Evidence for gliadin antibodies as causative agents in schizophrenia.

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Abstract

Antibodies to gliadin, a component of gluten, have frequently been reported in schizophrenia patients, and in some cases remission has been noted following the instigation of a gluten free diet. Gliadin is a highly immunogenic protein, and B cell epitopes along its entire immunogenic length are homologous to the products of numerous proteins relevant to schizophrenia ($p = 0.012$ to 3e-25). These include members of the DISC1 interactome, of glutamate, dopamine and neuregulin signalling networks, and of pathways involved in plasticity, dendritic growth or myelination. Antibodies to gliadin are likely to cross react with these key proteins, as has already been observed with synapsin 1 and calreticulin. Gliadin may thus be a causative agent in schizophrenia, under certain genetic and immunological conditions, producing its effects via antibody mediated knockdown of multiple proteins relevant to the disease process. Because of such homology, an autoimmune response may be sustained by the human antigens that resemble gliadin itself, a scenario supported by many reports of immune activation both in the brain and in lymphocytes in schizophrenia. Gluten free diets and removal of such antibodies may be of therapeutic benefit in certain cases of schizophrenia.

Introduction

A number of studies from China, Norway, and the USA have reported the presence of gliadin antibodies in schizophrenia [1-5]. Gliadin is a component of gluten, intolerance to which is implicated in coeliac disease [6]. Both gluten intolerance and coeliac disease have also been associated with schizophrenia [7, 8], and remission of schizophrenia, in specific subsets of patients , has occasionally been reported following the instigation of a gluten-free diet [9, 10]. Gliadin is a polyglutamine repeat protein (Fig 1), and de facto, a homologue of the mutant polyglutamine proteins in Huntington's disease, Dentatorubropallidoluysian atrophy (DRPLA) , spinal and Bulbar Muscular Atrophy (Kennedy disease) and Spinocerebellar ataxias [11]. Gliadin antibodies have also been found in Huntington's disease and spinocerebellar ataxias and gluten per se has been associated with various forms of ataxia [12 13]. These studies may implicate gliadin in the pathology of these diseases. This is not the subject of this article.

As reported below, polyglutamine repeats are highly immunogenic, the more so with each addition of glutamine. A number of schizophrenia susceptibility gene products contain polyglutamine repeats, while others also display a high degree of homology to other regions of gliadin. Gliadin antibodies may thus play a role in the pathology of schizophrenia by cross-reactive targeting of key schizophrenia-related proteins.

Results

Gliadin is a polyglutamine (polyQ) repeat protein with an internal contiguous sequence of 22 glutamines (Fig 1). Gliadin is highly immunogenic and 181/296 (61%) of its residues are considered as B cell epitopes with the server-defined cut off index of 0.35 (Fig 2). http://www.polygenicpathways.co.uk/gliadin.htm. Polyglutamine repeats are also immunogenic, and all are above the threshold of 0.35 (Fig 2). The antigenicity increases with the number of glutamine repeats. The BLAST of gliadin (whole protein) versus the human proteome yielded 29 significant results, again including highly relevant proteins, many, but not all, influenced by the polyglutamine repeat (Table 1). These proteins belong to members of the DISC1 interactome and also include pre- and postsynaptic proteins related to glutamate, GABA, and neuregulin signalling. They are also involved in dopaminergic function, myelination, and dendritic spine development and to neurogenesis, inflammation and oxidative stress (Fig 3).

A more detailed analysis revealed an interesting type of homology that is common to many more proteins than are listed in Table 1. This is exemplified in Fig 4. The Clustal alignment of KCNN3 with gliadin shows a non-extensive homology with 18% amino acid identity shared by the two proteins, within the homologous region. The gliadin protein is characterised by many short repeat motifs, other than polyglutamines. These include (PQPQP) *4 ;(PQPQ) *5; (QPQP)*5; (PQQP)*2; (QQPY)*2; (QPQPQ)*2; (QQQQF)*2 and (VLQQ)*2. Some of these motifs can also be found in the KCNN3 protein, which, with the polyglutamine repeat contains 9 such areas of identity, many concentrated in a 13 amino acid contiguous tridecapeptide (QPQPPQLQQQQ). The overall gliadin/KCNN3 identity including these contiguous peptides is 5.3%. However, these matching gliadin/KCNN3 motifs extend over the whole length of the gliadin protein, which displays 31% identity with these KCNN3 fragments.

These fragments are mostly (12/15) within highly immunogenic regions of the gliadin protein. Because this immunogenicity extends over many different regions, several different antibodies to gliadin or to its partially digested fragments are likely to be produced. These repeat motifs and their presence in human proteins are likely to dramatically increase the likelihood of cross-reactivity between gliadin, gliadin fragments and human antigens.

These areas in human proteins were identified by sequential BLASTS of contiguous 25 amino acid fragments, along the length of the gliadin protein, each BLAST overlapping by 5 amino acids. By plotting these homologues along the length of the gliadin protein, these multiple repeats and their antigenicity could be identified simultaneously. In all, a total of 459 human proteins contain at least one of these tetrapeptide matches, 60 with pentapeptide matches, and others with longer contiguous matches as shown in Table 2.

This procedure allowed the definition of the number of gliadin matches within each human protein, and of the antigenic index of each of these matches. These results, for 5 or more matches are shown in Table 3: FOXP2, SMARCA2, NUMBL, KCNN3, and RAI1 contain from 14 to 22 of such matches. Certain key gene products including DISC1, neuregulin 2, dysbindin and synapsin 2 contain 5 or more of these gliadin consensus sequences. In fact, of the 459 proteins identified, 158 (34%) are the products of genes listed as susceptibility candidates in association studies. (See http://www.polygenicpathways.co.uk/gliadin.htm for details) An example of peptide matching to the antigenicity profile is shown in Fig 5 for KCNN3. This also allowed antigenicity mapping by family as shown in for glutamate related proteins or for myelin related proteins, many of which match gliadin in highly immunogenic regions (Fig 6).

A number of autoantibodies have been reported in schizophrenia. Their targets include the dopamine (DRD2) [14], glutamate (GRIN1) [15], acetylcholine (CHRNA7) [16] and opioid (OPRM1) receptors [17], heat shock protein 60 (HSPD1) [18] and hsp90 (HSP90A1) [19], MYC binding protein 2 (MYCBP2) [18] nerve growth factor (NGF) [20] and striatin (STRN) [21] all of which are homologous to gliadin, with MYCBP2 and striatin particularly well represented (Fig 7). Myc inhibits myelination, and is also involved in dendrite and synapse formation [22, 23]. Striatin plays an important role in dendritic spine development [24].

Discussion

The high immunogenicity of gliadin, over almost its entire length, suggests that multiple antibodies could be formed by presentation of diverse antigens in different cellular and tissue compartments. Such antibodies might be produced to the entire protein, or to its partially digested fragments. The homology with key schizophrenia related proteins, often covering many regions of gliadin is striking and suggests that gliadin antibodies could also target these human proteins. Indeed 9 of the autoantigens reported in schizophrenia patient are homologous to gliadin. It has also been shown that gliadin antibodies cross react with calreticulin and synapsin 1 [25, 26]. Synapsin 1 was homologous to the particular gliadin tested (PQQQP, PQQP and PLQQ) while calreticulin was not. It was however homologous to gamma gliadins from Triticum aestivum and Triticum urartu (VPRD), Triticum monococcum (VRPD) and a related goat grass, Aegilops searsii (PVIQ).

