**Supplementary TEXT T1:** Databases used in the study.

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| --- | --- |
| Category | Major source/reference |
| HTT interacting proteins | http://www.ncbi.nlm.nih.gov/pubmed/ (high throughput data, reviews and others) |
| Genes identified to modulate pathogenesis of HD in models of HD | http://www.ncbi.nlm.nih.gov/pubmed/ (high throughput data) |
| HTT co-expressed genes | <http://coxpresdb.jp> [and <http://www.GeneFriends.org> [46,47] |
| Genes altered in the caudate of HD patients | EBI Array Express entry E-AFMX-6, processed data from Hodges A et al., 2006, Hum Mol Genet. 15, 965-977 [48] |
| Polymorphic variations in genes that modulates age at onset | http://www.ncbi.nlm.nih.gov/pubmed/ (reviews mainly) |
| Target Validation Score (TVS): Genes that may be targets for HD treatment taken from HD Cross Road website and published | Kalathur RKR et al., 2012, BMC Neurology, 12, 47 [89] |
| Tissue specific expression of genes, targets of FDA approved drugs and probable targets of drugs | <http://www.proteinatlas.org/>, Uhlén M et al., 2015, Science, 347, 1260419 [56] |
| Enrichment analysis for (a) Biological processes (BP) defined by Gene Ontology (GO), (b) Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways | GeneCodis3 (<http://genecodis.dacya.ucm.es/>), Tabas-Madrid D et al., 2012, Nucleic Acids Res. 40, (Web Server issue):W478-W483 [55] |
| Gene Ontology (GO) descriptors for Biological Processes | Data downloaded from <http://asia.ensembl.org/biomart/martview/>, accessed on Sept 4, 2012 |

**Supplementary TEXT T2:** HTT interacting proteins.

To identify function(s) of HTT, interacting partners of HTT have been identified in Yeast 2 Hybrid (Y2H) assay [16-18] and affinity pulls down followed by mass spectrometry assay [18]. In another approach, aggregates of mutant HTT are isolated, separated on gel and aggregate associated proteins are identified by mass spectrometry [22]. Faber et al identified 13 proteins and named as Huntington Yeast two Hybrid Proteins (HYPs) in Y2H assay [16]. Considering that Y2H assay is subject to high rate of false positives [23], it is necessary to establish physical interaction of the protein with HTT by a second method and has been observed in several cases. Some of these interactions are subsequently validated functionally to establish that the HTT interacting proteins can modulate the HD pathology at least in cultured cells or small animal models of HD or by a second method like Immuno Precipitation (IP); for example see [STR1]. In a similar Y2H assay, Goehler et al. identify 19 HTT interacting proteins, 4 of them was identified earlier. Most of these new proteins were confirmed by additional IP assay. Two hundred thirty four proteins are identified either in high stringent conditions of Y2H (104 proteins) or affinity pull down followed by mass spectrometry (130 proteins) using cell extracts from different types of cells. Only 4 proteins are common in these two methods. Eight randomly chosen proteins are confirmed by IP out of 11 proteins tested. Thus, only ~63% of the proteins obtained by high throughput assay are true interacting partner of HTT. In an attempt to establish functional role of the interacting proteins, randomly chosen proteins obtained in these two methods were tested in the fly model of HD. Either specific gene was over expressed together with mutant HTT or mutant HTT was expressed in flies with mutations in fly homologous genes. About 80% of the proteins (48/60) alter toxicity in the fly model showing that HTT interacting proteins might modulate HD pathogenesis [18]. From these result, we collected 154 HTT interacting proteins and designated as validated HTT interacting proteins. One hundred seventy four proteins were identified in high throughput assays but not confirmed subsequently by another method. Recently, more than 1200 proteins have been identified in high through put experiments [19-21]. From various published data, we have collated 328 proteins out of which 154 proteins were identified in more than one experiment or identified by co-immunoprecipitation (Co-IP) or functional relevance of the interacting partners of HTT protein in HD pathogenesis were determined as described above. Among the 174 non-validated proteins [18]**,** 68 proteins were also identified in any one of the published paper recently. We further collated HTT interacting proteins which were identified in more than one experiments [19-21]; there were 132 proteins. Besides two protein namely PRKRA, GNB2L1 were confirmed by Co-IP. In most of the studies, N-terminal human HTT with expanded polyQ length in the pathological ranges were used as bait to identify the mouse proteins that interact with it. These 355 proteins are either identified in more than one independent experiment; confirmed the interaction by co-IP or identified in large scale mass spectrometric based assays and functional relevance has been shown in models of HD. Recently, Caveolin-1 (CAV1) has been shown to interact with mutant HTT. Neurons expressing mutant HTT showed accumulation of cholesterol and compromised caveolar-related post-Golgi trafficking from endoplasmic reticulum/Golgi to plasma membrane. It has also been shown that reduced *CAV1* expression in a mouse model of HD rescues the cholesterol phenotype in neurons and significantly delays the onset of motor decline and development of neuronal inclusions [27]. It has also been shown that Methyl-CpG binding protein 2 (MeCP2) interacts preferentially with HTT in the nucleus compared to that of in the cytoplasm in cell and mouse model of HD. MeCP2 binds strongly with the Brain-Derived Neurotrophic Factor (BDNF) in the presence of mutant HTT. Knocked down of *MeCP2* in cells expressing mutant HTT increases the expression of *BDNF* [24]. Role of MeCP2 in axonal transport of BDNF has been observed to be mediated through HTT and its interacting partner HAP1 [30]. This result shows that MeCP2 might have a role in pathogenesis of HD. HIP14 homolog HIP14L/ ZDHHC13 was first identified based on its high amino acid sequence similarity to HIP14 and was later shown to be a bona fide HTT interactor that interacts weekly with mHTT [31,STR2]. Knockout mice for *Hip14L/ZDHHC13* exhibit neuropathological and behavioral features of HD indicating a functional role of the protein in HD pathogenesis [29]**.** EZR, PIK3R1 and RAC1 were identified to interact with HTT[18].Recently, it has been shown that knocked down of *EZR*, and *RAC1* protects mutant HTT induced toxicity, thus EZR and RAC1 are considered to be enhancer of mutant HTT induced toxicity, while knocked down of *PIK3R1* enhances the toxicity and considered to be a suppressor of HD pathogenesis [26]. Ubiquilin-2 has been shown to associate with the aggregates of mutant HTT. Ubiquilin proteins are known to act as chaperones and help in protein degradation. Presence of Ubiquilin-2 with the aggregates of mutant HTT throughout the progression of disease in mouse model of HD indicates that co-localization of ubiquilin-2 with the aggregates does not facilitate aggregate removal [28]. We combined all the data and catalogued 361well characterized HTT interacting proteins. This data is shown in the Supplementary Table S1**.** While we were preparing the manuscript, additional about 100 additional interacting partners of HTT have been reported [32]and not included in the present manuscript**.** Sixteen proteins were common to the validated list we made.

