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A Descriptive Analysis Of Huntington's Disease By Using Bioinformatics Tools

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Abstract
Huntington's disease is a neurological disorder marked with mental symptoms as well as severe cognitive and emotional impairments. In pre-symptomatic HD (pre-HD) individuals, several pathological alterations can already be seen. We review functions of the Huntington protein and discuss CAG repeat expansion has deleterious repercussions, resulting in an exceptionally lengthy polyglutamine tract. Using bioinformatics techniques, we go over some of the existing pharmaceutical treatments for delaying the progression of the disease. *We investigate the fundamental molecular pathways and discover important compounds in Huntington's disease. We go on molecular genetic testing, clinical characteristics of the disorder, and genetic counseling. The number of HTT CAG repeats is used to characterize drug development and gene expression profiles. Our study will assist in directing the development of medicines that target the disrupted pathways' altered genes and metabolites, resulting in a reduction in clinical signs and, perhaps, a delay in start age.*
Keywords: Huntington's disease; *HTT* gene; Molecular genetic testing; pathway; protein-protein interaction; transcription factors

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I. Introduction

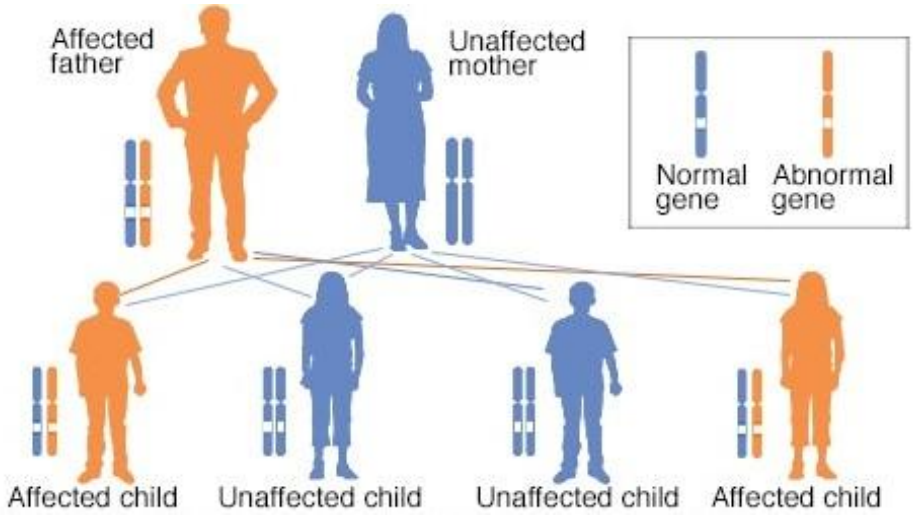
Huntington's disease is a physical, neurological, and mental condition that progresses over time. The usual age of beginning is 30 to 45 years, with a 14 to 20-year overall survival period [1]. Expanded CAG trinucleotide repeats have been discovered in the Huntingtin Gene of HUNTINGTON Disease, and they are linked to aberrant protein aggregates. Huntingtin binds to enzymes that play a role in the transcription of genes. And cell functions in a variety of ways. Huntington's disease is expected to affect 4 to 8 people per 100,000 who are of European ancestry. Japanese, Chinese, and African Americans. [2]

The HTT mutation, which causes HD, is connected to a CAG trinucleotide repeat is a DNA fragment The CAG Fragment is generally repeated 10 to 35 times inside a gene.[2,3,4] The development of a huntingtin protein mutant with an unusually long length is accompanied by a rise in the CAG segment's dimensions.[3] The more the stress, the more poisonous the fragments become, which bind together and concentrate in neurons, leading these cells to lose their normal functions.

As the mutant HTT, a gene is passed forward From generation after generation, the amount of CAG trinucleotide repeats increases A higher the quantity of repetitions is frequently accompanied with the onset of clinical symptoms occurring sooner Adult-onset HD patients have 50 to 60 CAG repeats in their HTT gene,[4] but juvenile-onset Huntington disease patients have more than 60 CAG repeats.

