Copy number variations conferring risk of psychiatric disorders in children

Reporting

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PSYCHCNVS

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Final Report Summary - PSYCHCNVS (Copy number variations conferring risk of psychiatric disorders in children)

Project context and objectives:

PSYCHCNVS goals were to generate knowledge on genetic variants conferring risk of psychiatric disorders in children and adolescents with focus is on autism spectrum disorder (ADS) and psychosis (schizophrenia and bipolar disorder). During the first reporting period, key instruments for diagnosing were translated into languages necessary for the project, specifically the ADI-R interview in Russian, Ukrainian, Georgian, FYROM and Serbian, the Kiddie SADS-PL in Georgian and FYROM and psychiatrists trained

in using the instruments by psychiatrist at KCL. During the first reporting period, most of the subjects needed for the genome wide association scan (GWAS) were recruited. During this second reporting period, samples from all partners were genotyped using IlluminaHumanHap 610 microarrays. Partners were trained in analysing array data, both SNPs and CNVs, by deCODE geneticist's. Variants were called and tested for association with autism, schizophrenia and psychosis. Samples from the different populations were analysed individually and jointly (meta-analysis). The collaboration has already led to findings shining new light on the aetiology of psychotic disorders.

First, we estimated the rate of de novo mutations in Icelandic parent offspring trios (schizophrenia and autism). We demonstrate that the diversity in mutation rate of single nucleotide polymorphisms is dominated by the age of the father at conception of the child. These observations therefore shed new light on the importance of the father's age on the risk of diseases such as schizophrenia and autism. The results were published in a Nature paper 'Rate of de novo mutations and the importance of father's age to disease risk' (1).

Second, we have associated several common variants with schizophrenia and bipolar disorder. Our meta-analysis from 2009 associated three loci with schizophrenia, MHC, TCF4 and Neurogranin (2). Our follow-up paper on the meta-analysis (3) added a second TCF4 marker and a marker in the VRK2 gene to the list of markers associated with schizophrenia. There are few examples of rare variants conferring high risk in genes previously associated with common variants conferring low risk. A paper by Steinberg et al. describes a common variant at 16p11.2 associating with psychoses in a very large sample (4). Interestingly that marker is within a CNV locus previously associated with psychosis and autism. Also, PSYCHCNV samples contributed to the replication and expansion of the range of variants associated with the ZNF804A gene (5). First, by confirming a previously reported signal and then by associating rare CNVs, disrupting the gene, with psychoses. PSYCHCNV samples have furthermore been used in several meta-analyses associating SNPs and CNVs with schizophrenia (6-18). Through collaboration, led by Cardiff University, biological pathways conferring risk of schizophrenia were studied using a system biology approach. The association analysis demonstrated specific abnormalities of postsynaptic signalling complexes in the pathogenesis of schizophrenia (19).

Third, we have studied CNVs in the East-European samples and find the same CNVs conferring risk in the Vest and the East. The subjects recruited for PSYCHCNV were early onset cases, still the frequency of the CNVs conferring high-risk were not greater in the early onset cases (unpublished data) compared to late onset cases.

The PSYCHCNV consortium has contributed to better understanding of the genetics of psychiatric disorders by: estimating de novo mutation rate and by uncovering both rare and common variants conferring risk. The PSYCHCNV discoveries help understanding the basis of the pathology. The main conclusions are that rare, often de novo, mutations conferring high-risk and under negative selection pressure are probably contributing more to the aetiology and accounting for a larger fraction of the overall genetic risk than previously assumed.

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Project results:

Work progress and achievements

WPs 1 and 2 (Recruitment and genome wide scan)

During this reporting period, we completed the genome wide scan which was delayed and should have been finished during the first reporting period. Some of the samples had though been genotyped and analysed during the first reporting period of the project and results published in a Nature paper, 'Common variants conferring risk of schizophrenia' (1). The regulatory framework in Russia and Ukraine, and the economic crises where Icelandic banks went bankrupt caused some complications resulting in late delivery of the pre-financing to RAMS and URISFPDA. This delayed the recruitment of cases and controls by URISFPDA and RAMS which also affected phase I genotyping (the genome wide scan) and subsequent analysis. As a consequence we asked for a six month extension of the PSYCHCNV grant which was granted. Early during this reporting period we finished genotyping all phase I samples and analysing the data. Thus, delayed deliverables from the first reporting period were delivered during the first months of the second reporting period.