**Supplementary TEXT T3:** Genome wide identification of Modulators of HD pathogenesis**.**

Several small animal models of HD have been utilized to identify modulators of HD pathogenesis by using genome wide knocked down of genes and studying the effects of mutant HTT for formation of aggregates and/or toxicity. These models include *S. cerevisiae* (Yeast), worm (*C. elegans),* fly (*D. melanogaster)* and human/mouse cells in culture. The small nematode, Caenorhabditis elegans (*C. elegans*, a small nematode), when transfected with Green Fluorescent Protein (GFP) tagged gene coding for expanded Polyglutamine (poly Q) protein exhibits an age and poly Q length dependent aggregates similar to that observed in brains of HD patients and different cell and animal models [STR3]. Using *C. elegans* model of poly Q expansion disease, knock down of 4 worm gene namely *Hsp70* genes (*F26D10.3* and *C37H5.8*), a single J domain gene (*F18C12.2*) and *hsf-1* (*Y53C10.A12*) resulted in increase of aggregates formed by the mutant HTT; while wild type HTT did not result any such effect. Using the RNAi library for 16,757 genes out of 19,427 total genes in *C. elegans*, 186 genes were identified to induce an earlier onset of aggregation phenotype. Since knocked down of the genes results in early formation of the aggregates, it is expected that these genes when over expressed help directly or indirectly slowing down the aggregation processes. Thus these genes could suppress formation of mutant HTT aggregates and are considered to be “suppressor” of aggregates formed by mutant HTT. On the basis of functional categorization, these proteins belong to broad functional classes like RNA metabolism, protein synthesis, protein folding, protein trafficking, and components of the proteasome. Among these genes in C. *elegans*, 16 human homolgues are known [34]. Subsequently, knocking down the human orthologs of the C. elegans genes by using shRNA constructs, it was shown that 26 human orthologs of the 186 *C. elegans* modifier genes had effect on the aggregates of mutant HTT. In addition, it was shown that eukaryotic translation initiation; elongation and termination factors also modified the aggregates [38].