These homologous sequences are short, and in most cases, tetrapeptides, although higher degrees of homology were observed in many proteins (from 5 to 9 amino acids, not including

polyglutamine repeats (Table 2). Antibodies are quite capable of binding to such short epitopes [27]. In addition the repeat motifs in gliadin have already been noted and are, *per se*, immunogenic [28].

The key pathological features of schizophrenia include reduced dendritic spine density and synaptic poverty [29], deficits in myelination and oligodendrocyte cell loss [30, 31], impaired neuregulin signalling [32]and imbalances in glutamate and dopamine neurotransmission [33]. Many gene products covering these networks are homologous to gliadin. The DISC1 network, connected to many of these areas[34] is also clearly targeted by gliadin homologues (Fig 1).

Antibodies are able to enter the brain via blood-brain barrier transporters [35] and can also enter cells via a high affinity immunoglobulin receptor, tripartite motif-containing 21 (TRIM21) [36].

This suggests that antibody related protein knockdown, of multiple proteins relevant to schizophrenia could be a direct consequence of gliadin allergy. Many studies have reported evidence of immune activation in schizophrenia patients, both in the brain [37, 38] and in lymphocytes [39, 40], and autoimmune attack of certain cells may well explain some of the ongoing pathology of schizophrenia, for example oligodendrocyte [30] and grey matter loss [41].

Following digestion, gliadin will be broken into peptide fragments that may also find their way into the brain via the circulation, and uptake via peptide transporters. As partial homologues of many relevant proteins, they may also be able to interfere with the signalling processes controlled by these proteins. Several pharmacological effects of gliadin or gluten have indeed been noted. For example gluten peptides have opioid activity [42]: Gliadin peptides are also able to activate protein kinase A [43] and bind to the chemokine receptor CXCR3 [44]. They are also able to interfere with epidermal growth factor signalling in a number of cell lines [45] and activate nuclear factor kappa beta signalling in monocytes [46] . This type of homology with human proteins may apply to allergens in general, whose deleterious effects are not necessarily restricted to immune activation, but also to the possibility of interaction with a multitude of host proteins that they resemble.

Similar protein matches are found in many proteins expressed by the viruses implicated in Alzheimer's disease [47] or schizophrenia, and indeed these viral consensus sequences tend to be longer. For example hexapeptide identity between influenza viral proteins and several schizophrenia relevant proteins has been noted: These include reelin, neurexin 1-alpha and DISC1 [48]. In fact several hundred schizophrenia susceptibility gene products display this type of homology to diverse viruses and parasites (T.Gondii and B. Burgdorferri) implicated as risk factors in schizophrenia. It has recently been shown that DNA from many common non-retroviral viruses is integrated into mammalian genomes [49]. BLAST analyses of the human proteome also shows that thousands of human proteins contain these viral (or in this case allergen) contiguous matching sequences. Indeed this type of viral homology appears to cover the entire human genome. (See http://www.polygenicpathways.co.uk/blasts.htm). The human proteome has been estimated to contain ~33869 proteins with an average length of 375 amino acids [50]. For pentapeptide matches, this yields a figure of 370*33869 potential matching blocks (12.53 million). These building blocks are identical to those in viral, bacterial, fungal and allergen proteins. Upon

infection or ingestion, these pathogenic proteins are likely to seed havoc in the panoply of the host's signalling networks via the mechanisms described above, and are likely to contribute to the pathology of many human diseases.

It should also be noted that the viral and allergen protein homology is of course reflected at the DNA level and that viral double stranded DNA, plant or bacterial DNA is indistinguishable from our own. It is thus plausible that many gene association studies, using blood samples, have been indexing infection and ingestion as well as identifying key susceptibility genes. This is less of a problem when using long DNA probes and in no way detracts from the gene association results, whose relevance is generally supported by a plethora of experimental data related to the function of the genes identified. However, the confluence of gene and risk factor homology suggests that many genes are risk factors precisely because they encode for proteins that are homologous to those expressed by the viral, bacterial and allergen risk factors. However, they may only act as risk factors when such confluence is achieved, perhaps explaining the problems of replication in both gene and risk factor association studies.

Clearly gliadin, a major dietary component, cannot cause schizophrenia in all cases. Gluten intolerance and gliadin allergy are evidently related to the immune system. Many immune related susceptibility genes (few of which were encountered in this study) have been reported in association studies, including genome-wide association studies [51]. The high proportion of other types of schizophrenia susceptibility gene products related to gliadin suggests that those genes that encode for proteins with gliadin homology may be considered as risk factors if and when their products are homologous to a particular form of gliadin. Many different forms of gliadin, from diverse plant and bacterial species exist, as do many polymorphic genes, and their resultant differing protein sequences. The marriage of genes and risk factors, and the status of our immune system are thus three variables whose convergence may be obligatory to initiate the processes described above.

Gliadin antibodies and gluten intolerance have often been associated with schizophrenia, and in some cases a gluten free diet has been reported to evoke the remission of symptoms (see introduction). These data suggest that this is more than a simple association and that gliadin antibodies could well be the causative agent of schizophrenia in genetically and immunologically compromised individuals, and illustrate how this might be achieved. If so, then the instigation of a gluten free diet, as already shown [9, 10], may be an effective substitute for drug related interventions. However in certain cases, even if gliadin is removed, the homologous human proteins might well be able to sustain the production of further antibodies, due to the permanence of autoantigens in the human biological network. Antigen and antibody removal by immunoadsorption techniques, or immunosuppression, might thus prove to be effective therapies. Ways of identifying the subsets of patients, who might benefit from such strategies, including routine antibody detection, may have a marked effect on the prevalence and severity of schizophrenia.

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Methods.

Gliadin is a polyglutamine (polyQ) repeat protein with an internal stretch of 22 glutamines. This sequence as well as gliadin or gliadin internal fragments were screened against the human proteome using the filters “schizophrenia”, “glutamate”, “dopamine” or “myelin” to trawl for proteins that might be related to gliadin (BlastP)[52]. Without these filters, many other polyglutamine proteins (Huntingtin, ataxins, the androgen receptor etc.) masked any underlying results. B-Cell epitopes within the gliadin protein were identified using the BepiPred server http://www.cbs.dtu.dk/services/BepiPred/, which predicts antigenicity related to the charge and hydrophobicity properties of the peptide [53]. The BLAST results and supplementary data can be visualised at http://www.polygenicpathways.co.uk/gliadin.htm where a NextBio highlighting tool provides details for all gene symbol abbreviations.