The most significant markers from the genome wide scan were followed up in phase II of the study. First it is worth mentioning that in phase I we decided to use the IlluminaHumanHap610 chip rather than the IlluminaHumanHap370 chip. We therefore generated twice as many genotypes as proposed in the Annex. Secondly, thanks to the 1000 genome project training sets for large scale imputations became available. By imputing the 1000 genome markers into the chip typed PSYCHCNV datasets from the microarrays we could test many million markers for association with autism and psychoses. Therefore the two-phase design was changed somewhat towards a much better powered study.

The 1000 genome training sets were used for imputing large numbers of common markers into the chip typed datasets. Thanks to the improvements in imputing we could combine the PSYCHCNV data with datasets from previous EU-funded projects by imputing the 1000 genome markers also into those dataset and analyze the markers jointly (meta-analysis). Phases I and II of the project were therefore much better powered which led to discoveries of several variants conferring risk of schizophrenia and psychoses. One meta-analysis was completed during the first reporting period1 and two have been completed during the second reporting period (2, 3). Below are short summaries describing the main findings from the two meta-analyses conducted by the PSYCHCNV consortium during this reporting period.

Steinberg et al. Common variants at VRK2 and TCF4 conferring risk of schizophrenia.

Hum Mol Genet. 2011 Oct 15;20(20):4076-81.

Here we extend our previous genome-wide association study and meta-analysis (totalling 7 946 cases and 19 036 controls) by examining an expanded set of variants using an enlarged follow-up sample (up to 10 260 cases and 23 500 controls). In addition to previously reported alleles in the major histocompatibility complex region, near neurogranin (NRGN) and in an intron of transcription factor 4 (TCF4), we find two novel variants showing genome-wide significant association: rs2312147[C], upstream of vaccinia-related kinase 2 (VRK2) [odds ratio (OR) = 1.09 P = 1.9 x 10-9] and rs4309482[A], between coiled-coiled domain containing 68 (CCDC68) and TCF4, about 400 kb from the previously described risk allele, but not accounted for by its association (OR = 1.09 P = 7.8 x 10-9).

Steinberg et al. Common Variant at 16p11.2 Conferring Risk of Psychosis. Molecular Psychoses (accepted manuscript).

Here, we consider a mixed schizophrenia and bipolar disorder (psychosis) phenotype (addition of 7945 bipolar disorder cases, 1168 schizophrenia cases, 332 other psychoses cases, 808 unaffected family members and 45 757 controls). Combined analysis reveals a novel variant at 16p11.2 showing genome-wide significant association (rs4583255[T], OR = 1.08 P = 7.0 x 10-11). The new variant is located within a 593 kb region that substantially increases risk of psychosis when duplicated. In line with the association of the duplication with low body mass index (BMI), rs4583255[T] also confers risk of reduced BMI (P= 0.0039 in the GIANT consortium; P = 0.00047 in additional Icelanders).

While we have successfully associated common variants with schizophrenia and autism we have not found any common variants conferring risk of autism. We have tested variants associated with autism by other groups but have not been able to replicate those findings (4).

During this second reporting period, PSYCHCNV partners also collaborated in a meta-analysis led by non-PSYCHCNV collaborators. Meta-analysis to which PSYCHCNV partners contributed is listed below:

Shi Y. et al. Common variants on 8p12 and 1q24.2 confer risk of schizophrenia. Nat Genet. 2011 Oct 30;43(12):1224-7.
Ripke S. et al. Genome-wide association study identifies five new schizophrenia loci. Nat Genet. 2011 Sep 18;43(10):969-76.
Sklar P. et al. Large-scale genome-wide association analysis of bipolar disorder identifies a new susceptibility locus near ODZ4. Nat Genet. 2011 Sep 18;43(10):977-83
Rietschel M. et al. Association between genetic variation in a region on chromosome 11 and schizophrenia in large samples from Europe. Mol Psychiatry. 2012 Sep;17(9):906-17.

We also searched for association with rare and common CNV in WP1 and 2. Again we collaborated with partners for previous EU-funded projects to increase the power in the analysis. The CNVs were called using the PennCNV caller and CNVs were tested for association with schizophrenia and autism in large samples. We decided to focus our attention on recurrent CNVs under negative selection pressure since autism and schizophrenia affect fecundity. Through this effort we have uncovered associations with several CNVs. The associated CNVs are all rare but confer high risk. In a manuscript by Gustafsson et al. ready for submission we test all recurrent CNVs under negative selection for association with schizophrenia and psychoses. There we associate a large duplication spanning the CHAT locus on chromosome 10 with psychosis, autism and developmental delay (5).

