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Title: *SIRPB1* Copy Number Polymorphism is a Quantitative Trait *Locus* for Impulsive-Disinhibited Personality

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ABSTRACT

Context: The impulsivity-disinhibited personality (IDP) trait is a behavioral disposition mainly characterized for getting immediate gratification at the expense of long-term and more enduring gains. This personality trait plays a main role in the development of several disinhibitory behaviors and syndromes as Psychopathy, Attention-Deficit and Hyperactivity Disorder, Cluster-B personality disorders, criminality or alcoholism. Available data consistently supports a strong heritable component in personality accounting for 30% to 60% of the observed variance.

Objective: To identify novel genetic pathways associated to impulsivity-disinhibited personality trait.

Design: Hypothesis free genome-wide copy-number variant (CNV) analysis on a group of subjects with maximized opposite IDP scores. Quantitative trait *locus* analysis of candidate CNVs in the entire IDP continuum. Bioinformatic and functional evaluation of the associated variant.

Participants: A series of 261 male subjects comprising 153 inmates and 108 population controls that underwent a deep psychological characterization.

Results: A common CNV mapping the immune-related gene *SIRPB1* was significantly associated to IDP scores in a dose-dependent manner (β=-0.172, p=0.017). Bioinformatic analysis revealed that the deletion allele traced a haplotype showing higher mRNA levels than those with the insertion alleles (p=0.04). Epigenetic marks highlighted the presence of two potential insulators within the deleted region that were confirmed by functional assays performed in zebrafish embryos. This suggests that *SIRPB1* expression rates are affected by the presence/absence of the insulator regions.

Conclusions and relevance: Here we first propose *SIRPB1* as a novel candidate gene to account for phenotypic differences on IDP trait. Up-regulation of SIRPB1 has been described in prefrontal cortex of schizophrenia patients, providing a link between

SIRPB1 and diseases involving failure in the impulse control and inhibition. To our knowledge this is the first common structural variant affecting an immune-related gene that is associated to a personality trait.

1. INTRODUCTION

The impulsive-disinhibition behaviour has been defined as the lack of active inhibitory processes that regulate the tendency to respond. Following this idea, Gorenstein and Newman (1980) used the Psychopathology of the Disinhibition construct to refer to a disposition focused on obtaining immediate gratification instead of long-term rewards, and contempt of negative future consequences. This construct underlies to several psychopathological syndromes defined by a failure in the inhibition -or control- of the own impulses as psychopathic personality, antisocial and histrionic personality disorders, Attention-Deficit and Hyperactivity disorder and primary alcoholism (Aluja, 1991; Zuckerman, 1999). The impulsive-disinhibited personality (IDP) describes a continuum from strong inhibition to an extreme pole of high impulsive-disinhibition characterized by a clear tendency to social transgression behaviours (Aluja et al, 2010). Research consistently supports the idea that there is a strong heritable component in personality traits typically accounting for 30 to 60% of the observed variance (Loehlin, 1992; Plomin, 1990). A large meta-analysis of twin and adoption studies conducted to estimate the magnitude of genetic and environmental influences on antisocial behaviour showed that the best fitting model included moderate proportions of variance due to additive genetic influences (0.32%), non-additive genetic influences (0.09%), shared environmental influences (0.16%) and non-shared environmental influences (0.43%)(Rhee et al 2002). Thus, about 40% of the differences in a behavioural pattern closely related with IDP were explained by genetic sources. Similarly, other studies suggest that around 45% of the variance in self-reported impulsivity is accounted by genetic factors (Eaves et al., 1989).

