## Nouvelle rubrique dans *M/S* : « *Scoop* commenté »

› Rompant avec sa tradition de ne pas publier d'articles originaux, *médecine/sciences* a conclu un accord avec le groupe de presse *Sciences Art & Facts* et accepté de participer à la promotion d'une idée originale : un nouveau magazine intitulé « *High Impact Controversial Sciences* » qui publiera à partir de mai 2007 une sélection des meilleurs articles soumis aux prestigieux magazines scientifiques de langue anglaise et refusés par au moins l'un d'entre eux. C'est dans ce contexte que nous proposons à nos lecteurs la chance de lire, en primeur, et dans sa version originale, un article d'une portée encore insoupçonnée : « *A same gene for altruism and selfishness in Primates* » by « *the IASP Consortium* » (*online advanced publication* 1 April 2007). En accord avec la tradition de *M/S*, le fac-similé est suivi des commentaires émanant de deux spécialistes français du domaine. ‹

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PARTICLE

# A same gene for altruism and selfishness in Primates

The International Alt/Self Map Consortium*

**The goal of the International Alt/Self Project (IASP) is to determine the molecular basis of societal altruistic and selfish behaviour in primate societies. In order to solve this difficult problem, an International Consortium comprising genomists and psycho-biologists from the G-8 countries has been created. In a first step it was decided to concentrate on extreme opposite phenotypes manifesting in *Homo sapiens sapiens*: the hyper-altruism syndrome (HAS) and the hyper-selfishness syndrome (HSS). Conventional association methods, using the most powerful tools provided by the SNP, and the HumMap projects, resulted in the preliminary mapping of the « altruist » locus, and the « selfish » locus, both in the pseudo-autosomal region of the short arm of chromosome X. Transcriptional studies using 1000K chips showed that an unannotated sequence was overexpressed in HAS and underexpressed in HSS individuals. This mirror pattern of expression suggested that the two deviant states might be allelic. This hypothesis was substantiated by genome studies using CGH-array. Ultimately different mutations in expressed genomic sequences showed a striking genotype-phenotype correlation: gain-of-function (GOF) mutations were invariably found in the HAS group, whereas loss-of-function (LOF) mutations were invariably found in the HSS group. These results demonstrate that a same and unique novel gene, coined *DARWIN*, is involved in the two oppposite deviant phenotypes, suggesting that the morbid locus is a QTL (*quantitative trait locus*). Preliminary comparative data obtained in non-human primates showed that the *DARWIN* gene is highly conserved. Like humans, chimpanzes (*Pan troglodytes*) have a single expressed gene copy located in a stable genomic domain, whereas the highly benevolent bonobo primate (*Pan paniscus*) has several expressed gene copies, located in a copy number variable region (CNVR), a situation that buffers phenotypic manifestation of LOF mutations.**

Human primates are social animals, exhibiting a wide range of behavioural patterns in society[1]. Dissecting the molecular basis of some stereotypes, once utopic[2,3], has become a feasible goal[4-6]. The « global village » is causing abrupt upheavals among humans, inducing in many countries severe societal dysfunctions[7]. These are invariably produced by economical mechanisms which are still largely uncontrolled. The massive impact of economics on mankind results today in an increasing mass of wealth among the happy few, contrasting with an ever increasing impoverishment of the « unhappy many », a potential

*Lists of participants and affiliations appear in Supplement 1.

source of conflicts[8]. This is why a number of academic scientists belonging to the most developed countries have decided to combine their expertise to study the causes of this phenomenon. Based on previous studies showing rare family clustering and identical social behaviour in reared apart identical twins[9], it was hypothesized that two hyper-deviant societal traits, namely compulsive altruistic behaviour, called hyper-altruism syndrome (HAS) and compulsive craving for money, called hyper-selfishness syndrome (HSS) could be monogenic and caused by mutations in two distinct genes. Dissecting the molecular basis of these extreme behavioural phenotypes was believed to help to understand the etiology of those societal dysfunctions, and to find evidence-based therapies[10]. This led to the the creation of the International Alt/Self Project (IASP).

## The IASP

This project has been elaborated and managed by a Consortium emanating from and funded by the G-8 organization (see Supplement 1). The main task of this Consortium was to design the protocol of patients selection, to build the two cohorts of HAS and HSS subjects, to collect blood samples and to create a common high-thruput platform for molecular investigations, located at the *Institute of Human Primatology on the Welcome Thrust* campus (Thinkston, Oxbridge, UK).