There are few studies using the Drosophila model of HD for screening of the genes that modulate aggregates formed by mutant HTT. The genes were classified as “suppressor” or “enhancer” depending on their ability to suppress or enhance the process of aggregate formation. Expression of mutant HTT in Fly with knocked down specific gene, when increases mutant HTT aggregates, the specific gene is considered to be “suppressor”. When the aggregates are reduced in fly with the background of gene knocked down, the gene is considered to be “enhancer”. Using the genome wide knock down of the fly genes, many repressor or enhancer were identified [37,39]. Taking data obtained in yeast models [33]**,** C. elegans model [34,40], fly model for HD[35-37], and human cell models[38,41]and human orthologues of the genes identified in small animal models including yeast, we collected human genes that modulate HD pathogenesis. We have omitted those genes which had opposite trend in different experiments and pseudogenes. For example AFG3L1/AFG3L1P was a pseudo gene and omitted from the list. Two genes, namely HSPA8 and UFD1L were identified but showed opposite trend in two different experiments and was not considered in the list. However if a gene was reported in more than 2 experiments, we have taken the result that was consistent in 2 experiments. For example, human homologue NAG/NAGLU was identified as suppressor in two studies, while in one study it was considered to be an enhancer. Thus in our list we considered the gene to be a suppressor. Altogether 594 unique gene was collected. Human homologous genes of yeast, fruit fly, and *C. elegans* were identified in these studies that are likely to modulate the HD phenotypes. ‘‘Enhancer’’ is defined genetically as the gene that causes reduction in aggregates after RNAi mediated knock down of the gene in the assay. Conversely, ‘‘suppressor’’ is defined as the gene that causes increased aggregates formation when its expression is knocked down [37,39]. Based on this criterion 240 genes were identified as “enhancer” and 359 genes were designated as “suppressor” of HD pathogenesis. The result is shown in the Supplementary Table S2**.**

Recently, two additional studies reported genes that modulated HD pathogenesis and not included in our list of genes [STR4,STR5].

**Supplementary TEXT T4:** Genes co-expressed with wild type *HTT.*

***HTT* co-expression genes**

Networks by the genes co-expressed together provide important information regarding the function of genes and their regulation. Genes with relatively unknown functions can be characterized if they co-express with genes with known functions. It has been shown that genes which are co-expressed together are likely to be functionally related [42-44]. We have used two independent databases to identify the genes which are expressed together with wild type *HTT*.

**Co-expressdb database**

Searching co-expression database (<http://coxpresdb.jp>) [45] with *HTT* gene (Entrenz Gene ID 3064) and setting a limit of 1000 genes (down loaded on April 9, 2013), it was observed that 231 genes (excluding *HTT*) were co-expressed with *HTT* in either more than 1 species or in 2 independent human samples. The Mutual Rank (MR) was chosen as ≤1000 indicating the strong correlation as described [59]**.** Among these genes, two genes namely *MIR600HG* (miRNA-600 containing gene) and *WASH3P* (pseudo gene) were further removed from the list. Thus, there are 229 genes (excluding *HTT*) co-expressed with wild type *HTT*. For example, Adducin 1 (alpha) gene (*ADD1*) was co-expressed with *HTT* having MR= 86.1 and 8.1 in two independent human samples. Similarly, exportin 6 (*XPO6*) and mediator complex subunit 15 (*MED15*) genes were co-expressed with *HTT* in two human samples and four other organisms. MR values for *XPO6* were 267.6, 543.5, 675.2 and 984.8 in Mcc (monkey), Mmu (mouse), Gga (chicken) and Dre (zebra fish) respectively. MR values for *MED15* were 346.6, 10.7, 559.4 and 526.4 in Mcc (monkey), Mmu (mouse), Gga (chicken) and Dre (zebra fish) respectively. All together 113 genes including *HTT* gene were co-expressed in two human samples (MR ≤1000) and 117 genes were co-expressed with *HTT* in human samples and at least any other organism (MR≤1000). Genes co-expressed with *HTT* in at least two independent human and other species together with their chromosomal location are shown in the Supplementary Table S3**.** It is to be mentioned that three gene symbols namely *MLL*, *MLL2* and *MLL4* having Entrenz Gene IDs 4297, 8085 and 9757 respectively were designated as myeloid/lymphoid or mixed-lineage leukemia (trithorax homolog, Drosophila), myeloid/lymphoid or mixed-lineage leukemia 2 and myeloid/lymphoid or mixed-lineage leukemia 4. However, when we searched the NCBI, Entrenz Gene IDs 4297, 8085 and 9757 correspond to lysine (K)-Specific Methyltransferase 2A (*KMT2A)*, lysine (K)-specific methyltransferase 2D (*KMT2D*) and lysine (K)-Specific Methyltransferase 2B (*KMT2B*) respectively. We thus replaced these genes with new symbols corresponds to the Gene IDs.

**GeneFriends database**

We have used GeneFriends database (<http://www.GeneFriends.org>), [47] an online resource to identify the genes co-expressed with wild type *HTT*. In this database, RNA sequencing data for gene expression has been used and provides the co-expressed protein coding genes, non-coding genes including microRNA, anti-sense RNA and pseudogenes. Positive correlation as well as negative correlation with *HTT* is provided as an output. We have omitted the non-coding genes and only positively correlated genes (correlation co-efficient ≥ +0.445) were collected. There are 221 *HTT* co-expressed genes and shown in the Supplementary Table S4.

