olfactory_region,_adult ovary,_adult,_pool1 pancreas,_adult,_donor1 parotid_gland,_adult penis, adult placenta,_adult,_pool1 prostate,_adult,_pool1 rectum,_fetal,_donor1 retina,_adult,_pool1 salivary gland, adult, pool1 seminal_vesicle,_adult skeletal_muscle_,_soleus_muscle,_donor1 skeletal_muscle,_adult,_pool1 skin,_fetal,_donor1 small intestine, adult, pool1 small_intestine,_fetal,_donor1 smooth_muscle,_adult,_pool1 spinal_cord_,_adult,_donor10196 spinal_cord,_adult,_donor10252 spinal cord, fetal, donor1 spleen,_adult,_pool1 spleen,_fetal,_pool1 stomach,_fetal,_donor1 submaxillary_gland,_adult testis,_adult,_pool1 testis,_adult,_pool2 throat,_adult throat,_fetal,_donor1 thymus,_adult,_pool1 thymus, fetal, pool1 thyroid,_adult,_pool1 thyroid,_fetal,_donor1 tongue,_adult tongue,_fetal,_donor1 tonsil,_adult,_pool1 trachea,_adult,_pool1 trachea,_fetal,_donor1 uterus,_adult,_pool1 uterus,_fetal,_donor1 vagina,_adult vein, adult

Supplementary table S2 - Spearman correlations of a set of representative DD genes

A - ALL TISSUES

	GCFC2	MRPL19	FOXP2	NCAN	KIAA0319	CYP19A1	KIAA0319L	DCDC2	PCNT	ROBO1	CTNND2	CNTNAP2	CEP63	DYX1C1	GRIN2B
GCFC2	1	0,070	0,041	-0,201	-0,217	-0,026	-0,110	0,218	0,075	0,118	-0,212	-0,134	0,207	0,075	-0,215
MRPL19	0,070	1	-0,221	0,430	0,354	-0,203	0,265	-0,247	0,187	0,203	0,471	0,503	0,294	0,237	0,435
FOXP2	0,041	-0,221	1	-0,183	-0,103	-0,099	-0,231	0,197	-0,072	-0,006	-0,320	-0,227	-0,247	-0,007	-0,088
NCAN	-0,201	0,430	-0,183	1	0,824	-0,282	0,343	-0,188	0,254	0,486	0,806	0,837	0,205	0,467	0,872
KIAA0319	-0,217	0,354	-0,103	0,824	1	-0,391	0,338	-0,030	0,264	0,411	0,793	0,754	0,280	0,577	0,813
CYP19A1	-0,026	-0,203	-0,099	-0,282	-0,391	1	-0,088	0,002	-0,272	-0,149	-0,290	-0,309	-0,188	-0,277	-0,263
KIAA0319L	-0,110	0,265	-0,231	0,343	0,338	-0,088	1	0,111	0,073	-0,031	0,361	0,311	-0,124	0,179	0,407
DCDC2	0,218	-0,247	0,197	-0,188	-0,030	0,002	0,111	1	-0,361	-0,093	-0,174	-0,186	-0,283	0,294	-0,247
PCNT	0,075	0,187	-0,072	0,254	0,264	-0,272	0,073	-0,361	1	0,264	0,272	0,219	0,366	0,159	0,321
ROBO1	0,118	0,203	-0,006	0,486	0,411	-0,149	-0,031	-0,093	0,264	1	0,417	0,467	0,153	0,362	0,449
CTNND2	-0,212	0,471	-0,320	0,806	0,793	-0,290	0,361	-0,174	0,272	0,417	1	0,784	0,271	0,473	0,716
CNTNAP2	-0,134	0,503	-0,227	0,837	0,754	-0,309	0,311	-0,186	0,219	0,467	0,784	1	0,272	0,476	0,717
CEP63	0,207	0,294	-0,247	0,205	0,280	-0,188	-0,124	-0,283	0,366	0,153	0,271	0,272	1	0,369	0,244
DYX1C1	0,075	0,237	-0,007	0,467	0,577	-0,277	0,179	0,294	0,159	0,362	0,473	0,476	0,369	1	0,406
GRIN2B	-0,215	0,435	-0,088	0,872	0,813	-0,263	0,407	-0,247	0,321	0,449	0,716	0,717	0,244	0,406	1