## The two models of deviant behavioural phenotypes

### *Hyper-altruism syndrome*

HAS is described in the OMEN catalog[11] under item #999 in which the different synonymous acronyms are listed. The most commonly used are IOS *(Irrepressible Oblative Syndrome)*, CCS *(Compulsive Compassionate Syndrome)*, NGOLS *(NGO[Non Governmental Organization]-like Syndrome)* and *OES (Over Empathic Syndrome*). Briefly this morbid entity is characterized by a pathological inclination to help people in distress, with complete oblivion of oneself. Following are a few examples of this extreme but rare form of misconduct: (i) the « righteous » gentiles who saved Jews during World War II, thereby compromising their own safety and that of their family; (ii) those upper-class individuals who abandon their social status to dedicate themselves to everyone else's welfare, because they believe that extreme poverty should be eradicated or at least contained; (iii) those wealthy people who donate most of their fortune to non-profit charity foundations working to combat illnesses, poverty, hunger; (iv) people who take the initiative to manifest publicly their disapproval of the increasing number of homeless people in large cities (see Figure 1).

**Figure 1** | Line of havens for homeless people provided in Paris by *« Les Enfants de Sancho-Pança »*, a community of individuals suffering from the HAS syndrome.

### *Hyper-selfishness syndrome*

HSS is described in the OMEN catalog under #666, under several synonymous acronyms such as SS *(Scrooge Syndrome)*, PS *(Predator Syndrome)*, UCS *(Unquenchable Cupidity Syndrome)*, CFMS *(Craving-For-Money Syndrome) and* SCS *(Steven Cohen Syndrome)*. This extreme phenotype, opposite to HA, is much more widespread. It is characterized by an overwhelming addiction to money, causing frantic pursuit of personal enrichment by any means without toil. Here are some examples: (i) tycoons who have piled up an incommensurable fortune in few years in buying (with borrowed money) big but financially challenged companies, and, then in dismantling and reselling them piece by piece, with immense profit, regardless of the social cost[12]; (ii) billionaire corporate owners whose unique goal is to swallow up any rival company; (iii) stock-brokers and raiders, sometimes called « golden boys », whose a single bonus amounts to 2000 years of salary of a manual worker[13]. (See Figure 2).

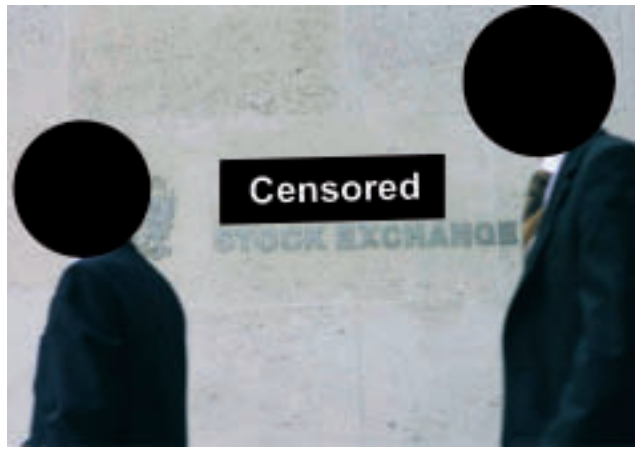


**Figure 2** | Photography illustrating a paper entitled « Stock traders finishing the year with record gains» published by the French daily newspaper *Le Monde (23 dec 2007, issue n°1925)*. The legend in French says: *« At the City 4000 super-privileged people will get a bonus of 1.5 million euros each.)*. Note the delighted face of the deeply affected HSS probands, unaware of the severity of their illness.

## Assessing and sampling deviant phenotypes

Unrelated volunteers, having given their informed consent, were pre-screened by a series of tests: (i) direct questions exploring their global financial status, way of earning and of spending money; (ii) multiple-choice questions exploring social behavioural features. Only those individuals exhibiting clearcut inclination to care exclusively either for others or for themselves were retained and classified into two groups: O (for « Others ») and E (for « Ego »). Individuals who had passed the first screen were subsequently submitted to an *Emotional Objective Biological Assessment Protocol (EOBAP)*[14]. In brief, indviduals of each group were exposed to visual stimuli containing strong societal connotations: fixed views of newspapers headlines, and videos showing contrasted events (such as lines of miserable people waiting for a bowl of soup in Paris[15]; documentary movie about the fifty golden Rolls-Royce cars collected by a

prince ruling an oil-rich territory, or about the St Barthelemy island in Caribbeans, a paradise for billionaires). During the test, the following parameters were recorded: heart rate, blood pressure, EKG, EEG, and PET scan brain imaging. The results were combined and treated by the *EOBAP* algorithm[14]. The resulting O/E ratio was used to score a Social Quotient (SQ) that was normalized between values of + 100 and – 100, a range covering 99% of normal human primates [unpublished]. In the IASP only those people falling off limits, ie with an SQ > +100 (defining the HAS group) or < – 100 (defining the HSS group) were included in the final sample comprising 50 males and 50 females in each group.