**Supplementary TEXT T5:** Genetic modifiers of age at onset (AAO) of HD pathogenesis.

Age at Onset (AAO), defined as the time of appearance of the first symptom(s) such as motor defects and cognitive impairment, and has been shown to inversely correlate with number of CAG repeats in the expanded allele of *HTT* gene. Investigations with large number of adult onset patients reveal that expanded CAG repeat number explains approximately 56% of the variations in AAO of motor signs. However, CAG repeat number did not explain variations in psychiatric phenotypes. Evidences are available to show that various genetic modifiers [49,50] and modifiable non genetic modifiers [STR6-STR9] alter AAO. In early studies, variations in different candidate genes have been reported to modify AAO. Polymorphic TAA variations in 3’-UTR of *GRIK2* gene, variations in *CNR1/CB1*, *PPARGC1A*, *HAP1*, *GRIN2A*, *GRIN2B*, *ATG7*, *ADORA2A*, *OGG1*, *TFAM*, *APOE*, *CA150* (*TCERG1*), *BDNF*, *UCHL1*, *TP53* and *DFFB* have been shown to modulate AAO [STR10 and references there in]. However, most of the results were not replicated in independent study with patients originated from different genetic backgrounds. Besides, the association was not observed in many cases when the sample size was increased with sufficient statistical power and statistical corrections for multiple testing were taken into account. Non replication of the association of genetic variations with AAO could, in principle, be due to genetic background of the patients. In recent time, unbiased Genome wide searches were made to identify the genetic loci that modify the age at onset. Family based linkage study identifies various chromosomal regions that may alter AAO. These regions include 2p25 (LOD score 4.29), 2q35 (LOD=3.39), 6q22 (LOD=2.48), 5p14 (LOD=3.31) and 5q32 (LOD=3.14). These regions harbor hundreds of genes [STR11]. Other loci identified were 6q23-24 [STR12], 4p16 [STR13,STR14], 6q21-23 (LOD=2.29), 6q24-26 (LOD= 2.28) [STR14]. Although variations of CAG repeat at the normal allele of *HTT* gene, variations in CCG repeats flanking the CAG repeats and other marker in *HTT* gene have been shown to modify AAO, haplotype analysis with various genetic markers at 4p16.3 argue against the involvement of these variations on AAO [STR15]. However, in a recent study a specific haplotype at 4p16.3 has been shown to be associated with AAO. In addition, the authors also reported involvement of polymorphisms in monoamine oxidase A (*MAOA*) and catechol-O-methyltransferase (*COMT*) genes that modified cognitive impairment and psychiatric symptoms in HD [STR16].Engineered knock-in mouse model of HD harboring human synteny region of human 6q23-26 was used to evaluate the role of this linked region **[**STR11,STR12**]** in modulation of AAO. Body weight, CAG instability, level of DARPP-32 and aggregates of mutant HTT were modified in this transgenic mice [STR 17] indicating possible role of this genetically linked region in AAO.