Table 1

Polyglutamine repeat proteins or proteins with significant overall homology to gliadin (BlastP gliadin vs. “schizophrenia”, “glutamate”, “dopamine” or “myelin”). Brief descriptions of function are provided for each protein. The number of glutamines is represented by, for example, Q22, or by the Q containing sequence in the human protein. E values are provided for the BLAST: If none is shown, the results were not significant (P> 0.05)

Proteins	QN and /or BLAST E value	
Glutamate and transmission		
GRINA | glutamate receptor, ionotropic, N-methyl D-aspartate-associated protein 1	E value 2e-11	Uncharacterised glutamate binding NMDA receptor subunit
GRIN3B | glutamate receptor, ionotropic, N-methyl-D-aspartate 3B	Q7	NMDA receptor subunit expressed in the human hippocampus and neocortex [54]
GRM1 | glutamate receptor, metabotropic 1	Q5	Metabotropic glutamate receptor
IQSEC2 | IQ motif and Sec7 domain 2	**No polyglutamines** **BLAST E value** 0.016	Part of the post-synaptic density, binding to psd95 (DLG4) [55]
NOS1AP : nitric oxide synthase 1 (neuronal) adaptor protein	HH**Q**M**Q**LL**QQ**LL**QQQQQQ**T**Q**	Plays a role in both presynaptic and postsynaptic (NMDA)

		glutamatergic function and controls dendritic spine development [56, 57]
RIMS2 : regulating synaptic membrane exocytosis 2	**QQFEMYKEQVKKMGEESQQQQEQ**	Regulates calcium dependent neurotransmitter release [58]
SYN3 : synapsin III	**QQ**RLSP**Q**G**QQ**PLSP**Q**SGSP**QQQ**	Presynaptic protein regulating neurotransmitter release [59]
GRIPAP1 | GRIP1 associated protein 1	**QQQQQEQEEALKQ-**	Part of the postsynaptic scaffold for glutamate (AMPA) receptors [60]
MAP1A : microtubule-associated protein 1A	**QQ**THE**QQQQ**	Part of the NMDA receptor postsynaptic density, that controls dendrite branching and synapse formation [61]; Binds to postsynaptic density proteins that connect to NMDA Kainate , AMPA and ERBB receptors
SPTAN1 : spectrin, alpha, non-	**QQQQ**	Part of the postsynaptic density that

erythrocytic 1 (alpha-fodrin)		regulates glutamate receptor signalling [62]
RORB : RAR-related orphan receptor B	**Q**KH**QQ**RL**Q**E**Q**R**QQQ**	Little is known about this protein: However it binds to MAP6, a microtubule protein that controls synaptic organisation, in particular of glutamatergic synapses where it controls the expression of the glutamate transporter and presynaptic genes , synaptophysin and GAP-43 , spinophilin and MAP2 [63].
Gamma amino butyric acid (GABA) related		
ATF5 cyclic AMP-dependent transcription factor ATF-5	No polyglutamines 0.008	Regulates the development of neurones, astrocytes and oligodendrocytes [64]
DGCR6 : DiGeorge syndrome critical region gene 6	**Q**KH**Q**EA**QQ**ACRPHNLPVL**Q**AA**QQ** **BLAST E value** 0.001	Little is known except that is binds to the GABA-b receptor GABBR1 [65]
SP4 : Sp4 transcription	**Q**NA**Q**D**Q**SNSL**QQ**V**Q**IVG**Q**PIL**QQ**I**Q**I**QQ**P**QQQ**	Regulatesglutamate

factor	**BLAST E =** 9e-05	(GRIN2A), GABA (GABRA4) receptors (and many others): Also controls dendritic function [66-68]
Dopamine and serotonin related		
FOXP2 Forkhead box P2	Q22 BLAST 3e-25	Controls pathways involved in embryonic and nervous-system development, neurogenesis, cell migration and cell death. FOXP2 knockout mice have lower cerebral dopamine concentrations. Expressed in dopamine and cyclic adenosine 3',5'-monophosphate-regulated phosphoprotein containing neurones in the cerebral cortex FOXP2 also controls dendritic spine development and synaptic plasticity. [69-72]
LMX1A : LIM homeobox	**QQQQQQ**D**QQ**	LMX1A and B control the

transcription factor 1, alpha		development of midbrain dopamine neurones [73]
LMX1B : LIM homeobox transcription factor 1, beta	H**QQQQ**E **QQ**	
KCNN3 potassium intermediate/small conductance calcium-activated channel, subfamily N, member 3	Q19 BLAST E Value: 2e-22	Regulates the activity of dopamine and serotonin neurones and plays a role in glutamate-mediated long term potentiation [74, 75]
MAGEL2 MAGE-like protein 2	**QQ**A**Q**ASGP**Q** BLAST E Value 2e-05	MAGEL2 and necdin bind to FEZ1 and are involved in the control of axonal growth and in the development of brain dopamine, serotonin and noradrenaline neurones [76]
NALCN : sodium leak channel, non-selective	**QQQ**SCSIIHSLRES**QQQ**E	Sodium channel activated by reducing extracellular calcium levels: It is activated by substance P and neorotensin in ventral tegmental and hippocampal

		neurones [77]
PDCD6IP programmed cell death 6 interacting protein	E value 6e-06	Apoptosis inhibitor that also binds to D1 and D3 dopamine receptors [78]
POU3F2 POU class 3 homeobox 2 brain-specific homeobox/POU domain protein 2	Q18 E value = 4e-15	Controls the expression of neural progenitors and of the tryptophan hydroxylase gene (TPH2) [79, 80]
PPP1R3F : protein phosphatase 1, regulatory (inhibitor) subunit 3F	**QQQQ**LP**Q**LEP**Q**	Protein phosphatase 1 regulates the activity of many transmitter systems (glutamate, GABA, dopamine . serotonin, inter alia): It also modifies dendritic spine development . [81-86]
RANBP9 | RAN binding protein 9	Q8	Binds to the D1 dopamine receptor as well as to nerve growth factor receptors NGFR and trkB (NTRK2) , androgen and glucocorticoid receptors and DISC1 [87-91]

SMARCA2 : SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 2	Q2 BLAST E value 3e-15	Binds to the promoter of the noradrenaline transporter SLC6A2 : It also controls neuronal development on the mid hindbrain [92, 93]
SMARCC1 : SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily c, member 1	**QQ**ME**QQQ**HG**Q**NP**QQ**AH**Q**H And E**QQ**R**QQ**LLTER**Q**NFHME**Q**LKYAELRAR**QQ**ME**QQQ**HG**Q**NP**QQ**	Regulates the function of the glucocorticoid receptors (NR3C1), and Nurr77 (NR4A1) [94] both of which play an important role in the control of dopamine neurones [95]
Neuregulin , NOTCH and growth		
NRG2 : neuregulin 2	**QQQQQQ**REE**QQQQQQQQ**RER**QQQQ**E**QQQ**	This particular neuregulin is localised to dendrites and controls the expression of DISC1 ; It also controls free radical release from microglia [96-98]
NUMBL numb homolog (Drosophila)-like	Q20 BLAST E value 6e-13	Important regulator of cortical neurogenesis [99, 100]
RAI1 retinoic acid induced 1	Q14	Regulates BDNF expression and

	BLAST E Value = 4e-10	also regulates autoimmunity by inhibiting lymphocyte activation and and triggen receptor signalling [101, 102]
Dendritic spines and plasticity		
HDAC4 : histone deacetylase 4	**QQQ**H**QQ**FLEKHK**QQ**F**QQQQ**L**Q** BLAST E value 0.006	Histone deacetylases regulate gene transcription by modifying histones. HDAC4 is localised in the brain and shuttles between the nucleus and cytoplasm in response to neuronal activity. HDAC4 is also localised in dendritic spines associated with the postsynaptic density: HDAC9 also shuttles from nucleus to cytoplasm in response to neuronal activity, and controls dendritic spine density [103-105]
HDAC5 | histone deacetylase 5	**QQQEMLAAKQQQEMLAAKRQQELEQQRQREQQRQ EELEKQRLEQQ** BLAST E value 5e-05	
HDAC9 : histone deacetylase 9	**QQQQQ**I**Q**K**Q**LLIAEF**Q**K**Q**HENLTR**Q**H**Q**A**Q**L**Q**EHIKL**QQ** ELLAIK**QQQ**	
MCF2 : MCF.2 cell	**QQ**D**Q**LTERDKF**Q**ISL**QQ**NDEK**QQ**	Controls dendritic spine

line derived transforming sequence		development [106]
MED25 | mediator complex subunit 25	VQQQ BLAST E Value 0.001	Regulates the retinoid receptor RAR , which controls dendritic spine formation, [107]
NR4A3 : nuclear receptor subfamily 4, group A, member 3 also known as nor-1	**QQQ**H**QQ**	Regulates pyramidal neurone survival and hippocampal axon guidance and controls neurite extension [108, 109]
PURA : purine-rich element binding protein A	E**Q**LH**QQQQQQQ**EE **BLAST E value** 0.014	A single stranded DNA (e.g. viral) binding protein involved in the transport of RNA to dendrites. Plays and important role in postnatal brain development and also controls the transcription of myelin basic protein in oligodendrocytes [110-112]
Myelin related		
FOXJ3 | forkhead box	QQQP	Involved in oodendrocyte

