GEPHE SUMMARY

Gephebase Gene
FRIZZLED8 (https://www.gephebase.org/search-criteria?/and+Gene Gephebase=^FRIZZLED8^#gephebase-summary-title)

GepheID
GP00001443

Entry Status
Published

Main curator
Prigent

PHENOTYPIC CHANGE

Trait Category
Morphology (https://www.gephebase.org/search-criteria?/and+Trait Category=^Morphology^#gephebase-summary-title)

Trait
Neocortex development (https://www.gephebase.org/search-criteria?/and+Trait=^Neocortex development^#gephebase-summary-title)

Trait State in Taxon A
chimpanzee

Trait State in Taxon B
human

Ancestral State
Taxon A

Taxonomic Status
Interspecific (https://www.gephebase.org/search-criteria?/and+Taxonomic Status=^Interspecific^#gephebase-summary-title)

Taxon A

Latin Name
Pan troglodytes (https://www.gephebase.org/search-criteria?/and+Taxon and Synonyms=^Pan troglodytes^#gephebase-summary-title)

Common Name
chimpanzee

Synonyms
chimpanzee; Chimpansee troglodytes

Rank
species

Lineage
cellular organisms; Eukaryota; Opisthokonta; Metazoa; Eumetazoa; Bilateria; Deuterostomia; Chordata; Craniata; Vertebrata; Gnathostomata; Teleostomi; Euteleostomi; Sarcopterygii; Dipnotetrapodomorpha; Tetrapoda; Amniota; Mammalia; Theria; Eutheria; Boreoeutheria; Euarchontoglires; Primates; Haplorrhini; Simiiformes; Catarrhini; Hominoidea; Hominidae; Homininae; Pan

Parent
Pan (chimpanzees) - (Rank: genus) (https://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?id= 9596)

NCBI Taxonomy ID
9598 (https://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?id= 9598)

is Taxon A an Infraspecies?
No

Taxon B

Latin Name
Homo sapiens (https://www.gephebase.org/search-criteria?/and+Taxon and Synonyms=^Homo sapiens^#gephebase-summary-title)

Common Name
human

Synonyms
human; man; Homo sapiens Linnaeus, 1758; Home sapiens; Homo sampiens; Homo sapeins; Homo sapian; Homo sapians; Homo sapien; Homo sapience; Homo sapiense; Homo sapients; Homo sapines; Homo spaiens; Homo spiens; Humo sapiens

Rank
species

Lineage
cellular organisms; Eukaryota; Opisthokonta; Metazoa; Eumetazoa; Bilateria; Deuterostomia; Chordata; Craniata; Vertebrata; Gnathostomata; Teleostomi; Euteleostomi; Sarcopterygii; Dipnotetrapodomorpha; Tetrapoda; Amniota; Mammalia; Theria; Eutheria; Boreoeutheria; Euarchontoglires; Primates; Haplorrhini; Simiiformes; Catarrhini; Hominoidea; Hominidae; Homininae; Homo

Parent
Homo () - (Rank: genus) (https://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?id= 9605)

NCBI Taxonomy ID
9606 (https://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?id= 9606)

is Taxon B an Infraspecies?
No

GENOTYPIC CHANGE

Generic Gene Name
FZD8

Synonyms
FZ-8; hFZ8

String
9606.ENSP00000363826 (http://string-db.org/newstring_cgi/show_network_section.pl?identifier=9606.ENSP00000363826)

Sequence Similarities
Belongs to the G-protein coupled receptor Fz/Smo family.

GO - Molecular Function
GO:0005102 : signaling receptor binding (https://www.ebi.ac.uk/QuickGO/term/GO:0005102)
GO:0030165 : PDZ domain binding (https://www.ebi.ac.uk/QuickGO/term/GO:0030165)
GO:0004930 : G protein-coupled receptor activity

UniProtKB Homo sapiens
Q9H461 (http://www.uniprot.org/uniprot/Q9H461)

GenebankID or UniProtKB
()

(https://www.ebi.ac.uk/QuickGO/term/GO:0004930)
GO:0031625 : ubiquitin protein ligase binding
(https://www.ebi.ac.uk/QuickGO/term/GO:0031625)
GO:0042813 : Wnt-activated receptor activity
(https://www.ebi.ac.uk/QuickGO/term/GO:0042813)
GO:0017147 : Wnt-protein binding (https://www.ebi.ac.uk/QuickGO/term/GO:0017147)