Reasons:

HD is characterized by a defective gene passed down through generations (Fig.1). It's a condition that runs in families. This means that only one faulty gene copy is required for the sickness to manifest itself With the exception of sex chromosomal genes, each parent gives each child two copies of each gene. [5] A parent who has a gene that is dysfunctional can pass on either the gene's faulty or normal copy to their children. As a result, every child in the family has a 60% chance of inheriting the genetic illness-causing gene. Each individual inherits two copies of each gene, one from each parent, with the exception of genes on the sex chromosomes. [5] A parent can pass on either the defective or healthy copy of a gene to their offspring if the gene is malfunctioning. As a result, there's a 60% risk of receiving the hereditary disease-causing gene.



Hazards:

A person with Huntington's disease's functional abilities gradually decline. The sickness progresses at a different rate and lasts for different amounts of time. In most cases, the time between the commencement of an illness and death is between 10 and 30 years. [6] Children with Huntington's disease die around 10 years of the first signs and symptoms. (Table1) Depressed mood caused by Huntington's illness has been linked to an increased risk of suicide [7]. Patients with Huntington's disease require the support of their families and healthcare.

Huntington's disease patients at various stages:

Table1

Stage	**Symptom**
One parent is impacted at the risk stage (50%)	apprehension about the future
Gene carrier, pre-manifest stage	Take care of the afflicted parent and his or her family.
Transitional period	Psychological and neurological activity changes
clinical investigation at stage I	unable to communicate and suicide behavior
Clinical investigation at stage II	Physical dependence starts
Clinical investigation at stage III	Patient completely dependent on care

Huntington's infection is characterized by a defective gene on chromosomal number four. The regular karyotype creates the protein huntingtin, whereas the defective gene has an aberrant region of CAG repeats. [7] A mutant type of Huntingtin is produced in this location, which is greater than normal. The aberrant Huntingtin has a strong influence on cells in regions of the brain, including the basal ganglia and parts of the cortex. As a result, they perform badly and finally perish. [8]. When this portion of the brain is injured, movement, behavior, and thinking become difficult to control. It's still unknown how aberrant Huntingtin impacts brain cells or why some people are much more reactive than any others.

Medical Science Investigations:

Individuals with any of the following symptoms should be suspected of having Huntington's disease (HD).

1. A chorea is a form of progressive motor impairment. It's possible that voluntary movement will be impaired as well.
2. Cognitive decline, personality changes, and/or depression are all examples of mental disorders.
3. Autosomal dominant inheritance is supported by family history.

HD is passed down through the generations in an autosomal dominant pattern. [8] A person's offspring have a 50% probability of receiving the genotype that causes sickness if their parent has a pathogenic variant. Routine assessments and regular evaluations of functional capacities are measured by applying the Behaviour Observation Scale Huntington and the Unified Huntington's Disease Rating Scale [9].

Because there is presently no cure for the illness, it is possible to perform a diagnostic assessment on symptoms of people who are at hazards (Tab2), but it requires careful consideration.For individuals under the age of 18 who are undiagnosed and at risk, predictive testing is not recommended. [10,11,12] Prenatal genetic testing and

preimplantation genetic testing are two types of prenatal genetic testing. If the parents have still not been genotyped, an exclusion test can be performed by comparing the embryo's genetic status to that of the parents. In this instance, the fetus faces either a 0% or a 10% risk., in which case the parent retains a 50% danger for the developing infant.[13,14,] The diseased grandparent gave the infant a chromosome, but it's unclear to which chromosome the HD gene is linked. In this situation, the infant faces a 50% chance of dying.

The number of HTT CAG repeats it is determined through targeted analysis in molecular genetic testing.[15,16] Because the test can be performed on any cell with a nucleus containing DNA, embryonic diagnosis is achievable. Between $(10 - 12)^{th}$ weeks of pregnancy, a chorionic villus sample can be done, and between the 15th and 17th weeks, amniocentesis and DNA testing can be done. [17, 18, 19] To avoid accidentally disclosing the genetic status of two people at the same time, only if both parents are aware of their genetic status is the treatment started. If the HD gene is found in the early phases of development, the technique is started to terminate the pregnancy [20, 21]. It is impossible to persuade the mother to accept this viewpoint.