J3	BLAST E value 5E-0.5	liferation [113]
NCOR2 | nuclear receptor corepressor 2	Q17 BLAST E value = 6E-11	Controls thyroid hormone, retinoic acid and steroid receptors[114]. Retinoids play a key role in dopamine function, dendritic spine development and oligodendrocyte differentiation [115-117]
PEG10 | paternally expressed 10	No Polyglutamines **BLAST E value** 0.006	Controls the expression of myelin basic protein [118]
SGCE : sarcoglycan, epsilon	**Q**T**QQ**NLPH**Q**T**Q**IP**QQQ**	Sarcoglycans are typically associated with muscle cells: However SGCE is expressed in Schwann cells, and in monoaminergic neurones and is believed to regulate dopaminergic activity [119-121]
Development and neurogenesis		
DISC1 : disrupted in schizophrenia	**QQ**LRREIEE**Q**E**QQ**L**Q**	Key “hub gene” connected to many schizophrenia

1		networks [34]
MACF1 : microtubule-actin crosslinking factor 1	**Q**L**QQ**L**Q**S**Q**LAH**Q**TE**Q**KTL**Q**K**QQ**NTCH**QQ**	MACF1 knockdown impairs cortical and other brain area development : It also plays a role in growth cone advance [122, 123]
PCM1 : pericentriolar material 1	**QQQQ**RELK**Q**L**Q**EE	Involved in neuronal migration and neurogenesis [124]
PCNT : pericentrin	**QQQ**ALHS**QQQ**	Regulates the neuronal progenitor cells in the developing cortex [125]
SEL1L3 : sel-1 suppressor of lin-12-like 3	**QQQQQ**	Little is known, except that SEL1L3 binds to tubulin TUBB3 which is involved in cortical development and neuronal migration [126]
Endocytosis		
CHERP | calcium homeostasis endoplasmic reticulum protein	**Q12** BLAST E value **7e-08**	No data: Endoplasmic reticulum location
CLINT1 : clathrin	**QQQ**NM**QQ**	Involved in clathrin

interactor 1		mediated endocytosis and the endosomal transport of SNARE proteins including STX7 [127]
STX7 : syntaxin 7	**QQ**L**QQ**K**QQ**	Involved in endosomal to lysosomal traffic and in phagocytosis. Also expressed in neutrophils and macrophages [128-131]
Apoptosis and oxidative stress		
EP400 | E1A binding protein p400	Q22 BLAST E value 1E-16	Involved in the regulation of oxidative stress [132]
HIPK3 : homeodomain interacting protein kinase 3	**QQ**KLTSAF**QQQ**H	Involved in the Fas apoptosis pathway, and also controls the expression of cytochrome p450 CYPA11, the enzyme responsible for pregnelonone synthesis, the firsts step in steroid hormone production [133, 134]
SETD2 : SET domain containing 2	**Q**REA**Q**K**QQQQ**M**Q**	Involved in embryonic vascular

(a histone methyltransferase)		development [135]
SHISA5 protein shisa-5 precursor	No polyglutamines **BLAST E value** e-04	Localised in the endoplasmic reticulum and nuclear membrane and involved in p53 and p73 mediated apoptosis [136-138]
TFAP4 | transcription factor AP-4	E value 0.002	AP4 controls the expression of p21 a cell cycle cyclin dependent kinase inhibitor induced by p53 [139]
Immune system		
HLX | H2.0-like homeobox	**Q8** BLAST E value **6e-06**	Regulates interferon gamma production in natural killer cells [140]
HOXA10 | homeobox A10	**PPQQQPPPPPQP** E value **0.012**	Part of a vitamin D3 dependent pathway regulating haematopoesis [141]
ITIH4 : inter-alpha (globulin) inhibitor H4 (plasma Kallikrein-sensitive	**QQQ**KSPE**QQ**E	Acute phase protein involved in inflammatory processes [142]

glycoprotein)		
NFAT5 | nuclear factor of activated T-cells 5, tonicity-responsive	**Q17** BLAST E value **1e-16**	Plays an important role in the immune system and in water homoeostasis : Polydipsia (excessive water drinking) and water imbalance have been observed in schizophrenia [143, 144].
Translation initiation		
ABCF1 | ATP-binding cassette, sub-family F (GCN20), member 1	**Q10** BLAST E value 9E-04	Regulates translation initiation [145]
EIF4G3 | eukaryotic translation initiation factor 4 gamma, 3	**No polyglutamines** **BLAST E value** 0.008	Translation initiation factor
Miscellaneous		
ALX4 | ALX homeobox 4	Q4 BLAST E value 9e-08	Involved in cranial bone development [66, 67, 109, 146, 147]
ARID3B | AT rich interactive domain 3B (BRIGHT-like)	**Q11** BLAST E value **1e-05**	No data
PHC2 | polyhomeotic homolog 2	**VIQQQPQPQQQQPPPQQ** BLAST E value 6E-0.6	No data

Table 2 Proteins with hexapeptide, or greater, matches to the gliadin protein. The consensus sequence is shown on the left followed by the gene symbols. N is the number of contiguous amino acids : DISC1 (N=5) is included for interest: Q = glutamine, followed by the number of Q's e.g. Q22. Full tables with abbreviations and data provided by a NextBio highlighting service are available at http://www.polygenicpathways.co.uk/gliadin.htm

Sequence and Gene symbol	**N**
Q22 FOXP2 SMARCA2	22
Q20 NUMBL	20
Q19 KCNN3	19
Q18 POU3F2	18
Q14 RAI1	14
TAVR-PVP PRODH (Proline dehydrogenase)	9
Q8 NRG2	8
LQQ-QQQ NOS1AP KCNN3	7
PSS --SLQQ ZDHHC8 (Zinc finger protein)	7
Q7 PURA	7
QP+RQVP FXR1 (Fragile X protein)	7
FPPQ+P CABIN1 (calcineurin binding protein)	6
P+PQQP SYN2	6
PQPQPQ PHLDA1 MYST3 (histone acetyltransferase)	6
CPEB2 (cytoplasmic polyadenylation element binding protein)	
PYPQPP SHISA5	6
Q6 LMX1A NOS1AP	6
QILQQQ FOXP2	6
QPQPQP MEF2A (myocyte enhancer factor) MED12L (Mediator complex)	6
Q-QGSV GRIP1(glutamate receptor interacting protein)	6
QQLCCQ SNX6 (sorting nexin)	6
QQPPQQ SMARCA2	6
QQPQQQ SP4	6
Q-QQLP DTNBP1 (Dysbindin)	6
QSGV-P MAP6	6
Q-SLQQ SLC1A6 (glutamate transporter) SQVS ABCA13 GABRA6 (GABA receptor)	6
QUAQGS SLC25A14 (mitochondrial carrier, brain)	6
SSQVSL PIK3C2G (phosphatidylinositol 3-kinase)	6
VQPQQ STRN	6
LQLQP DISC1	5