Assuming the relevant role of genetic component in the explanation of individual differences on personality traits, different genome-wide association studies have been

reported. These were focused to both personality traits and related psychiatric disorders such as schizophrenia, manic-depressive illness, bipolar disorder and autism (Allie & Rodriguez, 2011; Girirajan, 2011; Tucker; 2011; Schinka; 2004)} . However, the evidence for major genes involved in non-pathogenic personality traits such as novelty seeking and impulsive-disinhibited behavior is far from being conclusive (Munafo, 2003; Munafo, 2013). As abovementioned, studies revealed that no single model of inheritance can be easily applied on behavior and personality. As for other complex traits, to date only a few percentage of the estimated heritability of personality traits have been explained by association to single nucleotide polymorphisms (Munafo et al, 2003) In order to capture this missing heritability novel approaches are needed, including the evaluation of alternative genomic sources of variability. Copy number variants (CNVs) are structural polymorphic regions involving several kilobases that can be found widespread along the human genome. Some authors suggest that their effect over transcriptional regulation may be higher that the one attributed to single nucleotide polymorphisms (Henrichsen CN, 2009, Schlattl A, 2008). Associations between CNV and behavioral traits have been performed with encouraging results (Cook, 2008; Need, 2009; Vu et al., 2011, Luciano et al., 2012). Thus, the aim of the present study was to explore the role of CNVs on the IDP continuum.

2. METHODS

2.1. Participants.

The participants in this study were 261 males consisting in 153 inmates and 108 population donors recruited between voluntary university students. All subjects completed the personality questionnaires and gave a blood or saliva sample for DNA extraction. Excluding criteria were: 1) Non Caucasian; 2) Diagnosis of psychotic or affective disorder; and 3) Being a relative of one of the participants in the study.

Subjects who agreed to participate signed a voluntary consent. The study complied with the Code of Ethics of the Official Scientific Medical.

2.2. Personality variables and psychometric scales.

2.2.1. *Impulsive Sensation Seeking Scale* (ImpSS from Zuckerman-Kuhlman Personality Questionnaire [ZKPQ; Zuckerman et al., 1993]). This scale measures lack of planning and the tendency to act impulsively without thinking. The ImpSS items are general in content and do not describe specific activities such as drinking or sex. Most items describe the tendency to seeking experiences or the willingness to take risks for the sake of excitement or novel experience.

2.2.2. *Aggression-Hostility Scale* (Agg-Host from ZKPQ; Zuckerman et al., 1993) is also a scale from the ZKPQ. This scale has 17 items, but a validated shorter form of 13 items (Aluja et al., 2003a) was used. Half of the items describe readiness to express verbal aggression, while the other half tap rude, thoughtless or antisocial behaviour, revengefulness, and spitefulness. High scores in this scale indicate a quick temper and impatience with others.

2.2.3. *Novelty Seeking* (NS) is a 40-items scale from the TCI (Cloninger et al., 1994). NS reflects a tendency toward exploratory activity in response to novelty, impulsive decision making and active avoidance of monotony.

2.2.4. *BIS-10.* Barratt Impulsivity Scale (BIS-10) (Barrat, 1985). This inventory contains 34 items that measure three components of impulsiveness: Motor Impulsiveness, Cognitive Impulsiveness, and Non-Planning Impulsiveness, which correspond to acting without thinking, making quick cognitive decisions on the spur of the moment, and “present orientation” or lack of “futuring” respectively.

2.2.5. *Psychoticism* (P from EPQ-RS; Aluja et al., 2003b; Eysenck & Eysenck, 1997) is a 12-item scale derived from the short version of the Eysenck Personality Questionnaire-Revised. The Psychoticism scale measures lack of empathy, egocentrism and proneness to antisocial behaviour.

2.2.6. *Sensitivity to Reward Questionnaire* (SR from SPSRQ; Torrubia et al., 2001), is a 24-item scale from the Sensitivity to Punishment and Sensitivity to Reward Questionnaire.

2.3. Genome-Wide Comparative Genomic Hybridization.

Comparative Genomic Hybridization (CGH) analysis was performed using Agilent 2X400K CGH array in a discovery group of 20 subjects whose scores in impulsivity-disinhibition questionnaires fitted $>Q_{75}$. Whole genome amplification kit (WGA2, Sigma-Aldrich, USA) was used to amplify DNA whenever needed. DNA from each high scoring subject was compared with a pool of DNA obtained from 21 low scoring subjects ($<Q_{25}$). Arrays were processed by Oxford Gene Technology facilities (Oxford, UK). Agilent CytoGenomics 2.5.8.11 software was used to identify CNV regions (CNVR). Log2 ratios were corrected for GC content with a window of 10 Kb. Two arrays of self-to-self hybridization samples were used to set the Aberration Detection algorithm (ADM2) at a threshold of 9.5.