Pharmacologic treatment with typical neuroleptics, atypical neuroleptics, benzodiazepines, or the monoamine-depleting agent tetrabenazine for choric movements; anti-parkinsonian medications for hypokinesia and stiffness; psychotropic drugs or some types of antiepileptic drugs (Tab3) for psychological issues. Over the last decade, preimplantation testing has been made available in a number of countries. The technique's first stage is in vitro fertilization. At the 8-cell stage, 1- cell is removed from the embryo for DNA testing. [22, 23] The embryo with the extended CAG repeat is put in the mother's womb to allow a normal pregnancy to develop. Although this is not the case in all countries, before the treatment can begin, the family's genetic status must be determined. [24, 25]

Table 2. :(Diagnosis of Huntington's Disease)

Molecules	*Genes*	Disorder
Frontotemporal dementia &/or amyotrophic lateral sclerosis	*C9orf72*	Psychiatric abnormalities, Memory, and Movement Disorders
Huntington disease-like 1 [1]	*PRNP*	A wide range of clinical characteristics that are related to HD
Huntington disease-like 2	*JPH3*	identical from HD
Chorea-acanthocytosis	*VPS13A*	Progressive movement dysfunction, as well as abnormalities in cognition and behavior.
McLeod neuroacanthocytosis syndrome	*XK*	Psychiatric symptoms and cognitive impairment
Spinocerebellar ataxia type 17	*TBP*	Memory, Involuntary movements, and Psychiatric Disturbances
Dentatorubral-pallidoluysian atrophy	*ATN1*	Psychiatric abnormalities and progressive movement problems
Benign hereditary chorea	*NKX2-1*	Involuntary movements
Hereditary cerebellar ataxia	Many	problem with movement
Familial Creutzfeld-Jakob disease	*PRNP*	Late-onset dementia, movement difficulties, behavioral abnormalities, and psychiatric symptoms are common.
Early-onset familial Alzheimer's disease	*APP* *PSEN1* *PSEN2*	Schizophrenia
Familial frontotemporal dementia withparkinsonism-17	*MAPT*	Late-onset Parkinson's disease, dementia, and behavioral alterations

Treatment:

Huntington's disease patients may want to consider genetic testing and family planning options. If an at-risk parent is interested in genetic testing, meeting with a genetic counselor may be beneficial.[27,28,29] A genetic counselor will discuss the risks of a positive test result, which indicates that the parent is at risk of developing the disease.[30,31,32 Families must also decide whether or not to have children, as well as whether or not to seek options such as prenatal gene testing or in vitro fertilization with donor sperm or eggs.

Table 3.
Homeopathic Medicines:

Name of the chemical compound	Source	Preparation	Clinical application
Mygale	A large block cubna Spider	Tincture of the living spider	uncontrollable movements of arms, legs, and face
Tarentula Hispanica	Wolf Spider.	Tarentula is prepared is generally found in Europe and South America. it is poisonous for humans and not used in preparing any homeopathic medications	Repetitive moment
Agaricus	Mushroom species are Found in Brazil, China, Japan, Brazil, and the US.	Wetting and blending process.	It is given for both involuntary motion/jerking of single muscles of a body part as well as involuntary trembling/dancing of the whole body
Causticum	calcium sulfate and potassium hydroxide,	potassium hydrate,	Weakness, Worsening, Body movements
Cuprum Met	Copper	When copper is present in the uterus, it has a preventive function. It's added to some oral contraceptive methods, allowing them to shrink in size while also reducing associated adverse effects, including pain and bleeding.	The treatment of convulsions epilepsy spasmodic infections, cramps, and involuntary jerking of limbs and fingers accompanied by nausea.
Magnesia Phos	Whole grains, legumes, veggies (particularly broccoli, squash, and green leafy vegetables), seeds, and nuts are all excellent sources of protein (especially almonds).	Interaction of magnesium chloride or sulfate with phosphate salt.	Better sleep.
Secale Cor	Lactose and sucrose	one part tincture, four parts Purified Water and five parts Strong Alcohol	The arms and leg's constant motion
Kali Bromatum	the reaction of potassium carbonate with an iron(III, II) bromide,	Homeopathic Mother tinctures	involuntary motions of facial muscles