Gustafsson, O. et al. Recurrent CNVs affecting reproductive fitness: Association with psychosis

Here we search for recurrent CNVs under negative selection pressure and test for association with psychoses. The 55 recurrent CNVs identified by searching 37 176 genomes were confined to 31 loci. Twenty-eight were found to be under negative selection pressure and seven had previously been associated with schizophrenia or autism. The 55 CNVs were tested for association with schizophrenia,

bipolar disorder, autism / developmental delay in a sample of 18 700 patients and 56 000 controls. The strongest novel association was with a large duplication at 10q11.22-23. Refinement of that locus revealed a critical region of 1.6 Mb associating with neurodevelopmental disorders (OR = 58, P = 4.3x10-4). Eighteen genes including two coding for enzymes important in neurotransmitter synthesis, choline O-acetyltransferase (CHAT) and 2-oxoglutarate dehydrogenase-like (OGDHL), reside within the duplicated locus.

We have also collaborated with other research groups and demonstrated that CNVs conferring high risk are pleiotropic and confer risk of other diseases such as ADHD. In a collaboration led by colleagues from Cardiff, a large recurrent duplication at 16p13.1 was associated with ADHD6. This duplication had been associated with schizophrenia earlier by PSYCHCNV partners (7). This is one of the lessons learned by the PSYCHCNV efforts. CNV variants conferring high-risk of schizophrenia are pleiotropic, not only do the confer risk of schizophrenia but also to other psychiatric phenotypes such as autism, ADHD, developmental delay and bipolar.

Thus, deliverables and milestones were met for WP1 and 2. Subjects were recruited in keeping with the Annex and both CNVs and SNPs were associated with psychoses and data published in peer reviewed journals.

WP3 Characterisation of significant loci and search for causative variants or genes

In this WP, the objectives were to search for causative genes and variants in associated LD blocks by sequencing pools of DNA from cases and controls. The objectives were also to map the breakpoints of CNVs associating with ASD and psychosis, to find genes affected by CNVs and study their potential impact on the phenotype, to study expression of genes affected by CNVs and genes in LD blocks harbouring SNPs associating with ASD or psychosis in children and adolescents, to study complicated and rearranged regions associating with ASD and psychosis by FISH, to measure gene dosage in regions where the genomic architecture is complex and many copies of a given segment may exist, to find at-risk biological pathway associating with ASD, o find at-risk biological pathway associating with psychosis.

Work on this WP has progressed well. We have used several different approaches in the search for causative variants. New technologies such as exome sequencing and whole genome sequencing are techniques that became available during this reporting period and are fare better than for instance the planned low-throughput Southern blotting and FISH experiments in a search for small duplicated and deleted loci.

We first sequenced pools of DNA from 10 000 cases and compared to pool sequenced data for equally many controls. This approach we have used to search for rare causative variants conferring high risk and for studying whether there are more coding mutations in cases than in controls in genes associated with autism and schizophrenia. Second, we have analysed exome and whole genome sequence data from large number of cases and controls. The 2500 whole genome sequence Icelandic subjects at deCODE have been most valuable resource in the search for small insertions and deletions in loci associated with autism and schizophrenia.

The main published results from this WP are listed below. The paper expanding the range of ZNF804A variants by Stacy Steinberg is based on using CNV data to find high risk variants at a locus where common variants had previously been associated with schizophrenia.

Steinberg S et al. Expanding the range of ZNF804A variants conferring risk of psychosis. Mol Psychiatry. 2011 Jan;16(1):59-66.