In recent studies, genetic variations in the promoters of protein coding genes have been identified to influence the AAO. Promoter variation in Neuropeptide Y (NPY) receptor NPY2R has been associated with AAO. Functional luciferase reporter assay for detection of the influence of such promoter sequence variations (single nucleotide polymorphic marker rs2234759) reveals that specific allele that increased the expression of *NPY2R* in vitro was associated with delayed AAO. Thus increased expression of *NPY2R* is likely to delay manifestation of the symptoms and provides protection. Additional experiment with cultured cells provided functional involvement of the gene in HD pathogenesis. Treatment with NPY or agonist of NPY2R protects cells from apoptotic death [92]. Similarly, the polymorphic variation (rs13102260, G/A) at the putative promoter of *HTT* gene (-139 position from transcription start site) has been shown to be associated with AAO. This variation is localized in the binding site of transcription factor NF-ƙB. Prevalence of minor allele “A” frequency varies from 0.042 in Caucasian European to 0.411 in African Yorban. Binding of NF-ƙB to the promoter sequence was observed *in vivo* and *in vitro* and such binding activates the expression of *HTT*. It has also been shown that recruitment of NF-ƙB to this promoter sequence was significantly higher in striatum, the main affected tissue in HD compared to other tissues. It remains unknown whether the expression of *NF-ƙB* was different in different regions of brain. However, this result indicates the binding of NF-ƙB and regulation of genes by NF-ƙB may be relevant in HD. Binding of NF-ƙB to the promoter as well as activation of *HTT* gene was dependent on the DNA sequences at the promoter; sequence containing “A” allele that reduces the binding of NF-ƙB and expression of *HTT* gene. Allele specific modulation of AAO was observed in two different cohort of HD. It has been observed that when the A allele was linked to the wild type *HTT*, AAO was reduced, while A allele linked with mutant *HTT* resulted in delayed AAO [51]. This result indicates that reduction of wild type *HTT* enhances HD pathogenesis, while reduction of mutant *HTT* provides protection. Exogenous over expression of wild type *HTT* has been shown to protect mutant HTT induced toxicity in various models of HD. In models of HD, exogenous expression of wild type *HTT* protects cells from toxicity induced by the mutant HTT. Reduction of wild type *HTT* enhanced toxicity of the mutant *HTT.* Similar result has also been reported recently using the Yeast model of HD. All these results support the notion that wild type *HTT* is an anti-apoptotic/pro survival gene [STR18-STR23]**.** Reduction of mutant *HTT* by allele specific siRNA has been shown to protect the mutant *HTT* effects and considered to be an approach for HD treatment [STR24]. Polymorphic variation (rs2742976, G/A) at the putative promoters (-293 form the TSS) of transcription factor *E2F2* has been shown to be a potential modifier of AAO. This variation has been localized within the putative STAT transcription factor binding site. It has also been shown that expression of *E2F2* in lymphocytes HD patients with T/T homozygous was significantly lower compared to that of the patients with G/G homozygous [52]. Role of E2F2 in HD pathogenesis remains to be established. Very recently, genome wide association studies identify various loci to be associated with AAO. The most significant SNPs associated with AAO were rs146353869 (A/C) and rs2140734 (G/T) on chromosome 15 with p= 3x 10-20 and 7.1 x 10-14 respectively. Other loci rs1037699 (chromosome 8, T/C polymorphism, p=2.7x 10-8), rs147804330 (chromosome 2, A/G polymorphism, p=7.6 x10-7), rs144287831 (chromosome 3, C/T polymorphism, p=2.2x 10-7), rs11133929 (chromosome5, C/T polymorphism, p=2.1x 10-7), rs11061229 (chromosome 12, C/G polymorphism, 6.7x10-7), rs261453 (chromosome 13, A/C, 9.0X 10-7), rs143367341 (chromosome 21, G/A polymorphism, 2.5 x 10-7) [53]. Copy-number variation (CNV) of *SLC2A3* gene, coding neuronal glucose transporter GLUT3 could modulate AAO in HD. It is observed that increased dosage of *SLC2A3* delayed AAO in an HD cohort of 987 individuals [54]. On the basis of replication of some of the studies, studies with sufficient statistical power, or genes with functional implications in HD pathology, we have taken genes namely *OGG1*, *PPARGC1A*, *NPY*, *NRF-1*, *GLUT3/ SLC2A3*, *HTT*, *ATG7*, *CNR1*, *NPY2R*, *GRIN2A*, *HAP1* and *ADORA2A* for further study.

**Supplementary Table TEXT T6:** HD associated genes.

**HD associated genes**

Combining data from various resources, we identified proteins that are associated with HD. Among the various categories like HTT interacting proteins, proteins identified to alter pathogenesis of HD in various models where genes were knocked down by siRNA (Hdsi), *HTT* co-expressed genes (co-express db), expression of genes alter in caudate of HD patients (Caudate Up/Down) and genetic variations that modulate AAO (for detail please see the material and methods (sections 2.1-2.5), we considered only those genes which are reported to involve in at least two categories to be associated with HD. For example, *ADD1* belongs to 4 categories namely Caudate UP, Co-expressdb, Hdsi and HTT interacting protein. Thirty eight proteins belong to 3 of the seven categories. Four hundred twenty four proteins were identified at least in 2 of the seven categories (Supplementary Table S6). All together, these 463 proteins are considered to be associated with HD. In addition to these data, there are several studies where gene manipulation in mice results in modulation of HD pathogenesis. Number of HTT interacting proteins was shown to modify the HD pathogenesis, mainly in the fly model of HD [18]. We extended such approach by comparing genes identified in Genome wide siRNA screening as elaborated in Supplementary TEXT T3. Searching for HTT interacting proteins which were either suppressor or enhancer, we identified additional 47 HD associated proteins. These proteins interact with HTT and in models of HD shown to be modulators of HD pathogenesis (Supplementary Table S6). We designated 511 HD associated genes altogether.