B-BRAIN TISSUES

	GCFC2	MRPL19	FOXP2	NCAN	KIAA0319	CYP19A1	KIAA0319L	DCDC2	PCNT	ROBO1	CTNND2	CNTNAP2	CEP63	DYX1C1	GRIN2B
GCFC2	1	0,194	-0,030	-0,233	-0,110	-0,192	-0,328	0,166	0,239	0,156	0,028	-0,093	0,318	0,203	-0,209
MRPL19	0,194	1	-0,234	-0,150	-0,156	0,086	-0,011	-0,081	0,073	0,013	0,326	0,279	0,246	-0,033	-0,102
FOXP2	-0,030	-0,234	1	0,489	0,403	0,162	-0,001	0,011	0,278	0,320	0,085	0,083	-0,229	0,171	0,599
NCAN	-0,233	-0,150	0,489	1	0,746	0,140	0,244	0,089	0,077	0,215	0,036	0,141	-0,369	0,023	0,836
KIAA0319	-0,110	-0,156	0,403	0,746	1	-0,089	0,077	0,054	0,119	0,094	-0,107	0,089	-0,055	0,078	0,784
CYP19A1	-0,192	0,086	0,162	0,140	-0,089	1	0,484	0,084	-0,227	-0,021	-0,067	0,162	-0,586	-0,324	0,045
KIAA0319L	-0,328	-0,011	-0,001	0,244	0,077	0,484	1	-0,055	0,056	-0,092	-0,124	0,183	-0,449	-0,219	0,162
DCDC2	0,166	-0,081	0,011	0,089	0,054	0,084	-0,055	1	-0,060	0,126	-0,097	-0,087	-0,187	0,241	-0,070
PCNT	0,239	0,073	0,278	0,077	0,119	-0,227	0,056	-0,060	1	0,417	0,285	0,008	0,213	0,356	0,147
ROBO1	0,156	0,013	0,320	0,215	0,094	-0,021	-0,092	0,126	0,417	1	0,196	-0,141	-0,128	0,314	0,275
CTNND2	0,028	0,326	0,085	0,036	-0,107	-0,067	-0,124	-0,097	0,285	0,196	1	0,231	-0,087	-0,106	0,077
CNTNAP2	-0,093	0,279	0,083	0,141	0,089	0,162	0,183	-0,087	0,008	-0,141	0,231	1	0,017	-0,026	0,105
CEP63	0,318	0,246	-0,229	-0,369	-0,055	-0,586	-0,449	-0,187	0,213	-0,128	-0,087	0,017	1	0,408	-0,193
DYX1C1	0,203	-0,033	0,171	0,023	0,078	-0,324	-0,219	0,241	0,356	0,314	-0,106	-0,026	0,408	1	0,127
GRIN2B	-0,209	-0,102	0,599	0,836	0,784	0,045	0,162	-0,070	0,147	0,275	0,077	0,105	-0,193	0,127	1

C-NON-BRAIN TISSUES

	GCFC2	MRPL19	FOXP2	NCAN	KIAA0319	CYP19A1	KIAA0319L	DCDC2	PCNT	ROBO1	CTNND2	CNTNAP2	CEP63	DYX1C1	GRIN2B
GCFC2	1	0,226	0,002	0,088	-0,121	-0,056	0,044	0,174	0,131	0,223	-0,123	0,135	0,311	0,170	0,028
MRPL19	0,226	1	-0,016	0,070	-0,148	-0,059	0,083	-0,176	-0,027	0,012	-0,022	0,121	0,082	-0,003	0,255
FOXP2	0,002	-0,016	1	-0,145	0,182	-0,280	-0,132	0,172	-0,053	0,004	-0,201	0,014	-0,128	0,141	-0,066
NCAN	0,088	0,070	-0,145	1	0,398	-0,122	0,016	0,041	0,020	0,417	0,544	0,651	-0,083	0,312	0,440
KIAA0319	-0,121	-0,148	0,182	0,398	1	-0,271	0,071	0,284	-0,047	0,181	0,535	0,394	-0,032	0,476	0,325
CYP19A1	-0,056	-0,059	-0,280	-0,122	-0,271	1	-0,148	-0,102	-0,198	-0,057	-0,080	-0,213	0,127	-0,128	-0,181
KIAA0319L	0,044	0,083	-0,132	0,016	0,071	-0,148	1	0,333	-0,113	-0,335	0,196	-0,045	-0,250	0,065	0,185
DCDC2	0,174	-0,176	0,172	0,041	0,284	-0,102	0,333	1	-0,428	-0,057	0,091	0,050	-0,232	0,541	-0 <i>,</i> 087
PCNT	0,131	-0,027	-0,053	0,020	-0,047	-0,198	-0,113	-0,428	1	0,059	0,008	-0,060	0,306	-0,129	0,088
ROBO1	0,223	0,012	0,004	0,417	0,181	-0,057	-0,335	-0,057	0,059	1	0,181	0,482	0,071	0,280	0,194
CTNND2	-0,123	-0,022	-0,201	0,544	0,535	-0,080	0,196	0,091	0,008	0,181	1	0,352	-0,131	0,303	0,321
CNTNAP2	0,135	0,121	0,014	0,651	0,394	-0,213	-0,045	0,050	-0,060	0,482	0,352	1	-0,138	0,295	0,322
CEP63	0,311	0,082	-0,128	-0,083	-0,032	0,127	-0,250	-0,232	0,306	0,071	-0,131	-0,138	1	0,103	0,056
DYX1C1	0,170	-0,003	0,141	0,312	0,476	-0,128	0,065	0,541	-0,129	0,280	0,303	0,295	0,103	1	0,210
GRIN2B	0,028	0,255	-0,066	0,440	0,325	-0,181	0,185	-0,087	0,088	0,194	0,321	0,322	0,056	0,210	1