Ayurveda medicine

Citalopram	Racemic mixture	The anion technique and the double Grignard strategy have been presented as possible routes for the synthesis of citalopram.	depression
Deutetrabenazine	Monoamine –depleting agents	The advanced drug design method used	sudden movements that you cannot control
Fluoxetine	Gelatine, hypromellose, hypromellose acetate succinate, sodium lauryl	The advanced drug design method used	depression, obsessive-compulsive disorder

	sulfate, sucrose, sugar spheres, talc, titanium oxide, triethyl citrate, and other inactive ingredients.		
Fluphenazine	trifluoro-methyl phenothiazine	The advanced drug design method used	Hallucinations, delusions, and hostility.
Haloperidol	Butyraphenone	The advanced drug design method used	mental/mood disorders
Mirtazapine	Tetracyclic piperazino-azepine	The advanced drug design method used	depression
Olanzapine	A synthetic derivative of thienobenzodiazepine with antipsychotic, antinausea, and antiemetic activities	The advanced drug design method used	schizophrenia
Pimozide	Pimozide is a diphenylbutylpiperidine derivative and a dopamine antagonist with the antipsychotic property.	The advanced drug design method used	control motor or verbal tics
Risperidone	Risperidone is a benzisoxazole derivative with antipsychotic property	The advanced drug design method used	Irritability is associated with autistic disorder.
Sertraline	hydride of a tetralin.	The advanced drug design method used	depression, obsessive-compulsive disorder
Tetrabenazine	Monoamine Oxidase Inhibitors	The advanced drug design method used	sudden movements that you cannot control

II. Conclusion:

Huntington's disease is a chronic and degenerative disease that affects people of all ages. *We investigate the fundamental molecular pathways and discover important compounds in Huntington's disease*. There are currently few medicines available, and several clinical trials have failed. We've talked about the causes, problems, investigations, and treatments for HD in this review: These are in addition. Existing therapy targets will become better characterized as our understanding of the pathogenic pathways that contribute to HD improves, and new targets will be discovered. The resources to get HD medicines to the clinic are in place, and the first viable treatments for HD could be developed in the next decade.

References

[1]. Bates GP. History of genetic disease: the molecular genetics of Huntington disease - a history. Nat Rev Genet. 2005 Oct;6(10):766-73. doi: 10.1038/nrg1686.
[2]. Caron NS, Wright GEB, Hayden MR. Huntington Disease. 1998 Oct 23 [updated 2020 Jun 11].
[3]. Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Mirzaa G, Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2021.
[4]. Gonzalez-Alegre P, Afifi AK. Clinical characteristics of childhood-onset (juvenile) Huntington disease: report of 12 patients and review of the literature. J Child Neurol. 2006 Mar;21(3):223-9.
[5]. Imarisio S, Carmichael J, Korolchuk V, Chen CW, Saiki S, Rose C, Krishna G, Davies JE, Ttofi E, Underwood BR, Rubinsztein DC. Huntington's disease: from pathology and genetics to potential therapies. Biochem J. 2008 Jun 1;412(2):191-209. doi: 10.1042/BJ20071619.
[6]. Jones L, Hughes A. Pathogenic mechanisms in Huntington's disease. Int Rev Neurobiol. 2011;98:373-418. doi: 10.1016/B978-0-12-381328-2.00015-8.
[7]. Kent A. Huntington's disease. Nurs Stand. 2004 Apr 21-27;18(32):45-51; quiz 52-3.