Activation of PRKAA1 (AMPK1/ AMPKα1) enhanced the level of oxidative stress in cell model, primary neurons of R6/2 mice, and in the striatum of two different HD mouse models (R6/2 and Hdh (150Q/+). Inhibition of AMPK1 reduced the level of oxidative stress and neuronal toxicity indicating possible role of AMPK1 in HD pathogenesis [STR25]. Expression of *NGFR/ p75NTR/TNFRSF16* increased in mice models and postmortem brains of HD patients. Knocked down of *NGFR* in HD model prevented cognitive decline and neuronal plasticity was rescued by inhibiting the NGFR signaling [STR26,STR27]. Glutathione peroxidase 6 (*Gpx6*), an age regulated gene, has been identified to modulate the toxicity of mutant HTT in synthetic lethal screening. Over expression of *Gpx6* alleviates behavioral and molecular phenotypes associated with a mouse model of HD [STR 28]. Ube3a ubiquitin protein ligase E3A (ubiquitin protein ligase E3A) [STR29,STR30], USP14 ubiquitin-specific protease-14 [STR31] were also implicated in HD pathogenesis. Further *APAF1*, *DRD1*, *ATM*, *HDAC1*, *HDAC3*, *SQSTM1* and *SNCA* were shown to modulate HD pathogenesis. Knock of down of *APAF1* or treatment with pharmacological Apaf1 inhibitor SVT016426 reduced polyQ induced aggregation and apoptotic cell death in cell model of HD. APAF1 has been shown to interact with HTT as well as Hsp70; such interaction was inhibited in presence of the inhibitor APAF1 [STR32]. Expression of *APAF1* was increased in the caudate of HD (Supplementary Table S5B). Thus, APAF1 is likely to be involved in HD. R6/1 mice treated with antagonist (SCH23390) Dopamine D1 receptor (DRD1) and ADORA2A /A2AR protects the effects of transgenic HD mice [91]. Expression of *DRD1* is decreased in HD(Supplementary Table S5A).Expression of *ATM* is decreased in the caudate of HD (Supplementary Table S5B). Double cross mice of Atm heterozygous null allele onto BACHD mice expressing full-length human mutant HTT, it has been shown that reduced ATM decreased multiple behavioral abnormalities and improved partially neuropathology. Besides, ATM inhibitors reduced mutant HTT induced death of rat striatal neurons and induced pluripotent stem cells derived from HD patients [STR33]. SQSTM1/p62 interacts with wild type HTT [STR34]. Deletion of *SQSTM1/p62* in HD model led to longer life span and reduced nuclear inclusions [STR35]. Expression of *SQSTM1/p62* was increased the caudate of HD (Supplementary Table S5A). In R6/2 mice treated with HDAC inhibitors specific for HDAC3 and HDAC1 recover the gene expression phenotype. In fly model of HD such treatment improves the degeneration of eye observed in HD model [STR36]. Over expression α-Synuclein (*SNCA*) or deletion of *SNCA* increased or decreased respectively the pathogenesis in mouse models of HD [98]. Expression of *SNCA* is decreased in the caudate of HD (Supplementary Table S5A).

In addition to 511 HD associated genes, we add another 12 gene (*PRKAA1/AMPK*, *NGFR*, *Gpx6*, *Ube3a*, *USP14*, *APAF1*, *DRD1*, *ATM*, *HDAC1*, *HDAC3*, *SQSTM1* and *SNCA*); total 523 HD associated genes are catalogued and analyzed further.

**Supplementary TEXT T7:** Target Validation Score (TVS) based on experimental data and data collected from Kalathur RK et al., [89].

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| --- | --- |
| Experimental evidence for HD modifying effects | TVS |
| Drug or a gene therapy modulating the gene (target) has demonstrated efficacy in a Phase 3 clinical trial | 5.0 |
| Drug or a gene therapy modulating the gene (target) has demonstrated efficacy in a Phase 2 clinical trial or the HD phenotype in a non-rodent large animal mammalian model for HD (e.g. primate or sheep) is improved upon manipulation of the gene | 4.5 |
| Improvement of the HD phenotype in rodent models was observed using a therapeutically relevant drug or genetic intervention that is highly specific for this gene | 4.0 |
| Gene (target) is associated with HD in a linkage study in humans, or when the manipulation of the gene leads to changes in the HD phenotype in rodent models. | 3.5 |
| Causal relationship with HD observed in an in vitro cell culture or lower organism model of HD upon genetic or pharmacologic modification | 3.0 |
| Genes that show an altered pathway or functional activity in HD | 2.5 |
| Gene with a change in expression or cellular distribution in HD, or if the corresponding protein binds to mutant Htt. | 2.0 |
| Genes present and active in HD-relevant brain regions or linked to a HD-relevant biological mechanism | 1.0 |
| Genes implicated in neurodegeneration or polyglutamine dysfunction based on genome-wide screens | 0 |

**Supplementary TEXT T8:** HD associated genes, which are either targets of FDA approved drugs or are potential drugs potential new drugs not catalogued in HD Research *Crossroads (*http://www.hdresearchcrossroads.org/).