2.4. Multiplex Ligation-dependent Probe Amplification analyses.

Gene dosage variations on CNVR at *NEGR1*, *LCE3C*, *UGT2B17*, *SIRPB1* and *GSTTP1/2 loci* were analyzed by Multiplex Ligation-dependent Probe Amplification (MLPA) technology. Following MRC-Holland recommendations, we designed 5 sets of

probes using MAPD: MLPA probe design software (http://genomics01.arcan.stonybrook.edu/mlpa2/cgi-bin/mlpa.cgi) to detect copy-number variations affecting these genes (Supplementary Table 1). MLPA EK-1FAM P300A2 kit was supplied by MRC-Holland (MRC-Holland, Amsterdam, Netherlands). Capillary electrophoresis analysis was performed using an ABI PRISM Genetic Analyzer 3130 (Applied Biosystems, Foster City, CA, USA) and for data analysis we used GeneMarker v1.75 (Softgenetics L.L.C, State College, PA, USA).

2.5. Taqman genotyping assays.

SIRPB1 CNV-status was determined according to previously reported assay (Jin G 2001) using commercially available Taqman probe (Hs04057639). According to manufacturer´s instructions, RNaseP *locus* was used as internal control for gDNA copy-number standardization (reference PN4316831). Genotyping of *SIRPB1* rs2209313 marker was performed by Taqman assay (reference C1911298).

2.6. Data analysis.

The impulsiveness-disinhibition index (z-index) was formed by adding the z value of the six personality scales in order to get a standardized global continuous measure. The z values were obtained after computing the one-factor loadings. Gene ontology analysis was performed using Genotype-Phenotype Integrator (http://ncbi.nlm.nih.gov) and GeneDecks v3 online resource (http://www.genecards.org). eQTL analysis conducted for rs2209313 was performed correlating genotype data obtained from non-related CEPH individuals (Hapmap release 2) and *SIRPB1* mRNA expression levels of their respective lymphoblastoid cell lines, obtained from the GO profiles available at the NCBI web (DO ID: 25703673). eQTL analysis for rs6074896, rs1535882 and rs4814391 were directly captured from the Genevar resource (http://www.sanger.ac.uk).

The presence of *cis*-regulatory elements near *SIRPB1* promoter was evaluated taking into account the chromatin immunoprecipitation tracks from the ENCODE project (http://genome.ucsc.edu/). Statistical analyses were performed using IBM SPSS Statistics software v20.

2.11. In vivo enhancer-blocking assays.

To evaluate the potential insulator activity of the CTCF-associated regions we used a Tol2 transposase-derived vector assay previously described by Bessa J et al, 2009 [Royo et al 2011]. This construct contains a strong midbrain enhancer, a Gateway™ entry site and the cardiac actin promoter controlling the expression of GFP. Each candidate region was recombined between the midbrain enhancer and the cardiac actin promoter. As a reference, the original vector was used. One-cell stage wild type zebrafish embryos where injected with 3–5 nl of a solution containing 25 nM of each construct plus 25 nM of *Tol2* mRNA. Embryos where then incubated at 28°C and GFP expression was evaluated 24 hours post-fertilization (hpf). The midbrain/somite GFP intensity ratio was quantified using ImageJ freeware. The human regions tested (INS1 and INS2) were delimited by the following primers: Ins1F: (5´-CTCCACCTTGACTCCCAGTAA-3´) and Ins1R (5´-ATATGTTGCCACAGGCATCC-3´), on one side, and Ins2F (5´-CACAGCAGGCAGCTACAAAG-3´) and Ins2R (5´-TACTGGGTTTCAGGCATGGT-3´) on the other side.