Table 3

The number of gliadin matches (tetrapeptide or more) within human proteins

GENE SYMBOL	N
MACF1	24
ATP2A2	21
ANK3	19
RAI1	17
KCNN3, SMARCA2	15
SETD2, SP4, STAB1	14
ABCA13, NUMBL, SYN3	13
ADAM12, ATF7IP	12
ASTN1, BTN3A2, KIF13A, MED25,PCNT, PLXNA2, SPTAN1	11
CCDC141, CIT, FOXP2, RIMS2	10
ABCA7, CABIN1, MAGEL2, MAP1A, MAP6,MYCBP2, PPP1R3F	9
ATF5, EPB41L1, MYO1D, NR4A3, PCM1, RELN	8
CLINT1, HDAC9, ITIH4, KCNH5, LMX1B,	7
MMS22L, SELIL3, SEMA3D, SPTNB4, SYN2, UTRN	7
DNAJC6, HDAC10, LMX1A, POM121L2, RAPGEF6, SIM1, SMARCC1	6
ANK2, BAP1, BRD1, CACNA1B, CDC42SE2, CELF4, DISC1, EGR4, FNIP1, FUBP1, GPR125, GRIP1, HIPK3, MDGA1, NALCN, NCS1, NOTCH4,, TMEM200C	5

Fig 1: The sequence of the gliadin protein used in this study: Polyglutamine or other repeat sequences are highlighted in bold or in grey.

Fig 2:

Top:

The B cell epitope index values of the gliadin protein (amino acid 1-276) as predicted by the Bepipred server. The cut-off value of 0.35 is illustrated by the thick horizontal line.

Bottom

The B cell epitope indices for various glutamine repeats (QQQ) * 1-7

Fig 3

An interactome network for the proteins identified in this study. Proteins in grey boxes show a significant degree of homology with gliadin in the BLAST analyses, or are polyglutamine repeat proteins. Linked boxes represent binding between two components; these data were gleaned from the protein interaction section of Entrez Gene. Arrows indicate other effects on transcription or other functional effects. See Table 1 for details.

Fig 4

A) Clustal line up between gliadin and the potassium channel, KCNN3

B) Gliadin consensus sequences with the KCNN3 protein

C) KCNN3 consensus sequences within the gliadin protein

Fig 5

The B cell epitope index for KCNN3 sequences within the gliadin protein. Other human proteins trapped in passing are also shown.

Fig 6

The B cell epitope indices for sequences of glutamate (top) and myelin related proteins (bottom) sharing consensus sequences with gliadin.

Fig 7

The B cell epitope indices for sequences of schizophrenia-related autoantigens sharing consensus sequences with gliadin.