To gather comprehensive information of the proteins which are targets of known drugs or potential drugs, we gather information from diverse sources. For identification of functions of the gene, especially the biological processes annotated in Gene Ontology (GO), we used Gene Ontology database down loaded from BioMart (<http://www.ensembl.org/biomart/martview/3a7414d2ce1af7d18191aa71e329251b>). We further searched online Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways from (<http://www.genome.jp/kegg/pathway.html>). Besides, expression of HD associated genes in 32 normal major tissues was collected from the data published by Uhlén et al., [56].On the basis of expression, genes were categorized as (a) expressed in all tissues (mRNA detected in all tissues with reads per kilobase per million (FPKM) >1, (b) group enriched (levels of mRNA at least 5 times those in a group of 2-7 tissues), (c) Mixed (detected in less than 32 tissues equally), (c) tissue enhanced (detected 5 times more than the average of expression of all tissues), (d) tissue enriched (levels of mRNA was at least 5 times higher than those in all other tissues) and (e) not detected (FPKM < 1) as described [56]. Target Validation Score (TVS) was taken from the published data (Supplementary TEXT T7, 89) originally derived from HD Research Crossroads *(*<http://www.hdresearchcrossroads.org/>).

To identify whether there is any relation between expressions of genes and target of drugs, we analyzed the FDA approved drugs and their expression in different tissues. Expression data was downloaded from http://www.proteinatlas.org/ as reported [56]. Number of FDA approved gene/protein targets of drug was 625. We have clubbed together group enriched, tissue enhanced and tissue enriched categories. Comparing FDA approved drug targets and their expressions, we observed that majority of the FDA approved drug target genes (~56%) were tissue enhanced/enriched/group enriched indicating genes which expressed mainly in specific tissue or a group of tissues are target of drug compared to housekeeping genes (~ 28% of drug targets are housekeeping genes). On the basis of this observation, we concentrate only on the genes that are enriched /enhanced in brains as the possible targets for HD.

**Supplementary TEXT T9:** Other targets not included in the main text.

In the main text of the manuscript, we have concentrated on the HD associated proteins, which are either targets of FDA approved drugs or potential drug targets and expression was enriched/enhanced in normal brain. However, in this section, we discussed other targets with or without TVS and mainly housekeeping genes as possible targets.

SLC18A2, a member of solute carrier family18, also known as VMAT2, is a vesicular monoamine transporter that involves in accumulating cytosolic monoamines in synaptic vesicles. Tetrabenazine (TBZ), an inhibitor of SLC18A2/VMAT2, is the first drug approved by the FDA treatment of HD patients, especially reduces the chorea by depleting monoamines like dopamine [STR37,STR38]. Reorganization of various dopamine receptors and dopamine level alter in HD resulting in toxic effects of mutant HTT [STR39,STR40]. SLC18A2/VMAT2 is ubiquitously expressed in all 32 tissues. SLC18A2/VMAT2 is associated with 26 biological processes namely transmembrane transport (GO:0055085), glucose homeostasis (GO:0042593), GO:0007568 (aging), response to herbicide (GO:0009635), post-embryonic development (GO:0009791), neurotransmitter secretion (GO:0007269), response to cocaine (GO:0042220), locomotory behavior (GO:0007626), response to corticosterone stimulus (GO:0051412), synaptic transmission (GO:0007268), response to starvation (GO:0042594), response to zinc ion (GO:0010043), response to amphetamine (GO:0001975), cellular response to drug (GO:0035690), insulin secretion (GO:0030073), death (GO:0016265), endocytic recycling (GO:0032456), monoamine transport (GO:0015844), negative regulation of neurotransmitter transport (GO:0051589), cellular response to ammonium ion (GO:0071242), response to toxic substance (GO:0009636), serotonin transport (GO:0006837), response to metal ion (GO:0010038), neurotransmitter transport (GO:0006836) and response to drug (GO:0042493). SLC18A2/VMAT2 is associated with 7 KEGG pathways namely amphetamine addiction (KEGG: 05031), cocaine addiction (KEGG: 05030), alcoholism (KEGG: 05034), synaptic vesicle cycle (KEGG: 04721), serotonergic synapse (KEGG: 04726), dopaminergic synapse (KEGG: 04728) and Parkinson's disease (KEGG: 05012).