3. RESULTS

3.1. Comparative Genomic Hybridization

The series (n=261) presented a normal IDP z-index distribution (p=0.563, Kolmogorov-Smirnov test). The inclusion on both immates and controls in the series allowed us to

create a single study population with enlarged variance on the IDP scores and therefore increasing statistical power to perform quantitative trait *loci* analysis (Supplementary Fig1). On this first stage we selected subjects with higher IDP z-index ($>Q_{75}$, n=20) to perform a high-resolution CGH using as reference a pool of genomic DNA obtained from subjects with lower IDP z-index ($<Q_{25}$, n=21). The rational for this opposite-phenotype comparison was to maximize the genomic differences between both subsets. Results from CGH arrays are summarized in Supplementary Fig2. A total of 54 copy number variant regions (CNVR) were detected, 25 (46%) containing gains, 27 (50%) containing losses and 2 (4%) containing gains and losses (Supplementary Table 2). CGH analysis evidenced that one of the subjects carried an extra chromosome X. This subject was therefore diagnosed as Klinefelter Syndrome and was excluded from further analysis. On average, we observed 6.6 CNVRs per individual with a maximum of 14 and a minimum of 2.

Most CNVRs were present on a single individual (33.66%) with 2 frequent CNVs, present in 11 and 15 individuals (chr2:179385858-179528531 and chr20:1558379-1584485, respectively). On average, CNVR expanded 109 Kb, ranging from 9 to 800 Kb and all but seven were already described. We selected a total of 76 genes mapping on the genomic intervals defined by the 54 CNVRs. Gene Ontology analysis performed by Genotype-Phenotype Integrator and GeneDecks on-line resources, allowed us to select candidate genes located in these regions by their function or biological attributes. Taking into account these data five CNVR affecting *NEGR1, LCE3C, UGT2B17, SIRPB1* and *GSTTP1/2* genes were selected, based on either prevalence or potential phenotypic involvement on behavior disturbances.

3.2. Copy-number variation analysis of selected candidates reveals SIRPB1 CNVR as a quantitative trait locus for impulsive-disinhibited personality.

On a second stage, MLPA probes for each of the five selected CNV regions were designed taking into account the interindividual variation. Thus, only the common gained/lost regions of each CNVR were analyzed. A subset series of 57 subjects representing the total ID>Q_{75} sample were subjected to MLPA analysis for the five CNVR. For quality control, 10% duplicates were included in the experiment showing 100% concordance. MLPA results fitted the data obtained from the CGH analysis. Copy number distribution of the different CNVR is summarized in Supplementary Table 3. *SIRPB1* copy-number state significantly correlated with different Impulsivity-Disinhibited parameters including the Impulsive sensation seeking (Kendall-Tau non parametrical correlation´s tests = -0.349; $p < 0.008$), Barratt impulsivity scale, (Tau= -302; $p < 0.022$), Psychoticism (Tau= -0.278; $p < 0.036$) and Novelty Seeking (Tau= -0.262; $p < 0.049$) (Table 1). According to these data, those subjects with increasing dosage of *SIRPB1* CNV tend to exhibit lower scores of Sensation-Seeking and Impulsivity, resulting on a statistically significant overall reduction of the Impulsivity-Disinhibited Index (Tau= - 0.324; $p < 0.014$). Given these results, we extended the analysis of the *SIRPB1* CNV using Taqman assay to the total 261 subjects from the series. Table 2 shows the results of linear regression analysis of *SIRPB1* CNV-genotypes according to the different personality variables. When including age on the equation, regression analysis showed statistical significance for Impulsive sensation-seeking (Beta=-0.863, $p < 0.001$)Barratt impulsivity scale-10 (Beta =-3.212, $p < 0.015$) and IDP z-index (Beta=-0.172, $p < 0.017$). Figure 1 illustrates the significant reduction on the IDP z-index depending on the *SIRPB1* CNV status. Thus, we could conclude that the presence of additional copies of the *SIRPB1* CNV correlated with reducing scores in different personality traits, especially those measured by Impulsive Sensation Seeking and the Barrat impulsivity scales. The nature of this association was consistent in both

inmates and population donor subsets, although only in the second one statistical significance was reached (data not shown).