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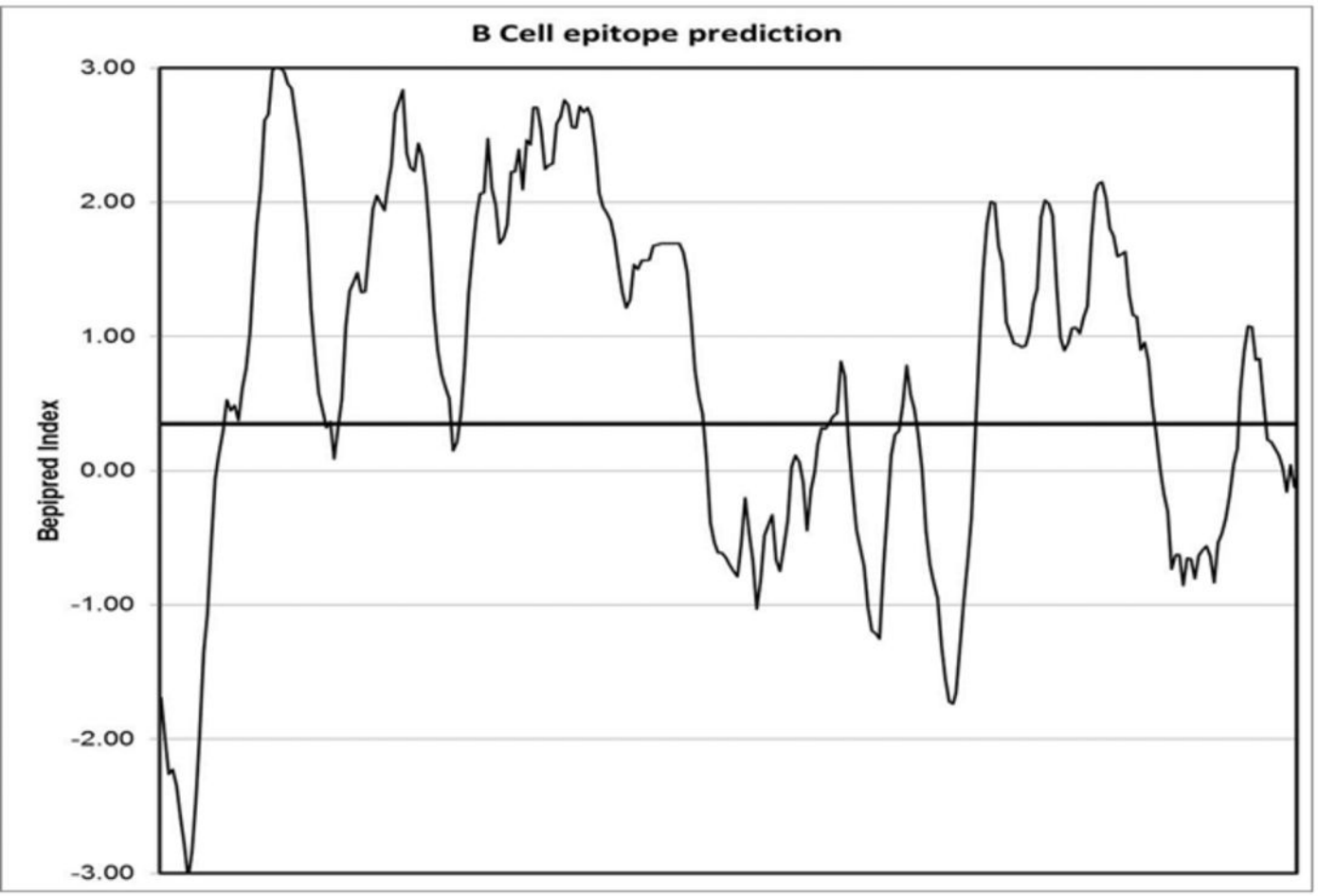
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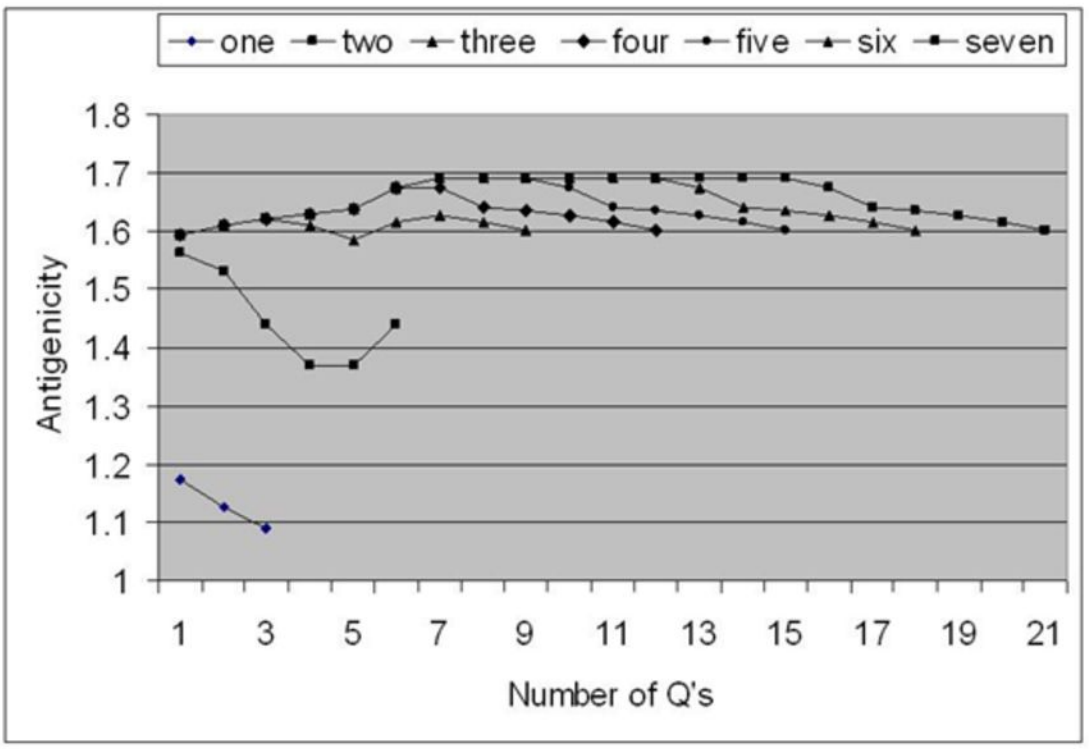
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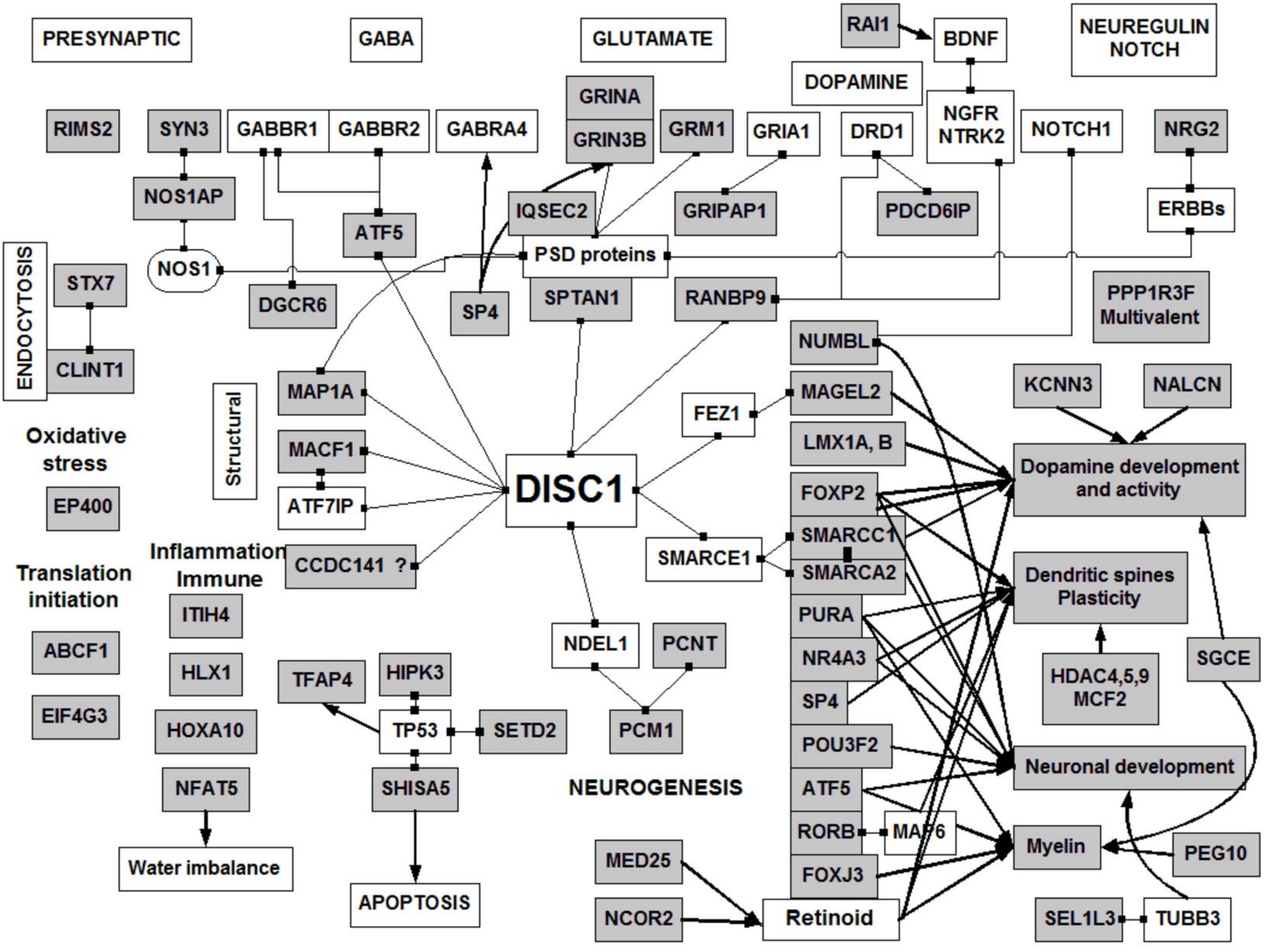
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NOS1
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Dopamine development
and activity
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Gliadin   PQQPYPQPQPFPSQQPYLQLQPFP-------QPQPFPPQLPYPQPPPFSPQQPYPQPQPQ  111
KCNN3     PQPPQLQQQQQQQQQQQQQQPPHPLSQLAQLQSQPVHPGLLHSSPTAFRAPPSSNSTAIL  120
          ** *  * *   .**   *  *.*       *.**. * * :..*..* .  .  ..
Gliadin   YPQPQQPISQQQAQQQQQQQQQQQQQQ------QQQQILPQILQQQLIPCRDVVLQQHN-  164
KCNN3     HPSSRQGSQLNLNDHLLGHSPSSTATSGPGGGSRHRQASPLVHRRDSNPFTEIAMSSCKY  180
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GliadinHQQQQQQQPSSQVSLQQPQQQYPSGQGFFQPSQQNPQAQG-------------------  250
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*::*:   .:*..::: :.:::  .. *:    ::    :
Gliadin-SVQPQQLPQFEEIRNLALQTLPRMCNVYIP----PYCSTTTAPFGIFGTN---------  296
KCNN3   ETELSWGLYSKDSMFSLALKCLISLSTIILLGLIIAYHTREVQLFVIDNGADDWRIAMTY  360
:  .  * . :.: .***: *  :..: :     .* :  .  * * .
```

Identities= 54/300 = 18%

B)Tetrapeptide or greater gliadin consensus sequences within the KCNN3 protein

```
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3 isoform a [Homo sapiens]
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Identities= 38/720 5.3%