A trio of genome-wide association studies recently reported sequence variants at three loci to be significantly associated with schizophrenia. No sequence polymorphism had been unequivocally (P less than5 x 10(-8)) associated with schizophrenia earlier. However, one variant, rs1344706[T], had come very close. This polymorphism, located in an intron of ZNF804A, was reported to associate with schizophrenia with a P-value of 1.6 x 10(-7), and with psychosis (schizophrenia plus bipolar disorder) with a P-value of 1.0 x 10(-8). In this study, using 5164 schizophrenia cases and 20,709 controls, we replicated the association with schizophrenia (odds ratio OR = 1.08 P = 0.0029) and, by adding bipolar disorder patients, we also confirmed the association with psychosis (added N = 609, OR = 1.09 P = 0.00065). Furthermore, as it has been proposed that variants such as rs1344706[T]-common and with low relative risk-may also serve to identify regions harbouring less common, higher-risk susceptibility alleles, we searched ZNF804A for large copy number variants (CNVs) in 4235 psychosis patients, 1173 patients with other psychiatric disorders and 39 481 controls. We identified two CNVs including at least part of ZNF804A in psychosis patients and no ZNF804A CNVs in controls (P = 0.013 for association with psychosis). In addition, we found a ZNF804A CNV in an anxiety patient (P = 0.0016 for association with the larger set of psychiatric disorders).

We have also reported association with a common variant within a CNV locus associated with schizophrenia. This association helps narrowing the 1 Mb 16p11.2 locus to one LD block.

Steinberg et al. Common Variant at 16p11.2 Conferring Risk of Psychosis. Molecular Psychoses (accepted manuscript).

Here we consider a mixed schizophrenia and bipolar disorder (psychosis) phenotype (addition of 7945 bipolar disorder cases, 1168 schizophrenia cases, 332 other psychoses cases, 808 unaffected family members and 45 757 controls). Combined analysis reveals a novel variant at 16p11.2 showing genome-wide significant association (rs4583255[T], OR = 1.08 P = 7.0 x 10-11). The new variant is located within a 593 kb region that substantially increases risk of psychosis when duplicated. In line with the association of the duplication with low body mass index (BMI), rs4583255[T] also confers risk of reduced BMI (P= 0.0039 in the GIANT consortium; P = 0.00047 in additional Icelanders).

In a search for at-risk biological pathways associating with ASD and schizophrenia we collaborated with University of Cardiff. George Kirov (Cardiff) led the analysis which implicates specific abnormalities of postsynaptic signalling complexes in the pathogenesis of schizophrenia.

Kirov, G. et al. Mol Psychiatry. 2012 Feb;17(2):142-53. De novo CNV analysis implicates specific abnormalities of postsynaptic signalling complexes in the pathogenesis of schizophrenia

A small number of rare, recurrent genomic copy number variants (CNVs) are known to substantially increase susceptibility to schizophrenia. As a consequence of the low fecundity in people with schizophrenia and other neurodevelopmental phenotypes to which these CNVs contribute, CNVs with large effects on risk are likely to be rapidly removed from the population by natural selection. Accordingly, such CNVs must frequently occur as recurrent de novo mutations. In a sample of 662 schizophrenia proband-parent trios, we found that rare de novo CNV mutations were significantly more frequent in cases (5.1 % all cases, 5.5 % family history negative) compared with 2.2 % among 2623 controls, confirming the involvement of de novo CNVs in the pathogenesis of schizophrenia. Eight de novo CNVs occurred at four known schizophrenia loci (3q29, 15q11.2 15q13.3 and 16p11.2). De novo CNVs of known pathogenic significance in other genomic disorders were also observed, including deletion at the TAR (thrombocytopenia absent radius) region on 1q21.1 and duplication at the WBS (Williams-Beuren syndrome) region at 7q11.23. Multiple de novos spanned genes encoding members of the DLG (discs large) family of membrane-associated guanylate kinases (MAGUKs) that are components of the postsynaptic density (PSD). Two de novos also affected EHMT1, a histone methyl transferase known to directly regulate DLG family members. Using a systems biology approach and merging novel CNV and proteomics data sets, systematic analysis of synaptic protein complexes showed that, compared with control CNVs, case de novos were significantly enriched for the PSD proteome (P=1.72 x 10).This was largely explained by enrichment for members of the N-methyl-D-aspartate receptor (NMDAR) (P=4.24 x 10) and neuronal activity-regulated cytoskeleton-associated protein (ARC) (P=3.78 x 10) postsynaptic signalling complexes. In an analysis of 18 492 subjects (7907 cases and 10 585 controls), case CNVs were enriched for members of the NMDAR complex (P=0.0015) but not ARC (P=0.14). Our data indicate that defects in NMDAR postsynaptic signalling and, possibly, ARC complexes, which are known to be important in synaptic plasticity and cognition, play a significant role in the pathogenesis of schizophrenia.