3.3. The haplotype bearing SIRPB1 CNV-deleted allele correlates with increasing levels of SIRPB1 expression.

SIRPB1 CNV expands along chr20:1558379-1584485 coordinates that includes *SIRBP1* intron 1. Linkage disequilibrium (LD) analysis of the region based on HapMap release 2 data shows an LD block with two SNPs (rs2873569 and rs2982585) exhibiting a strong imbalance of Hardy-Weinberg equilibrium ($p<0.002$), consistent with the presence of the CNV in the region (Figure 2 A). Previous works reported that *SIRPB1* CNV-deleted allele could be in strong linkage disequilibrium ($r^2=0.93$, $D´=1$) with rs2209313 allele-C (Jin G, Carcinogenesis 2011). We integer the rs2209313 genotypes available from the CEU series with the independently obtained mRNA levels from their corresponding lymphoblastic cell lines. As illustrated in Figure 2B, those individuals harboring the rs2209313 CC genotype correlated with increased levels of *SIRPB1* ($p=0.040$). Inspection of the polymorphisms flanking the CNV and the available eQTL data series from Genevar revealed three SNPs (rs6074896, rs1535882 and rs4814391) exhibiting a significant correlation with *SIRPB1* mRNA expression (Supplementary Figure 3)(Grundberg 2012; Dimas 2009 and Zeller et al 2010). This data independently allow us to infer that the haplotypes containing rs2209313 allele C and rs1535882 A allele that captured *SIRPB1* CNV-deleted allele, are associated to increased levels of *SIRPB1*.

3.4. SIRPB1 CNV contains CTCF-associated insulator regions.

To explore the potential link between an intronic deletion and the variations in mRNA levels of *SIRPB1* we examined the genomic environmet to determine the presence of potential *cis* regulatory elements. Interestingly, two potential binding sites for the

transcriptional repressor CTCF were present in the deleted region acting as insulators. We postulated that the absence of these insulators might alter the regulatory landscape of *SIRPB1* and therefore allow the interaction of additional enhancers. In order to evaluate this hypothesis we isolated the regions designed as INS1 and INS2 (Supplementary Figure 4) and evaluated their insulator activity using *Tol*2-metiated transgenesis in zebrafish embryos.

As shown in Figure 3A, whenever an insulator is placed between the midbrain enhancer and the actin promoter, the resulting embryos exhibit a significant decrease in the GFP expression levels in the brain. Some illustrative examples are shown in Figure 3 panels C, D and E. Upon quantification, we determined that both INS1 and INS2 exhibited a statistically significant reduction of the midbrain/muscle GFP expression ratio when compared to the control transposon ($p < 0.007$ and $p < 0.001$ respectively, Kruskal-Wallis test). These results may suggest that on their natural genomic context these regions would contribute to prevent the *cis*-regulatory action of downstream enhancers that may compromise an adequate regulation of the *SIRPB1* promoter.

4. DISCUSSION

Differences on personality traits, including impulsive disinhibited dimensions, are associated to the genetic background. However, the search for what specific variant is associated with concrete behavioral traits is being elusive. Considering the state-of-the art in the genetic approach to quantitative traits, Munafo et al., (2003) suggested some recommendations including extensive psychological evaluation based on several phenotypic measures, using an extreme groups design and developing of new genetic approaches. This study was designed to follow these recommendations.

We have conducted a three-stage analysis in order to find common CNV regions associated to the impulsivity-disinhibited trait. Subjects were measured using several

personality questionnaires. Extreme phenotype groups (top-scoring ID vs. low-scoring ID subjects) were subjected to a discovery analysis of copy number variants.

Given the quantitative nature of the different traits under analysis, we performed correlation tests taking into account both personality scores and the copy-number status of the candidate CNV regions. We found a CNV affecting *SIRPB1* intron 1 that statistically correlated with different impulsivity measurements. The presence/absence of the 26.1 Kb region within *SIRPB1* intron 1 correlates with the levels of impulsivity and sensation seeking in a copy-number dependent manner. This association allowed us to propose *SIRPB1* as a novel candidate gene associated to impulsivity-disinhibited trait in men.