### Mapping the loci and gene hunting

Conventional association studies were performed, using highly automated genotyping protocols (SNPs and HumMapping, described in ref. 16). To avoid possible contaminations, each group was analyzed by a different set of 300 000 markers, each covering the whole genome with a resolution of 10 kb. A first result was that both HAS and HSS loci mapped to the same pseudo-autosomal region of chromosome X. A second run of genotyping was then performed after swapping the set of markers used in the first round. The data confirmed the first mapping results. Ultimately the genomic territory harbouring the two suspected loci was narrowed down to 100 kb. In this territory, haplotypes varied greatly and did not correlate to the HAS or HSS status.

### Finding and validating a single causal gene by LOF/GOF defects

In build 36 of the Human Genome sequence[17] this region is poorly annotated, without protein gene reported. In the absence of candidate gene it was decided to resequence the 100 kb in every subject, seeking for possibly pathogenic variations in putative genes. This strategy was successful and showed a highly polymorphic sequence containing a single open reading frame. The functional consequences of the observed sequence variations in this putative gene were analysed. They fell into two distinct categories: GOF *(Gain Of Function)* mutations and LOF *(Loss Of Function)* mutations affecting the same gene. To our surprise, GOF mutations were exclusive to the HAS group, and LOF mutations exclusive to the HSS group. The complete list of mutations of each type is given in Supplement 2.

### The gene and its products

Full description of structural, regulatory, functional, cellular and evolutionary characteristics of the novel gene, called *DARWIN** will be given in another paper (manuscript in preparation). We only give here a brief account of the most salient features. The *DARWIN* gene is 33 kb long, with 2 exons (8 kb and 10 kb respectively) separated by an intronic sequence of 15 kb. The CDS, 684 bp, is entirely comprised in exon 2, with a stretch of 10 CGA codons (polyArg)**, subjected to minor contraction/amplification in normal population, but to extreme variations in rare clinically affected subjects *(data not shown)*. The mature mRNA is remarkable by the length of flanking 5'– and 3'– UTR (the entire sequence of the gene is given in Supplement 3). The site of expression is restricted to a minute brain structure *(nucleus succumbens)* located in the posterior superior temporal cortex, an archaic structure related to the rhinencephalon. The resulting translation product undergoes multistep proteolytic processing yielding a mature arg-rich protein of 198 residues, called *darwinin*, exported in the portal vascular system of brain. The precise function of this factor is still unknown. Noteworthy is the fact that upon brain imaging during visual emotional stress a number of distant brain areas were lightened, in particular hypothalamic, thalamic and cortico-prefrontal regions. This indicates that the *darwinin* protein has an impact on several brain structures. Preliminary data (*not shown*) suggest that specialized synaptic structures enriched in *synapto-altruin* are preferential targets.

* Homologation by the HGNC is pending.

** A well established hallmark of the money gene family[18].

## Discussion

### *A genetic basis for two highly contrasted social deviant behaviours*

The most significant result obtained by the cooperative study led by the IASP Consortium is the finding that dominant hyperfunction of the *DARWIN* gene, produced by GOF mutations, is highly correlated with hyperaltruism (subjects with a SQ > +100), whereas hypofunction of this same gene, produced by LOF mutations, is highly correlated with the symmetrical opposite behavioural trait, hyperselfishness (subjects with an SQ < – 100).

It must be emphasized that this study was deliberately conducted in two non-overlaping classes of social behaviour. Such a bipolar mechanism immediately raises the question of the more common intermediary phenotypes that are displayed by 99% of the populations of the countries belonging to the G-8 organization. It is tempting to speculate that « hypomorphs » of the extreme phenotypes of HAS and HSS might result from combinations of subtle mutations, possessing a lesser drastic effect than the GOF or LOF mutations found in the extreme phenotypes. In favour of this hypothesis is the astounding number of SNPs that we observed in both coding and non-coding sequences of the *DARWIN* gene, which may be reasonably assimilated to a quantitative trait locus (QTL).

### *The gender paradox*

In the course of the sampling campaign, it appeared that the HS trait was much rarer in females than in males. This gender effect is readily explained by the location of the *DARWIN* gene in the pseudo-autosomal region of chromosome X, which escapes inactivation. Females are protected from the deleterious effect of recessive LOF mutations affecting only one chromosome X. Only the rare females who carry a LOF mutation on both X chromosomes are clinically affected. In contrast, in males, a single hemizygous LOF suffices to produce the full-blown HS syndrome. Conversely, since GOF mutations, are dominant, heterozygous females may be clinically affected. This explains the higher HAS/HSS frequency ratio in females.