C)KCNN3 matching contiguous sequences within the gliadin protein

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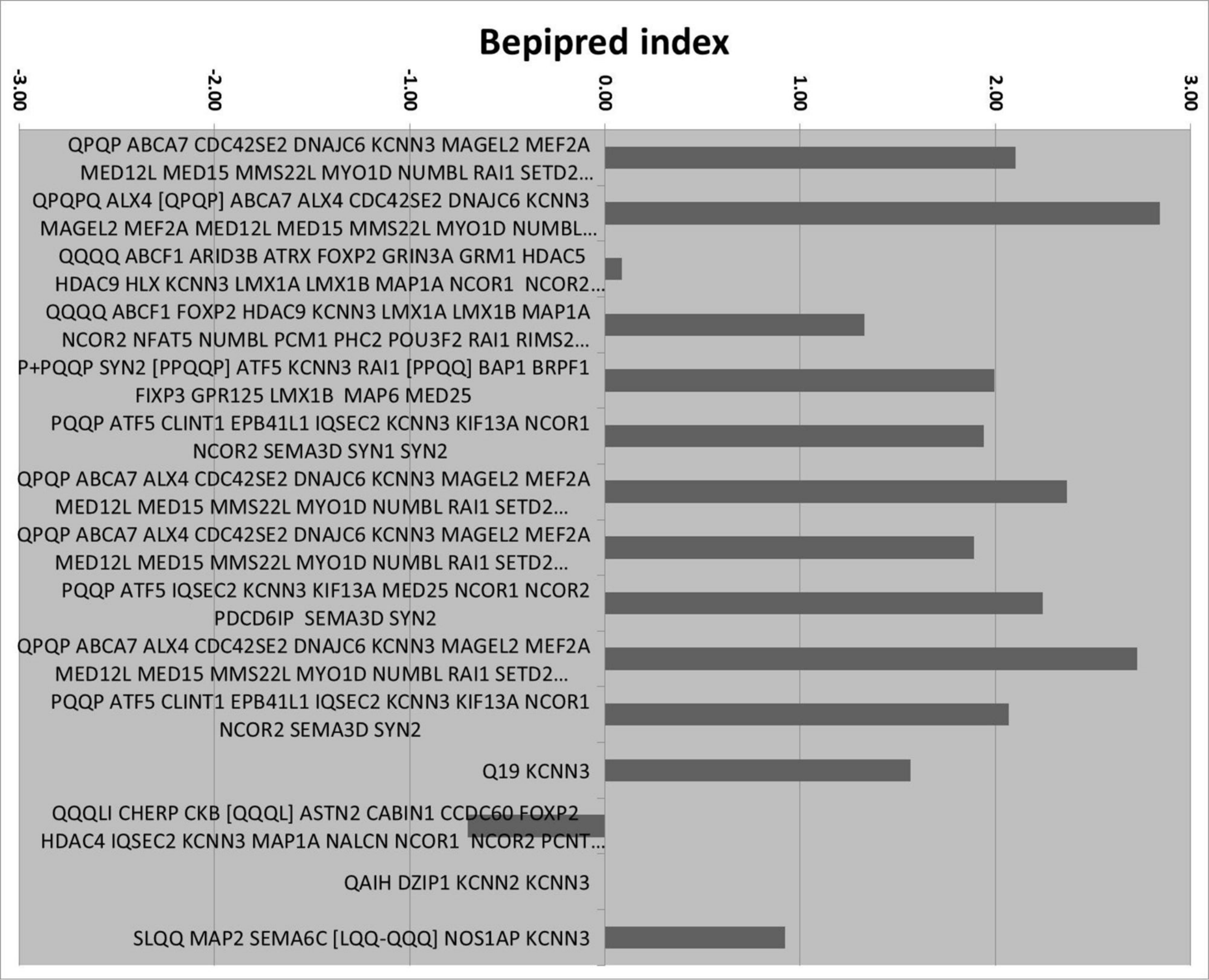
Identities 94/296=32%
a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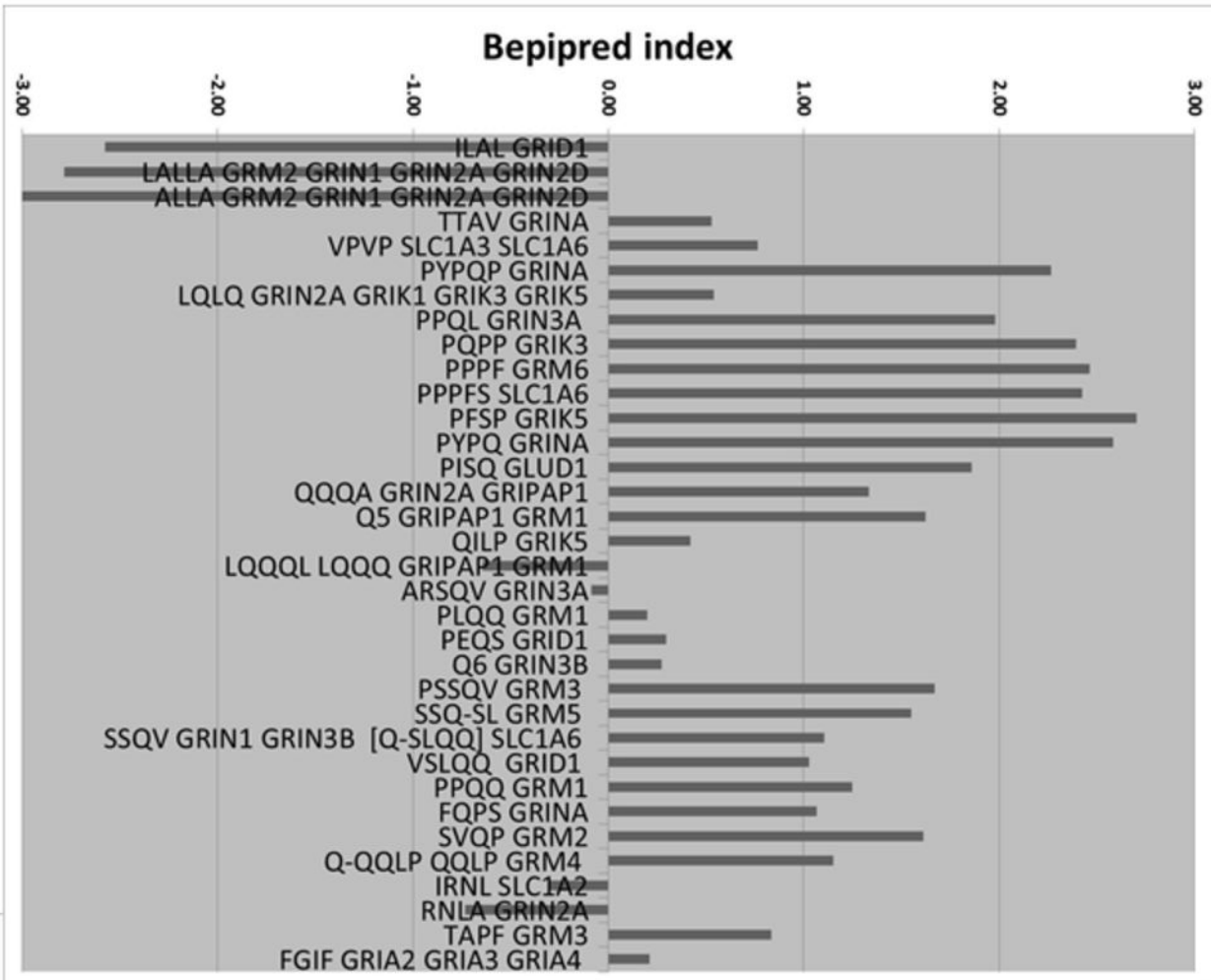