GO - Biological Process

GO:0030182 : neuron differentiation (https://www.ebi.ac.uk/QuickGO/term/GO:0030182)
GO:0045944 : positive regulation of transcription by RNA polymerase II
(https://www.ebi.ac.uk/QuickGO/term/GO:0045944)
GO:0000122 : negative regulation of transcription by RNA polymerase II
(https://www.ebi.ac.uk/QuickGO/term/GO:0000122)
GO:0001525 : angiogenesis (https://www.ebi.ac.uk/QuickGO/term/GO:0001525)
GO:0060070 : canonical Wnt signaling pathway
(https://www.ebi.ac.uk/QuickGO/term/GO:0060070)
GO:0035567 : non-canonical Wnt signaling pathway
(https://www.ebi.ac.uk/QuickGO/term/GO:0035567)
GO:0043507 : positive regulation of JUN kinase activity
(https://www.ebi.ac.uk/QuickGO/term/GO:0043507)
GO:0033077 : T cell differentiation in thymus
(https://www.ebi.ac.uk/QuickGO/term/GO:0033077)

GO - Cellular Component

GO:0016021 : integral component of membrane
(https://www.ebi.ac.uk/QuickGO/term/GO:0016021)
GO:0005886 : plasma membrane (https://www.ebi.ac.uk/QuickGO/term/GO:0005886)
GO:0005794 : Golgi apparatus (https://www.ebi.ac.uk/QuickGO/term/GO:0005794)
GO:1990851 : Wnt-Frizzled-LRP5/6 complex
(https://www.ebi.ac.uk/QuickGO/term/GO:1990851)

Presumptive Null

No (https://www.gephebase.org/search-criteria?/and+Presumptive Null=^No^#gephebase-summary-title)

Molecular Type

Cis-regulatory (https://www.gephebase.org/search-criteria?/and+Molecular Type=^Cis-regulatory^#gephebase-summary-title)

Aberration Type

Unknown (https://www.gephebase.org/search-criteria?/and+Aberration Type=^Unknown^#gephebase-summary-title)

Molecular Details of the Mutation

10 mutations fixed on the human branch in the Hs-HARE5 genomic locus resulting in enhancer activity in developing neocortex

Experimental Evidence

Candidate Gene (https://www.gephebase.org/search-criteria?/and+Experimental Evidence=^Candidate Gene^#gephebase-summary-title)

Main Reference

Human-chimpanzee differences in a FZD8 enhancer alter cell-cycle dynamics in the developing neocortex. (2015) (https://pubmed.ncbi.nlm.nih.gov/25702574)

Authors

Boyd JL; Skove SL; Rouanet JP; Pilaz LJ; Bepler T; GordÃ¢n R; Wray GA; Silver DL

Abstract

The human neocortex differs from that of other great apes in several notable regards, including altered cell cycle, prolonged corticogenesis, and increased size [1-5]. Although these evolutionary changes most likely contributed to the origin of distinctively human cognitive faculties, their genetic basis remains almost entirely unknown. Highly conserved non-coding regions showing rapid sequence changes along the human lineage are candidate loci for the development and evolution of uniquely human traits. Several studies have identified human-accelerated enhancers [6-14], but none have linked an expression difference to a specific organismal trait. Here we report the discovery of a human-accelerated regulatory enhancer (HARE5) of FZD8, a receptor of the Wnt pathway implicated in brain development and size [15, 16]. Using transgenic mice, we demonstrate dramatic differences in human and chimpanzee HARE5 activity, with human HARE5 driving early and robust expression at the onset of corticogenesis. Similar to HARE5 activity, FZD8 is expressed in neural progenitors of the developing neocortex [17-19]. Chromosome conformation capture assays reveal that HARE5 physically and specifically contacts the core Fzd8 promoter in the mouse embryonic neocortex. To assess the phenotypic consequences of HARE5 activity, we generated transgenic mice in which Fzd8 expression is under control of orthologous enhancers (Pt-HARE5::Fzd8 and Hs-HARE5::Fzd8). In comparison to Pt-HARE5::Fzd8, Hs-HARE5::Fzd8 mice showed marked acceleration of neural progenitor cell cycle and increased brain size. Changes in HARE5 function unique to humans thus alter the cell-cycle dynamics of a critical population of stem cells during corticogenesis and may underlie some distinctive anatomical features of the human brain.

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Additional References

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