### Profession bias

The distribution of GOF and LOF mutations was highly skewed when plotted against subjects' profession (*data not shown*): the former is significantly more frequent in doctors, nurses, nuns, social workers, caritative NGO members, whereas the latter is highly represented in hedge-fund managers, stock gamblers, car dealers, rigid bureaucrats. Suprisingly the distribution was gaussian among high-ranked members of the ecclesiastic hierarchy (data not shown)

### Evolutionary considerations

An ortholog of the *DARWIN* gene, also located on the pseudo-autosomal region of the X chromosome, with a 100% identical CDS, was found in non-human Primates. The social behaviours of chimpanzes (*Pan troglodytes*) and bonobos (*Pan paniscus*) are highly contrasted, the latter exhibiting a strange tendency to prefer love to war[19]. This induced us to compare the *DARWIN* gene in these species. A major difference was found in the number of active copies of the gene: one single copy in *sapiens sapiens* and in *troglodytes;* several copies (2 to 5) in *paniscus*. Quantitative PCR of *DARWIN* transcripts showed that the multiple copies of the gene were functional in bonobos, a result substantiated by the much stronger signal displayed on semi-quantitative western-blots of *darwinin* performed in extracts from *nucleus succumbens* in these animals (samples obtained by stereotaxic neurosurgical biopsy in compliance with the « *Non-Human Primate Experimentation Civil Rights Act* »). This provides a molecular explanation of the peculiar empathic and altruistic character of *P. paniscus*[19]. Using the recently published first map of CNVR (Copy Number Variable Regions)[20, 21], we found that the *DARWIN* gene is included in a CNVR only in *paniscus*, who are thus more protected against LOF/GOF induced extreme behavioural phenotypes. In contrast, *troglodytes* and *sapiens sapiens* do not benefit from this buffering effect, because their *DARWIN* gene is located in a region which is no longer subject to copy number variation. Moreover in the latter two species the single active *DARWIN* gene is surrounded by many unexpressed pseudo-genes, increasing the risk of LOF by gene conversion. These findings shed some light not only on the molecular basis of chimps and humans aggressiveness vs bonobos peacefulness, but also on evolutive divergence of genomes in great apes. It definitely places bonobos before the divergence between man and chimp.

### Societal implications

It is tempting to apply the monogenic dualistic model we have uncovered to the less extreme social behaviours manifested by 99% of human primates. However this model appears to be too simplistic to account for intermediate phenotypes, with a mixture of both HAS and HSS personality*, commonly observed in human primates. Monogenic models are enlightening, but rarely paradigmatic, since they do not provide ready applications to polygenic conditions[22]. Obviously other epistatic and epigenetic mechanisms must govern subtle combinations of altruism and egotism governing everyone's personality, and we agree with Frans de Waal[19] when he writes that « *Pure states are not nature's way* ».

It is also tempting to assume that the *DARWIN* gene is implied in social behaviours of more ancient species. Work is in progress to find ortholog(s) of the *DARWIN* gene along the phylogenic tree. Preliminary data indicate that some features of this gene are highly conserved in the remote genome (600 My) of *Cænorhabditis elegans*[23]. In this respect, it is appropriate to quote Charles Darwin himself, who wrote in 1859 this visionary phrase: « *Any animal whatever endowed with well-marked social instincts would inevitably acquire a moral sense or conscience, as soon as its intellectual powers had become as well or nearly as well developed as in man* »[24].

### Towards socio-therapy?

« *It has not escaped our notice that* » the dual model we have postulated immediately suggests a possible manipulation of the *DARWIN* gene[25]. Because of the exquisite quantitative regulation of this gene, classical gene therapy[26] would not be suitable, but drug-induced modulation of the products expression or activity could be envisioned. Clearly this poses serious ethical problems. Is it acceptable to try to soften predators or to harden individuals with excessive caritative proneness? This crucial issue deserves thorough consideration by ethicists. We bet that whatever will be the first statements edicted by official ethical committees, there will be enough HS/HA-balanced decision makers in the pharmaceutical industry to make the good choice.

## METHODS

See supplement 3 for full description

* Not speaking of the monstruous Jekyll/Hyde syndrome (OMEN 2222)[27].

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* Note: after submission of this manuscript we became aware of the paper by Tankersley, D., Stowe, C.J., Huettel, S.A. Altruism is associated with an increased neural response to agency. *Nat Neurosci* **10**, 150-151 (2007).

Supplements available upon request at fflori@edk.fr

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