[8]. Maiuri T, Mocle AJ, Hung CL, Xia J, van Roon-Mom WM, Truant R. Huntingtin is a scaffolding protein in the ATM oxidative DNA damage response complex. Hum Mol Genet. 2017 Jan 15;26(2):395-406. doi: 10.1093/hmg/ddw395.
[9]. Sturrock A, Leavitt BR. The clinical and genetic features of Huntington disease. J Geriatr Psychiatry Neurol. 2010 Dec;23(4):243-59. doi: 10.1177/0891988710383573. Epub 2010 Oct 5.
[10]. Tost H, Wendt CS, Schmitt A, Heinz A, Braus DF. Huntington's disease: phenomenological diversity of a neuropsychiatric condition that challenges traditional concepts in neurology and psychiatry. Am J Psychiatry. 2004 Jan;161(1):28-34.
[11]. Walker FO. Huntington's disease. Lancet. 2007 Jan 20;369(9557):218-28.
[12]. Young AB. Huntingtin in health and disease. J Clin Invest. 2003 Feb;111(3):299-302.
[13]. Futter, M., Diekmann, H., Schoenmakers, E., Sadiq, O., Chatterjee, K., Rubinsztein, D. C. Wild-type but not mutant Huntingtin modulates the transcriptional activity of liver X receptors. J. Med. Genet. 46: 438-446, 2009. [PubMed: 19451134, images, related citations]
[14]. Godin, J. D., Colombo, K., Molina-Calavita, M., Keryer, G., Zala, D., Charrin, B. C., Dietrich, P., Volvert, M. L., Guillemot, F., Dragatsis, I., Bellaiche, Y., Sandou, F., Nguyen, L., Humbert, S. Huntingtin is required for mitotic spindle orientation and mammalian neurogenesis. Neuron 67: 392-406, 2010. [PubMed: 20696378, related citations]
[15]. Guo, Q., Huang, B., Cheng, J., Seefelder, M., Engler, T., Pfeifer, G., Oeckl, P., Otto, M., Moser, F., Maurer, M., Pautsch, A., Baumeister, W., Fernandez-Busnadiego, R., Kochanek, S. The cryo-electron microscopy structure of huntingtin. Nature 555: 117-120, 2018. [PubMed: 29466333, related citations]
[16]. Henshall, T. L., Tucker, B., Lumsden, A. L., Nornes, S., Lardelli, M. T., Richards, R. I. Selective neuronal requirement for Huntingtin in the developing zebrafish. Hum. Molec. Genet. 18: 4830-4842, 2009. [PubMed: 19797250, images, related citations]
[17]. Jeong, H., Cohen, D. E., Cui, L., Supinski, A., Savas, J. N., Mazzulli, J. R., Yates, J. R., III, Bordone, L., Guarente, L., Krainc, D. Sirt1 mediates neuroprotection from mutant Huntingtin by activation of the TORC1 and CREB transcriptional pathway. Nature Med. 18: 159-165, 2012. [PubMed: 22179316, related citations]
[18]. Lopes, F., Barbosa, M., Ameur, A., Soares, G., de Sa, J., Dias, A. I., Oliveira, G., Cabral, P., Temudo, T., Calado, E., Cruz, I. F., Vieira, J. P., Oliveira, R., Esteves, S., Sauer, S., Jonasson, I., Syvanen, A.-C., Gyllensten, U., Pinto, D., Maciel, P. Identification of novel genetic causes of Rett syndrome-like phenotypes. J. Med. Genet. 53: 190-199, 2016. [PubMed: 26740508, related citations]
[19]. Marcora, E., Kennedy, M. B. The Huntington's disease mutation impairs Huntingtin's role in the transport of NF-kappa-B from the synapse to the nucleus. Hum. Molec. Genet. 19: 4373-4384, 2010. [PubMed: 20739295, related citations]
[20]. McFarland, K. N., Huizenga, M. N., Darnell, S. B., Sangrey, G. R., Berezovska, O., Cha, J.-H. J., Outerio, T. F., Sadri-Vakili, G. MeCP2: a novel huntingtin interactor. Hum. Molec. Genet. 23: 1036-1044, 2014. [PubMed: 24105466, images, related citations]
[21]. Rodan, L. H., Cohen, J., Fatemi, A., Gillis, T., Lucente, D., Gusella, J., Picker, J. D. A novel neurodevelopmental disorder associated with compound heterozygous variants in the huntingtin gene. Europ. J. Hum. Genet. 24: 1826-1827, 2016. Note: Erratum: Europ. J. Hum. Genet. 24: 1838 only, 2016. [PubMed: 27329733, related citations]
[22]. Sassone, F., Margulets, V., Maraschi, A., Rodighiero, S., Passafaro, M., Silani, V., Ciammola, A., Kirshenbaum, L. A., Sassone, J. Bcl-2/adenovirus E1B 19-kDa interacting protein (BNip3) has a key role in the mitochondrial dysfunction induced by mutant Huntingtin. Hum. Molec. Genet. 24: 6530-6539, 2015. [PubMed: 26358776, related citations]
[23]. Seong, I. S., Woda, J. M., Song, J.-J., Lloret, A., Abeyrathne, P. D., Woo, C. J., Gregory, G., Lee, J.-M., Wheeler, V. C., Walz, T., Kingston, R. E., Gusella, J. F., Conlon, R. A., MacDonald, M. E. Huntingtin facilitates polycomb repressive complex 2. Hum. Molec. Genet. 19: 573-583, 2010. [PubMed: 19933700, images, related citations]
[24]. Mith, R., Bacos, K., Fedele, V., Soulet, D., Walz, H. A., Obermuller, S., Lindqvist, A., Bjorkqvist, M., Klein, P., Onnerfjord, P., Brundin, P., Mulder, H., Li, J.-Y. Mutant Huntingtin interacts with beta-tubulin and disrupts vesicular transport and insulin secretion. Hum. Molec. Genet. 18: 3942-3954, 2009. [PubMed: 19628478, related citations]
[25]. Song, W., Chen, J., Petrilli, A., Liot, G., Klinglmayr, E., Zhou, Y., Poquiz, P., Tjong, J., Pouladi, M. A., Hayden, M. R., Masliah, E., Ellisman, M., Rouiller, I., Schwarzenbacher, R., Bossy, B., Perkins, G., Bossy-Wetzel, E. Mutant Huntingtin binds the mitochondrial fission GTPase dynamin-related protein-1 and increases its enzymatic activity. Nature Med. 17: 377-382, 2011. [PubMed: 21336284, images, related citations]
[26]. Woerner, A. C., Frottin, F., Hornburg, D., Feng, L. R., Meissner, F., Patra, M., Tatzelt, J., Mann, M., Winklhofer, K. F., Hartl, F. U., Hipp, M. S. Cytoplasmic protein aggregates interfere with