All objectives for WP3 were addressed and significant findings were published in peer reviewed journals. Somewhat more modern approaches were used for this WP, mining whole genome sequencing and whole exome sequencing data rather than carrying out low throughput Southern and FISH experiments. Thus, we consider that all deliverables and milestones were met.

WP4 Proving causality

The objectives in WP4 were to: replicate association results in more populations, to investigate whether variants significantly associating to ASD or childhood and adolescent onset psychosis are recurrent de novo variants, to investigate whether identified variants also confer risk to late onset disease, to study expression of genes affected by CNVs or SNPs associating with the psychiatric diseases studied here, to investigate whether available knockout animals have a phenotype resembling the psychiatric disorders studied here.

In the subsequent meta-analysis, we followed up on markers from our previous meta-analysis. Thus, associated variants were confirmed in the more recent meta-analysis (1-3). We also published papers were we specifically tested and replicated variants previously associated with schizophrenia (8, 9). Vassos Biol Psychiatry. 2012 May 4. Replication Study and Meta-Analysis in European Samples Supports Association of the 3p21.1 Locus with Bipolar Disorder.

Background:
Common genetic polymorphisms at chromosome 3p21.1 including rs2251219 in polybromo 1 (PBRM1), have been implicated in susceptibility to bipolar affective disorder (BP) through genome-wide association studies. Subsequent studies have suggested that this is also a risk locus for other psychiatric phenotypes, including major depression and schizophrenia.

Methods:
To replicate the association, we studied 2562 cases with BP and 25 439 control subjects collected from seven cohorts with either genome-wide association or individual genotyping of rs2251219 and tagging single nucleotide polymorphisms across the PBRM1 gene. Results from the different case-control groups were combined with the inverse variance weighting method.

Results:
In our dataset, rs2251219 was associated with BP (odds ratio [OR] = .89, p = .003), and meta-analysis of previously published data with our non-overlapping new data confirmed genome-wide significant association (OR = .875, p = 2.68 x 10(-9)). Genotypic data from the SGENE-plus consortium were used to examine the association of the same variant with schizophrenia in an overall sample of 8794 cases and 25 457 control subjects, but this was not statistically significant (OR = .97, p = .21).

Conclusions:
There is strong evidence of association of rs2251219 with BP. However, our data do not support association of this marker with schizophrenia. Because the region of association has high linkage disequilibrium, forming a large haplotype block across many genes, it is not clear which gene is causally implicated in the disorder.

The PSYCHCNV subjects were early onset cases. Comparing chip data from those subjects with late onset cases did not show significant difference between the samples and therefore we have published results from the larger dataset including both early onset and late onset subjects (better powered study).

We have focused our attention on de novo mutations in autistic and schizophrenia patients. In a recent paper by Kong et al. (10) whole genome sequenced trios were studied. Relationships between parents' age and the number of mutations were examined using all 78 trios. The number of mutations increases with father's age (P = 3.6x10-19) with an estimated effect of 2.01 mutations per year (standard error = 0.17). Mother's age is substantially correlated with father's age (r = 0.83) and, not surprisingly, is also associated with the number of de novo mutations (P = 1.9 x10-12). However, when father's age and mother's age were entered jointly in a multiple regression, father's age remained highly significant (P = 3.3 x10-8), whereas mother's age did not (P = 0.49). On the basis of existing knowledge about the mutational mechanisms in sperm and eggs, the results support the notion that the increase in mutations with parental age manifests itself mostly, maybe entirely, on the paternally inherited chromosome.

Consistent with other epidemiological studies in Iceland, the risk of schizophrenia increases significantly with father's age at conception (n = 569, P = 2 x10-5). Father's age is also associated with the risk of ASD. The observed effect is limited to non-familial cases (n = 631, P = 5.4 x10-4), defined as those in which the closest ASD relative is farther than cousins. The epidemiological results, the effect of father's age on de

novo mutation rate shown here, together with other studies that have linked de novo mutations to autism and schizophrenia, including three recent studies of autism through exome sequencing, all point to the possibility that, as a man ages, the number of de novo mutations in his sperm increases, and the chance that a child would carry a deleterious mutation (not necessarily limited to SNP mutations) that could lead to autism or schizophrenia increases proportionally. However, this model does not indicate that the relationship observed here between mutation rate and father's age would have been much different if the probands studied were chosen to be all non-ASD / schizophrenic cases instead. For example, assume that autism / schizophrenia is in each case caused by only one de novo mutation. Then autism / schizophrenia cases would on average have more de novo mutations than population samples. The magnitude could be substantial if the distribution of father's age has a large spread in the population, but then most of the difference would be caused by the cases having older fathers. If we control for the age of the father at the conception of the individual, then this difference in the average number of de novo mutations between control individuals and those with autism / schizophrenia would be reduced to approximately one.