Signal regulatory proteins (SIRP) constitute a family of transmembrane glycoproteins with extracellular Ig-like domains. Several SIRP family members have thus far been identified on myeloid and other cells. Different reports have addressed the immunological properties of SIRP family members. More specifically, SIRPB1 have been associated to innate immune system (van Beek, EM, J Imm 2005). There is evidence that ionic interaction between SIRPB1 and adapter protein DAP12 leads to phosphorylation of spleen tyrosine kinase (SYK) and mitogen-activated protein kinase (MAPK) and further promotes phagocytosis by macrophages and migration of neutrophils as part of the regulation of the inflammatory response (Barclay AN, 2006). The relation of the immune system status and behavior is not new and constitute one of the most evolutionary conserved circuits in vertebrates. Different behavioral traits have been associated to pro-inflammatory cytoquines. Upon infection, the body naturally undergoes a series of behavior alterations. This consist on disinterest in social interactions, with the environment, lethargy, reduction in motor activity, somnolence and failure to concentrate. This is an adaptive response that enhances recovery by conserving energy to combat acute inflammation.

There is evidence that this behavior is mediated by pro-inflammatory cytokines such as IL-1, TNFa or IL6. (Maes, 2012). Therefore, we cannot rule out the possibility that common variants affecting immune-related genes such as *SIRPB1* are associated to different behavior traits. Interestingly, a recent genome-wide screen performed at a 10 cM resolution in depressive patients of Turkish origin reveals a region within 20p13 as a *locus* for depression (LOD=1.95). The critical region mapped between D20S103 and D20S484 and contains *SIRPB1* gene (Bulayeva et al., 2012). Results of the present study are in agreement with Bulayeva et al., (2012) since Depression correlates negatively with some personality constructs used in this study as Sensation Seeking (Farmer et al., 2001), and related traits as Extroversion (Duggan, et al., 2003).

eQTL analysis suggest that haplotypes containing the CNV-deleted allele exhibit higher *SIRPB1* transcription rates that those bearing at least one insertion of the CNV. We have identified two CTCF-enriched regions within the *SIRPB1* intron 1 that were affected by the CNV. These two sequences (here named INS1 and INS2) displayed clear *in vivo* enhancer-blocking capacity when assayed in zebrafish embryos. This allow us to postulate that the lack of these insulators on the 3´ region of *SIRPB1* promoter as it appears on the CNV-deleted allele, would facilitate the interaction of downstream enhancers leading to an increase of *SIRPB1* transcription rates.

Reports found an overexpression of SIRPB1 in superior temporal neocortex from Alzheimer Disease patients as well as in prefrontal cortex samples from schizophrenia patients (Gaikwad S, 2009; Martins-de-Souza, 2009). Importantly, the prefrontal cortex plays a major role in gating impulsive actions in several behavioral tasks (Kim & Lee, 2011). Whether the SIRPB1 reported overexpression in a disease involving failure in the impulse control and inhibition such as Schizophrenia is related to the CNV here presented remain to be answered.

Our study opens a new avenue for future research providing the first evidence for the association of *SIRPB1* CNV in a personality complex trait such as IDP. Replication in other cohorts will be needed to further validate the association here described. In addition, a deeper molecular characterization would also be required to better understand the contribution of the CNV on *SIRPB1* regulation.

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Figure legends

Figure 1. A) Box plot of the impulsivity-disinhibited score according to the *SIRPB1* CNV genotype. Lines represent the range, grey boxes both Q_{25} and Q_{75}. Dashes represent their respective mean. B) Relative distribution of subjects under study according to impulsive-disinhibited score and *SIRPB1* CNV genotype.

Figure 2. A) Linkage disequilibrium analysis of the *SIRPB1* region in CEU, according to HapMap. Dashed line corresponds to the CNV. Asterisks label the SNPs that do not fit Hardy-Weinberg equilibrium. Boxed highlight the SNP with eQTL data. B) Box plot showing *SIRPB1* expression levels determined for CEU lymphoblastoid lines according to their rs2209313 genotype. Lines represent the range, grey boxes both Q_{25} and Q_{75}. Dashes represent means. Beta score and p-value were obtained from linear regression analysis.