nucleocytoplasmic transport of protein and RNA. Science 351: 173-176, 2016. [PubMed: 26634439, related citations]

[27]. Y. P., Kremer, B., Squitieri, F., Theilmann, J., Zeisler, J., Telenius, H., Adam, S., Almquist, E., Anvret, M., Lucotte, G., Stoessl, A. J., Campanella, G., Hayden, M. R. Huntington disease without CAG expansion: phenocopies or errors in assignment? Am. J. Hum. Genet. 54: 852-863, 1994. [PubMed: 8178825, related citations]

[28]. Goldfarb, L. G., Brown, P., McCombie, W. R., Goldgaber, D., Swergold, G. D., Wills, P. R., Cervenakova, L., Baron, H., Gibbs, C. J., Jr., Gajdusek, D. C. Transmissible familial Creutzfeldt-Jakob disease associated with five, seven, and eight extra octapeptide coding repeats in the PRNP gene. Proc. Nat. Acad. Sci. 88: 10926-10930, 1991. [PubMed: 1683708, related citations]

[29]. Laplanche, J.-L., El Hachimi, K. H., Durieux, I., Thuillet, P., Defebvre, L., Delasnerie-Laupretre, N., Peoc'h, K., Foncin, J.-F., Destee, A. Prominent psychiatric features and early onset in an inherited prion disease with a new insertional mutation in the prion protein gene. Brain 122: 2375-2386, 1999. [PubMed: 10581230, related citations] [Full Text]

[30]. Moore, R. C., Xiang, F., Monaghan, J., Han, D., Zhang, Z., Edstrom, L., Anvret, M., Prusiner, S. B. Huntington disease phenocopy is a familial prion disease. Am. J. Hum. Genet. 69: 1385-1388, 2001. [PubMed: 11593450, related citations]

[31]. Van Gool, W. A., Hensels, G. W., Hoogerwaard, E. M., Wiezer, J. H., Wesseling, P., Bolhuis, P. A. Hypokinesia and presenile dementia in a Dutch family with a novel insertion in the prion protein gene. Brain 118: 1565-1571, 1995. [PubMed: 8595485, related citations]

[32]. Xiang, F., Almqvist, E. W., Huq, M., Lundin, A., Hayden, M. R., Edstrom, L., Anvret, M., Zhang, Z. A Huntington disease-like neurodegenerative disorder maps to chromosome 20p. Am. J. Hum. Genet. 63: 1431-1438, 1998. [PubMed: 9792871, related citations]

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