It is well known that demographic characteristics shape the evolution of the gene pool through the forces of genetic drift, gene flow and natural selection. With the results from the de novo sequencing paper in mind, it is now clear that demographic transitions that affect the age at which males reproduce can also have a considerable effect on the rate of genomic change through mutation. There has been a recent transition of Icelanders from a rural agricultural to an urban industrial way of life, which engendered a rapid and sequential drop in the average age of fathers at conception from 34.9 years in 1900 to 27.9 years in 1980, followed by an equally swift climb back to 33.0 years in 2011, primarily owing to the effect of higher education and the increased use of contraception. On the basis of the fitted linear model, whereas individuals born in 1900 carried on average 73.7 de novo mutations, those born in 1980 carried on average only 59.7 such mutations (a decrease of 19.1 %), and the mutational load of individuals born in 2011 has increased by 17.2 % to 69.9. Demographic change of this kind and magnitude is not unique to Iceland, and it raises the question of whether the reported increase in ASD diagnosis lately is at least partially due to an increase in the average age of fathers at conception. Also, the observations here are likely to have important implications for the use of genetic variation to estimate divergence times between species or populations, because the mutation rate cannot be treated as a constant scaling factor, but rather must be considered along with the paternal generation interval as a time-dependent variable.

The whole genome sequencing effort has also associated de novo missense mutations to autism10. Proving causality is very difficult for the high-risk de novo mutations. Examination of the 4933 de novo mutations showed that 73 are exonic, including two stop-gain SNPs and 60 non-synonymous SNPs. One non-familial schizophrenic proband carries a de novo stop-gain mutation (p.Arg113X) in the neurexin 1 (NRXN1) gene, previously associated with schizophrenia. One non-familial autistic proband has a stop-gain de novo mutation (p.R546X) in the cullin 3 (CUL3) gene. De novo loss of function mutations in CUL3 have been reported to cause hypertension and electrolyte abnormalities. Recently, a separate stop-gain de novo mutation (p.E246X) in CUL3 was reported in an autistic case. Another one of our mutations is a non-synonymous variant (p.G900S) two bases from a splice site in the EPH receptor B2 (EPHB2), a gene implicated in the development of the nervous system. A de novo stop-gain mutation (p.Q858X) in this gene has recently been described in another autistic case. Given the small number of loss of function de novo mutations we and others have reported (approximately 70 genes in the three autism exome scans), the overlap is unlikely to be a coincidence. Hence, CUL3 and EPHB2 can be added to the list of genes that are

relevant for ASD. Effective genome coverage, computed by discounting regions that have either very low (less than half genome average) or very high (more than three times genome average) local coverage, the latter often a symptom of misaligning reads, was estimated to be 2.63 billion base pairs. From that, 4,933 mutations correspond to a germline mutation rate of 1.20 x10-8 per nucleotide per generation, falling within the range between 1.1 x10-8 and 3.8 x10-8 previously reported.

Kong et al. Nature. 2012 Aug 23;488(7412):471-5. Rate of de novo mutations and the importance of father's age to disease risk.

Mutations generate sequence diversity and provide a substrate for selection. The rate of de novo mutations is therefore of major importance to evolution. Here we conduct a study of genome-wide mutation rates by sequencing the entire genomes of 78 Icelandic parent-offspring trios at high coverage. We show that in our samples, with an average father's age of 29.7 the average de novo mutation rate is 1.20 x10(-8) per nucleotide per generation. Most notably, the diversity in mutation rate of single nucleotide polymorphisms is dominated by the age of the father at conception of the child. The effect is an increase of about two mutations per year. An exponential model estimates paternal mutations doubling every 16.5 years. After accounting for random Poisson variation, father's age is estimated to explain nearly all of the remaining variation in the de novo mutation counts. These observations shed light on the importance of the father's age on the risk of diseases such as schizophrenia and autism.