Figure 3. A) Representative scheme of the basis of the enhancer-blocking assay. In the absence of an insulator, the enhancer (E) contacts the promoter (P) and activates transcription both in the muscles and the midbrain. Whenever an insulator (I) is located between the enhancer and the promoter, midbrain expression is compromised (Panel A´). B) Box plot of the midbrain/somite GFP expression ration obtained 24 hpf from individual zebrafish injected with each construct (Control n=72, INS1 n= 55 and INS2 n= 53). Lines represent the range, grey boxes both Q_{25} and Q_{75}. Dashes represent means. (**) represent a p-value< 0.01 and (*) a p-value=0.007 in Kurskal-Wallis tests. Somite expression did not show differences between constructs (p>0.1, Kurskal-Wallis test). Panels C to E show a representative animal of each series (Control, INS1 and INS2 respectively) under visible light and fluorescence (C´to E´).

Supplementary Figure 1. Distribution of z-index on the entire series (histogram) together with its respective fitted normal distribution (line). The histogram illustrates the origin -control population *vs* immate- of the subjects. The z-index of both immate and control subsets also fit normal distributions (p=0.673 and 0.468 respectively, Kolmogorov-Smirnov test)

Supplementary Figure 2. A) Overall view of the CNV regions identified by comparative genome hybridization. B) Representative plots of the five CNV regions selected for subsequent studies.

Supplementary Figure 3. A) Linkage disequilibrium plot of the *SIRPB1* promoter region and haplotype frequencies obtained for CEU population. B) Genevar eQTL analysis of SIRPB1 and rs6074896 obtained from Dimas et al 2009. C) Genevar eQTL analysis of *SIRPB1* and rs1535882 obtained from Grundberg et al 2012. D) Genevar eQTL analysis of *SIRPB1* and rs4814391 obtained from Grundberg et al 2012.

Supplementary Figure 4. Epigenetic marks of the *SIRPB1* proximal regulatory landscape, according to ENCODE project and the BROAD institute public chromatin immunoprecipitation data. Boxed region correspond to the CNV found within *SIRPB1* intron 1. H3K4me1 stands for monomethylation of histone-3 lysine 4. H3K27ac stands for acetylation of histone-3 lysine 27. CTCF ChIP from both H1-hESC and GM12878 cell lines are also plotted. Squared region reflects the CNV region. INS1 and INS2 label the two regions that were selected for enhancer-blocking assays.

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THIS INFO IS NICE BUT I WOULD KEEP IT HIDDEN UNLESS DEMANDED. (JL)

	Immates (n=153)			Non-interned (n=108)			All sample (n=261)		
	B[(1)]	95%CI (lower:upper)	p-value	B[(1)]	95%CI (lower:upper)	p-value	B[(1)]	95%CI (lower:upper)	p-value
Personality variables									
Impulsive sensation-seeking	-0.576	-1.205:-0.053	0.072	-0.943	-1.589:-0.297	***0.005***	-0.863	-1.342:-0.385	<***0.001***
Aggression hostility	-0.038	-0.659:-0.584	0.905	-0.307	-0.899:-0.286	0.307	-0.184	-0.616:0.248	0.402
Psychoticism	0.055	-0.426:-0.536	0.821	-0.407	-0.885:-0.071	0.094	-0.237	-0.592:0.118	0.190
Figure 1Sensitivity to reward	-0.222	-1.162:-0.718	0.641	0.301	-0.605:-1.206	0.511	-0.105	-0.788:0.578	0.763
Novelty seeking	-0.04	-1.138:-1.059	0.943	-1.162	-2.245:-0.08	***0.036***	-0.653	-1.428:0.122	0.098
Barratt impulsivity scale-10	-1.808	-5.560:-1.945	0.343	-3.87	-7.111--0.628	***0.02***	-3.212	-5.796:-0.628	***0.015***
Impulsive-disinhibited index	*-0.081*	*-0.274:-0.112*	*0.41*	*-0.206*	*-0.385:-0.028*	***0.024***	*-0.172*	*-0.312:-0.031*	***0.017***

Note: Regression analysis was performed including age in the equation
[(1)] unstandardized coefficient