Supplementary table S3. White matter density correlates with variation in dyslexia genes

Variant	Gene	Cluster p-value	Pe	eak coordina	ites	Genotypes*	Brain region
rs3743204	DYXICI	1.28×10^{-10}	-16	-54	18	GG>GT/TT	bilateral temproparietal
rs793842	DCDC2	8.19×10^{-5}	-28	-70	33	CC>CT>TT	left temporoparietal
rs6935076	KIAA0319	3.33×10^{-10}	-34	-58	31	CC>CT>TT	bilateral temproparietal
rs917235	MRPL19	1.27×10^{-3}	-13	-8	8	AA>GG	bilateral temproparietal
rs2561622	CTNND2	1.28×10^{-5}	-47	25	22	GG>AG>AA	left frontal
rs7519451	CEP63	7.60×10-3	28	-55	29	AA/AC>CC	right temporoparietal
ra1064205	NCAN	1.56×10 ⁻⁶	44	-36	13	TC>CC	right temporoparietal and frontal
181004393	INCAIN	4.48×10^{-10}	-39	20	20	TC>CC	left temporoparietal, frontal and occipital

 $\ensuremath{^*}$ Genotype groups ordered according to the highest white matter density in each specific cluster

Supplementary table S4

Associations to white mattter volume p < 0.01

Brain region	Coordina	ates in SPM M	NI space	Cluster size	peak	clus	ster
	х	У	z		Т	p(FWE-corr)	p(FDR-corr)
right temporoparietal and frontal	44	-36	13	7878	6,51	1.56×10^{-6}	1.04×10^{-6}
left temporoparietal, frontal and occip	-39	20	20	14355	5,13	4.48×10^{-10}	5.96×10 ⁻¹⁰

Associations to white mattter volume p < 0.001

Brain region	Coordina	ates in SPM M	NI space	Cluster size	peak	clus	ster
	х	У	Z		Т	p(FWE-corr)	p(FDR-corr)
right temporoparietal and frontal	44	-36	13	3549	6,51	8.13×10 ⁻⁸	2.88×10^{-7}
left temporoparietal, frontal and occip	-39	20	20	3312	5,13	1.82×10^{-7}	3.23×10^{-7}

Associations to white mattter volume p < 0.05 (FDR)

Brain region	Coordinates in SPM MNI space			Cluster size	peak	clus	ster
	x	У	z		Т	p(FWE-corr)	p(FDR-corr)
right temporoparietal and frontal	44	-36	13	361	6,51	9.6×10-6	1.8×10^{-3}
left temporoparietal, frontal and occip	-39	20	20	75	5,13	2.5×10^{-3}	0,04

Supplementary table 5. Linear regression analysis of rs1064395 (*NCAN*) to grey matter volumes in newfant brain.

A	Rs1064395*	
Grey matter volume	β	Р
Total	.347	.175
Brain regions:		
Frontal	.424	.115
Cingulate	.516	.049
Limbic	.365	.183
Occipital	.226	.393
Parietal	.414	.077
Temporal	.196	.406

* MAF=.12; for genotypes Maj/Maj n=20, Maj/Min n=6

В	Rs1064395	
Parietal lobe	β	Ρ
Postcentral gyrus	.515	.045
Superior parietal gyrus	126	.614
Inferior parietal lobule	.501	.042
Supramarginal gyrus	.657	.005
Angular gyrus	085	.718
Precuneus	.463	.066
Paracentral lobule	.148	.571
С	Rs1064395	

Cingulate	β	Р	
Anterior cingulate gyrus	.419	.121	
Middle cingulate gyrus	.547	.031	
Posterior cingulate gyrus	.180	.517	

Supplementary table S6

A. Associations to infant grey matter volume p < 0.001, FDR corrected

Brain region (iBEAT AAL label)	Coordina	ates in SPM N	1NI space	Cluster size	peak	cluster	
	х	У	Z		Т	p(FDR-corr)	
Left inferior parietal lobule (61)	-30	-6	14	484	4.72	0.001	
Right precentral gyrus (2)	28	10	12	411	4.40	0.001	
Right middle frontal gyrus (8)	30	26	10	192	3.99	0.011	

B. Associations to infant grey matter volume p < 0.01, FDR corrected

Brain region (iBEAT AAL label)	Coordina	ates in SPM N	INI space	Cluster size	peak	cluster	
	х	У	z		Т	p(FDR-corr)	
Left inferior parietal lobule (61)	-30	-6	14	1681	4.72	0.000	
Right precentral gyrus (2)	28	10	12	3387	4.40	0.000	
Right middle frontal gyrus (8)	30	26	10		3.99		
Right postcentral gyrus (58)	34	4	16		3.17		
Right middle cingulate gyrus (34)	4	14	6	1806	3.46	0.000	
Left middle cingulate gyrus (33)	-4	20	8		2.97		











