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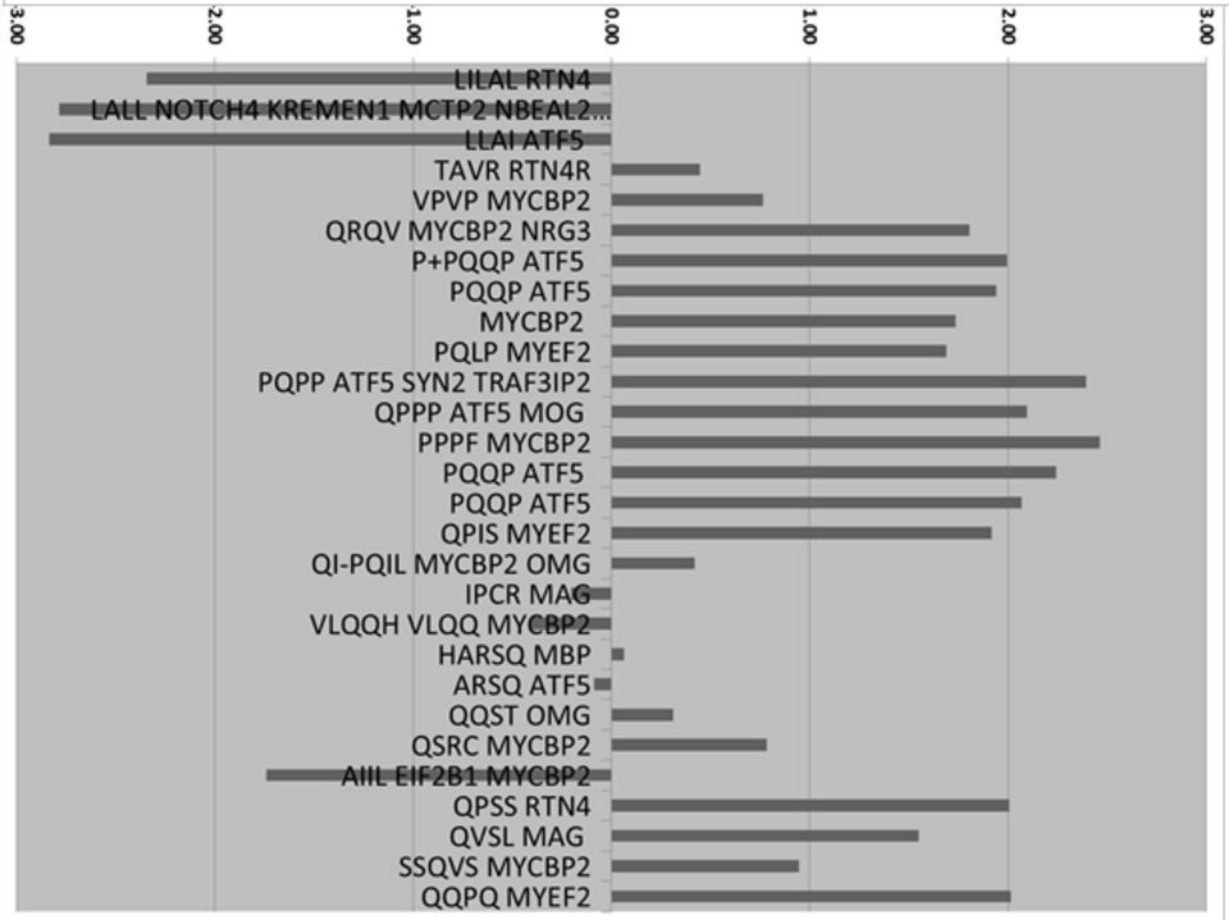
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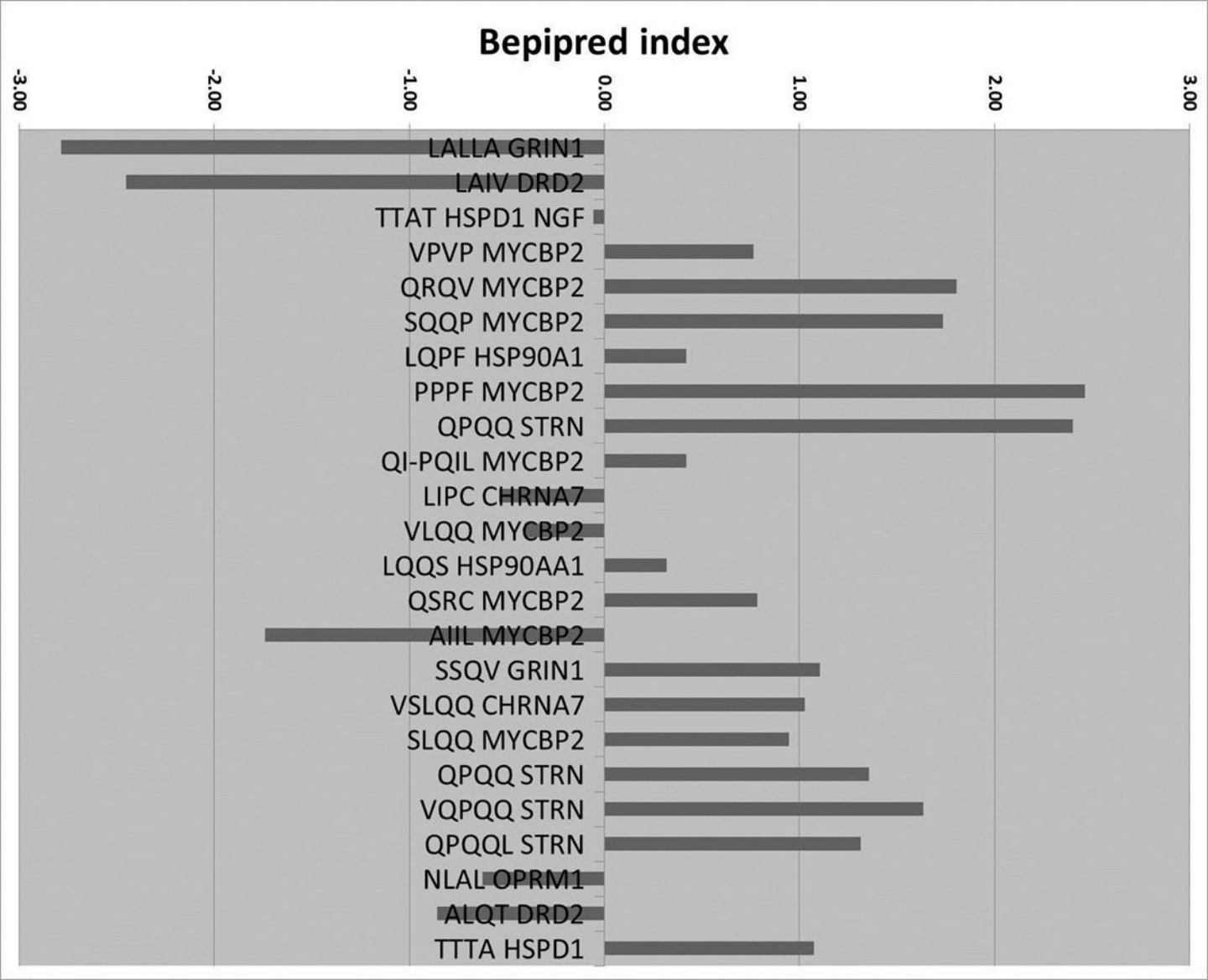
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