A summary list of main achievements in PSYCHCNV

1. Translation of diagnostic instruments
2. Training of psychiatrists one week course given by KCL
3. Recruitment and genotyping of GWAS samples
4. Training course in analyzing genetic data
5. Identification of SNPs and CNVs conferring risk of schizophrenia and autism
6. Determination of rate of de novo mutations in trios. We showed that the diversity in mutation rate of single nucleotide polymorphisms is dominated by the age of the father at conception of the child which is important for better understanding the genetics of both autism and schizophrenia.
7. Collection of papers has been published in high-ranked peer reviewed journals. In this summary we have referred to those we think are most important. Some of these papers have gotten enormous media coverage, in particular two Nature papers 'Rate of de novo mutations and the importance of father's age to disease risk' (10) and 'Common variants conferring risk of schizophrenia' (1).

One thing is always debatable whether we have proven causality of any of the mutations we have associated with schizophrenia, bipolar and autism. Proving a causal link between a variant and a psychiatric phenotype can present particular difficulties and many of these can be traced to the complexity of the phenotypes themselves. We have replicated significant association signals, we have also demonstrated pleiotropic effects of the associated variants, we have demonstrated that some of the associated variants affect expression of genes in carriers and publicly available data for knockout animals furthermore support our findings. Furthermore, based on the finding reported here some partners of this application have gotten funds to study the phenotypic stamp of the variants conferring high risk of psychoses and for generating animal models to further study the effect of the associated variants in model

organisms.

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Potential impact:

Expected final results and potential impact

The PSYCHCNV consortium has contributed to discoveries that will used in diagnostic tests. Using its unique expertise and population resources, deCODE and collaborators have discovered key genetic risk factors for dozens of common diseases. deCODE employs its capabilities to develop DNA-based tests and personal genome scans to better understand individual risk and empower prevention. It also licenses its tests, intellectual property and analytical tools to partners, and provides comprehensive value-adding genotyping, sequencing and data analysis services to companies and research institutions around the globe.

deCODE genetics employs its discoveries in a growing range of market-leading DNA-based risk assessment tests that enable individuals to better understand their risk of disease and to empower better prevention, targeted screening and earlier intervention. deCODE's tests for assessing risk of common diseases are for clinical use and can be ordered with the authorisation of physicians or other healthcare professionals.

Through the PSYCHCNV collaboration, and collaboration with other consortia including the EU-funded

SGENE and PSYCHGENE projects, deCODE and collaborators have uncovered many common variants conferring low risk and rare variants conferring high risk of schizophrenia. The consortium did only seek a patent on the high-risk variants as they are more likely to be valuable diagnostic markers. One patent has been filed based on early collaboration between decode and KCL at the start of this collaboration (and at the end of the EU funded SGENE collaboration). deCODE and collaborators plans to develop prediction algorithms for using these variants and other uncovered variants in diagnostic products and offer to clinicians.

The PSYCHCNV papers have received much attention in media, particularly the Nature papers 'Common variants conferring risk of schizophrenia' (1) and 'Rate of de novo mutations and the importance of father's age to disease risk' (2). These papers are very important contributions to better understanding the genetics of psychiatric disorders, landmark papers. Many groups have already replicated the associations reported in the 'Common variants conferring risk of schizophrenia' (1) and many groups are studying the effects conferred by the associated variants to neuropsychological phenotypes as well as psychiatric phenotypes. Thus, these papers have paved the way for future research in schizophrenia and autism.

Effective treatment for schizophrenia and other psychiatric disorders is still an unmet clinical need. The PSYCHCNV discoveries contribute to current understanding of the basis of the pathology of psychiatric disorders which hopefully will become useful in drug discovery.

Patent:

Copy number variations predictive of risk of schizophrenia European Patent Application EP2313520
Inventors: Stefansson, Hreinn (Krokamyri 30, IS-210 Gardabaer, IS) Ingason, Andres (Sondre AIle 5, DK-4000 Roskilde, DK)
Application number: EP20090773073
Publication date: 27 April 2011
Filing Date: 3 July 2009
Assignee: Decode, Genetics Ehf (Sturlugata 8, 101 Reykjavik, IS)

International classes: C12Q1/68
European classes: C12Q1/68M6

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2. Kong, A. et al. Rate of de novo mutations and the importance of father's age to disease risk. Nature 488, 471-475, doi:10.1038/nature11396 (2012).

Project website: http://www.psych-cnv.eu/aims.php

Related documents

Final Report - PSYCHCNVS (Copy number variations conferring risk of psychiatric disorders in children)

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