Genetic variation in monoamine oxidase A (*MAOA*) gene has been shown to modulate AAO [STR16]. Abnormal activities of MAOA and MAOB have been implicated in HD pathogenesis. Increased expression of the genes has been observed in models as well as in post-mortem brains of HD patients. Long term inhibition of MAOA by pharmacological inhibitor clorgyline in YAC128 mouse model of HD, recovered the defects in neurotransmitters dopamine, serotonin, and norepinephrine and reduced anxiety and depressive-like behavior [STR41]. Inhibition of MAOA and MAOB resulted in decreased cell death in pluripotent stem cell (hiPSC) derived from HD patients [STR42]. This result shows that inhibitors of MAOA and MAOB could be used as potential therapeutic approach for HD treatment. MAOA and MAOB are associated with 10 and 13 BPs respectively. BPs xenobiotic metabolic process (GO:0006805), oxidation-reduction process (GO:0055114) and small molecule metabolic process (GO:0044281) are common between them. MAOA is associated with unique BPS namely cellular biogenic amine metabolic process (GO:0006576), synaptic transmission (GO:0007268), neurotransmitter secretion (GO:0007269), behavior (GO:0007610) neurotransmitter catabolic process (GO:0042135), neurotransmitter biosynthetic processes (GO:0042136) and dopamine catabolic process (GO:0042420). MAOB is associated with unique BPs response to toxic substance (GO:0009636), response to aluminum ion (GO:0010044), response to selenium ion (GO:0010269), negative regulation of serotonin secretion (GO:0014063), response to lipopolysaccharide (GO:0032496), response to drug (GO:0042493), response to ethanol (GO:0045471), positive regulation of dopamine metabolic process (GO:0045964), response to steroid hormone stimulus (GO:0048545) and response to corticosterone stimulus (GO:0051412). Even though, these two proteins are associated with different BPs, they are associated with 13 common KEGG pathways namely metabolic pathways (KEGG:01100), tyrosine metabolism (KEGG:00350), tryptophan metabolism (KEGG:00380), drug metabolism - cytochrome P450 (KEGG:00982), dopaminergic synapse (KEGG:04728), cocaine addiction (KEGG:05030), amphetamine addiction (KEGG:05031), alcoholism (KEGG:05034), glycine, serine and threonine metabolism (KEGG:00260), arginine and proline metabolism (KEGG:00330), histidine metabolism (KEGG:00340), phenylalanine metabolism (KEGG:00360) and serotonergic synapse (KEGG:04726).

Activation of PRKAA1 (AMPK1/ AMPKα1), catalytic subunit of 5'-prime-AMP-Activated Protein Kinase (AMPK) enhanced the level of oxidative stress in cell model, primary neurons of R6/2 mice, and in the striatum of two different HD mouse models of HD. Inhibition of AMPK1 reduced the level of oxidative stress and neuronal toxicity indicating possible role of AMPK in HD pathogenesis [STR43]. Contradictory result showing activation of AMPK protects the toxicity in diverse models of HD has also been published. It was proposed that activation of AMPK in early stage of the disease may be protective. It has further been shown that low-dose metformin treatment that activates AMPK protects the effects of mutant HTT in models [STR44-STR46]. PRKAA1 (AMPK1/AMPKα1) is a target of FDA approved drug without having TVS. The gene coding for the protein is ubiquitously expressed in all 32 tissue. PRKAA1 gene is associated with 43 BPs and 15 KEGG pathways (Supplementary Table S9A). Relevant BPs associated with HD pathogenesis are transcription, protein phosphorylation, fatty acid biosynthetic process, cholesterol biosynthetic process, autophagy and others. Similarly, pathways like regulation of autophagy (KEGG: 04140), mTOR signaling pathway (KEGG: 04150), Insulin signaling pathway (KEGG: 04910) and other (Supplementary Table S9A)are known to involve in HD.This analysis shows that PRKAA1 (AMPK1/AMPKα1) could be a possible target for HD treatment.

There are several reports to show that inhibitors of histone deacetylase improve the HD pathogenesis in different models of HD. In R6/2 mice treated with HDAC inhibitors specific for HDAC3 and HDAC1 recover gene expression phenotype. In fly model of HD such treatment improves the degeneration of eye observed in HD model [STR36] indicating role of HDAC3 and HDAC1 in HD pathogenesis. This observation has been confirmed in many other studies [STR47- STR49] and reviewed [STR49]. HDAC2 was identified in genome wide screen as modulator of HD [37] and the expression was decreased in the caudate (Supplementary Table S5A). Decrease in HDAC2 by inhibitor protects the toxic effects of mutant HTT [51]. HDAC1, HDAC2 and HDAC3 are associated with 31, 37 and 17 biological processes respectively. BPs include chromatin modification (GO:0016568), transcription, DNA-dependent (GO:0006351), negative regulation of cell cycle (GO:0045786) and neurotrophin TRK receptor signaling pathway (GO:0048011) and cell cycle, known to involve in HD pathogenesis. HDAC1, HDAC2 and HDAC3 are associated with 13, 11 and 3 KEGG pathways respectively (Supplementary Table 9A). These genes ubiquitously express in all normal tissues and altered expression has been observed in HD. HDC1 had TVS 4; HDAC2 and HDAC3 had TVS 1. All 3 genes are known targets of FDA approved drug.

HTT had TVS 4. Allele specific down regulation of the mutant *HTT* by antisense modified oligo has been used to modify pathogenesis of HD [STR24, STR52 and STR53].

**References for the Supplementary TEXT**

**Reference number within third bracket is same as that of in the main text**

**Additional references (not included in the main text) are denoted by “STR”**

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